

ACADEMIC PRESS SERIES IN BIOMEDICAL ENGINEERING



BIOFLUID MECHANICS

AN INTRODUCTION TO FLUID
MECHANICS, MACROCIRCULATION,
AND MICROCIRCULATION

THIRD EDITION

DAVID A. RUBENSTEIN
WEI YIN
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Quotes on Engineering, Science, Research, and Related Matters

"The Sun, with all the planets revolving around it and dependent on it, can still ripen a bunch of grapes as though it had nothing else in the Universe to do." *Galileo Galilei*

"The scientists of today think deeply instead of clearly. One must be sane to think clearly, but one can think deeply and be quite insane." *Nikola Tesla*

"Life is pretty simple: You do some stuff. Most fails. Some works. You do more of what works. If it works big, others quickly copy it. Then you do something else. The trick is the doing something else." *Tom Peters*

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change." *Charles Darwin*

"Equipped with his five senses, man explores the universe around him and calls the adventure Science." *Edwin Hubble*

"It would be nice if all of the data which sociologists require could be enumerated because then we could run them through IBM machines and draw charts as the economists do. However, not everything that can be counted counts, and not everything that counts can be counted." *William Bruce Cameron*

Preface

The purpose of this textbook is to serve as an introduction to biofluid mechanics with emphasis on the macrocirculation, microcirculation, and other important biological flows in the human body. As readers will see as they progress through this textbook, an integral and essential component of the human body is the cardiovascular system. Consequently, the cardiovascular system may be one of the most important biofluid mechanics scenarios to study. Combining this importance with the prevalence of vascular diseases in the Western world supports the amount of scientific research that explores the cardiovascular system and the duration of explorations in this area, which have been ongoing for decades. Furthermore, many implantable devices, therapeutic agents, and any other device that can come into contact with the body may augment biofluid properties.

Although the cardiovascular system is very important, the authors hope that the readers of this textbook will gain an appreciation for the importance of other systems within the human body and how biofluid mechanics principles can be used to describe those systems. We will learn that many of the principles that are developed in the context of the cardiovascular system can be applied to these other systems, sometimes with slight modifications. We will discuss some of these systems in this textbook to help the reader gain this appreciation.

New to this edition is a more rigorous discussion of the foundations of heat transfer. In classical engineering curricula, heat

transfer and fluid mechanics courses are complementary. In classical engineering disciplines, many fluid mechanics problems involve heat transfer properties, such as heating a building, refrigeration, engine cooling, and motion of aircraft. In biofluid mechanics situations, heat transfer may be a very important part of the problem, but in some situations, heat transfer may be neglected. For example, inspiring air into your respiratory system may have significant heat transfer properties that should be incorporated into your analysis. In contrast, blood movement through the heart, although it may experience heat transfer phenomena, may not be significant and included in your analysis.

When covering all of these topics, the authors hope to provide a systematic teaching and learning tool that will motivate students to continue their education in biofluid mechanics and provide an effective educational structure to aid in biofluid mechanics instruction. To complete these aims, the authors have provided a rigorous review of the salient fluid mechanics principles and have related these principles to biological systems. This is followed by two sections on the application of these principles to the cardiovascular system and specifically the macrocirculation and microcirculation, the two most commonly studied systems in biofluid mechanics. Next, sections on biological flows within other important physiological systems and some common experimental techniques for biofluid mechanics are included to illustrate that

(1) fluid mechanics principles are not restricted to the cardiovascular system and (2) advanced techniques are needed to tease out biofluid mechanics properties. Finally, the authors relate this material to many principles that the readers should be familiar with to provide concrete and relevant examples to supplement learning. The authors think that the combination of all of these features makes the book novel and unique and hope this will facilitate the learning of biofluid mechanics at all levels. The authors also take the approach of relating this material to common engineering courses with which the reader may be familiar.

This textbook has been put together to fill a need in the evolving biofluid mechanics community and to fill a void in biomedical engineering (and allied bioscience disciplines) curriculum. As more undergraduate biomedical engineering departments become established, textbooks tailored to undergraduate education are needed in the core biomedical engineering courses. This book has made use of a problem-based approach and modern pedagogy in its development. The problem-based approach is used to engage the reader's interest and provide insight into biofluid properties. Furthermore, extensive problems are worked out in detail in each section to provide examples of how to approach biofluid mechanics problems, typical pitfalls, and a structured solution methodology that students can follow when studying at home (asterisks denote more difficult example problems throughout the book and also illustrate entire sections that can be omitted without the loss of continuity but are provided for those interested in a more in-depth analysis of biofluid mechanics). Numerous pedagogical tools have been implemented in this book to aid student understanding. Each chapter starts with a learning outcomes section, so the reader can

anticipate the key concepts that will be covered in the particular chapter. Furthermore, each chapter concludes with a summary section that reiterates the salient points and key equations. Further readings and classical biofluid mechanics papers are cited for supplemental reading. These sections hopefully will be used as a springboard for learning and will reinforce key concepts.

Ancillaries

For instructors using this text in a course, a solutions manual and a set of electronic images are available by registering at <http://www.textbooks.elsevier.com> or by visiting our new textbook website, Elsevier Educate: <https://inspectioncopy.elsevier.com/>

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This book has also been class-tested by students in manuscript form, and their feedback has proved valuable in improving the usefulness of the book. We appreciate all the efforts of these individuals in helping improve the quality of the book but

recognize that any errors that might still exist despite our best efforts are the responsibility of the authors themselves.

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Introduction

LEARNING OUTCOMES

- Identify basic engineering skills that will be used in this course
- Describe the fields and the importance of biomedical engineering, fluid mechanics, and biofluid mechanics
- Review concepts of dimensions and units
- Discuss two of the salient dimensionless numbers in biofluid mechanics

1.1 Note to students about this textbook

The goal of this textbook is to clearly describe how fluid mechanics principles can be applied to different biological systems and, in parallel, discuss current research avenues in biofluid mechanics and common pathological conditions that are associated with altered biofluids, biofluid flows, and/or biofluid organs. We aim to highlight fundamental fluid relationships and how these relationships can be applied to the cardiovascular system, but importantly, we will illustrate how these principles can also be applied to other physiological systems and research in general. Classic fluid mechanics laws, which the reader may be familiar with from a previous course in fluid mechanics (but will be reviewed in Part I of this textbook), have been used extensively to describe blood flow through the vascular system for decades. One major goal of this textbook is to discuss how these laws apply to the vascular system, but we also aim to highlight some of the specialty flows that can be described using the same fluid mechanics principles. We want to point out that one of the primary purposes of this textbook is to introduce fluid mechanics principles, thus there are many more advanced concepts that will not be described in this text but are referenced in our Further Readings Section and Reference Lists. Part II, Macrocirculation, and Part III, Microcirculation, focus on the application of these classic fluid mechanics principles to the vascular system and the development of specific mathematical formulas and relationships to help the reader understand the fluid mechanics associated with blood flow through blood

vessels of various sizes. Note that we also discuss the heart and some diseases that relate to cardiac changes. Part IV, Specialty Circulations, describes fluid flows through the lungs, eyes, diarthroses joints, kidneys, and the splanchnic circulation, which are not traditionally covered in biofluid mechanics courses but are very important biological flows in the human body. We will use these examples to show that some of the fundamental relationships apply to other physiological scenarios in the body, and perhaps other relationships will need to be used to describe these biofluid flow conditions. Note that there are other important specialty circulations that can be modeled using the fluid mechanics principles that will be developed in Part I of this textbook. We may touch on some of those circulations, but we will not fully develop an analysis of these flows in this text. For the most part, similar fluid mechanics principles that were used to describe the flow in the vascular system can be used to describe the specialty circulations with some slight modifications to accurately depict the particular special conditions associated with the circulation. Part V, Experimental Techniques, briefly highlights different procedures currently being used in biofluid mechanics laboratories to elucidate flow characteristics under various conditions. At the same time, we will highlight some of the current innovative work that is being conducted to elucidate biofluid mechanics phenomena. The overarching goal of this textbook is to establish a foundation for students' future studies in biofluid mechanics, whether in a more advanced course or in a research environment.

In writing this textbook, we hope to meet the needs of both the students and the instructors who may use this textbook. This textbook is written in a way that instructors can use the material presented either as the sole course material (introductory biofluid mechanics course, with omissions of the more advanced concepts as noted by an asterisk following the section title in subsequent chapters) or as the foundation for more in-depth discussions of biofluid mechanics (upper-division/graduate courses, with omitting some of the more introductory fluid topics). However, an introductory textbook, such as this one, cannot include every detail of importance to biofluid mechanics, and it does not try to cover every topic. Multiple exceptional references can be used in conjunction with this textbook (some of which are highlighted in the Further Reading section). Therefore, we encourage you to visit your local libraries or to search the Internet for more in-depth details that are not included in this textbook. In addition, this textbook cannot and does not aim to replace traditional fluid mechanics or physiology textbooks, but it will provide the information necessary to (1) set the foundation for a broad biofluid mechanics discussion, (2) analyze some of the particular biofluid mechanics principles, (3) quantify some of the salient biofluid mechanics flows, and (4) serve as a springboard for future more detailed and in-depth discussions on biofluid principles. At the end of most of the chapters, we provide suggested references for students and instructors, if more information is desired. These sources will typically be related to some of the more important broad topics covered in the section but are not necessarily related to every specific example used.

Your instructor and other students in your class are other good resources to learn about biofluid mechanics. However, we think that you will learn these principles best by working example problems at home. We included extensive examples within the text, all completely worked out, so you can see the level of detail needed to solve biofluid mechanics problems. We also include various levels of homework problems at the end of each chapter for you to practice on your own. We have made a concerted effort to extend these examples and

problems, providing extra information where applicable. Your success in this course will depend not only on the material presented within this textbook and from your instructor's notes, but also on your willingness to comprehend the material and work through example biofluid mechanics problems yourself. We hope that this textbook can serve as a stepping-stone on your way to becoming experts in biofluid mechanics principles and applications. If you think there are shortcomings or omissions in this textbook, please let us know so it can be remedied in future editions.

1.2 Biomedical engineering

One of the first questions that should arise when studying biomedical engineering (in this textbook the term *biomedical engineering* will be used interchangeably with bioengineering) is: What is biomedical engineering? The National Institutes of Health's working definition (as of July 24, 1997) of biomedical engineering is:

Biomedical engineering integrates physical, chemical, mathematical, and computational sciences and engineering principles to study biology, medicine, behavior, and health. It advances fundamental concepts; creates knowledge from the molecular to the organ systems level; and develops innovative biologics, materials, processes, implants, devices and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health.

This definition is broad and can encompass many different engineering disciplines, and, in fact, biomedical engineers can apply electrical, mechanical, chemical, and materials engineering (among others) principles to the study of biological tissue and to how these tissues function and respond to different conditions. Biomedical engineers also focus on many other fundamental engineering disciplines, such as systems and controls problems through the design of new devices for medical imaging, rehabilitation, and disease diagnosis. The nature of biomedical engineering is thus interdisciplinary because of the need to understand both engineering principles and physiology and to apply concepts from both disciplines to your area of investigation. The broad goal of biomedical engineering is to meld these disciplines together to describe biological systems or design and fabricate devices to be used in a biological or medical setting.

In this textbook, the focus is on traditional mechanical engineering principles and how they are related to biofluid mechanics. This is not to say that other engineering principles are not or cannot be applied to biofluid mechanics. For example, we will illustrate how thermodynamics principles can be applied to the vascular system in the context of bioheat transfer engineering. For this textbook, we will take an approach that starts with the fundamental engineering mechanics laws and principles to derive the fluid mechanics equations of state. In parallel, fundamental thermodynamics equations will be developed for the study of heat transfer within biological systems. These equations will be developed in both the context of fluid mechanics and then in a slightly different manner in the context of heat transfer engineering. Most of these equations should be familiar from earlier engineering or physics courses, but we will discuss and develop them in subsequent chapters where a review is warranted. Most biofluid mechanics situations focus on describing the flow in a particular tissue, which can be considered an extension or a special case of the fluid mechanics problems

that have been studied previously (if a fluid mechanics course was taken before this course). For example, if we were interested in describing the blood flow through the coronary artery, we can use fluid mechanics principles, but we would also need to consider the mechanical properties of the blood vessel and how this may alter the fluid flow. We will develop the solutions in a simplified context (e.g., a rigid vessel wall) and then relax some of these constraints as we progress through the content of the book. Likewise, if you are interested in designing a new implantable cardiovascular device, you would need to understand and consider not only the mechanical flow principles but also the material properties, the electrical components, and the physiological effects that the device may have on the cardiovascular system. This type of problem approaches the heart of what a biomedical engineer does: design a device to remedy a physiological problem and describe the effects of that device in physiologically relevant settings. Some biomedical engineers focus solely on the engineering design aspect, and others focus on physiological applications. Herein, we discuss both aspects of biofluid mechanics to solve multiple types of problems and attempt to illustrate how these two fields converge.

1.3 Scope of fluid mechanics

Now that we have defined what a biomedical engineer is and what a biomedical engineer does, the question should arise, “Why do we need to study biofluid mechanics?” We will first answer the question, “Why should we study fluid mechanics?” and return to the earlier question later. Any system that operates in a fluid medium can be analyzed using fluid mechanics principles. This includes anything that moves in a gas (e.g., airplanes, cars, trains, birds) or in a liquid (e.g., submarines, fish), or anything that is designed to have at least one boundary surface with a gas or a liquid (e.g., bridges, skyscrapers, boats, cells). Situations may arise in which objects can be described as “flowing” through a fluid medium (fish swimming); in other conditions the object may be solely convected through the fluid medium. These types of situations are typically concerned with both the flow of the object (fish) and the flow of the medium (water surrounding the fish). It is important to note that in any of these scenarios it is possible that the movement of the object alters the flow of the medium and that the flow of the medium alters the movement of the object (e.g., for a simple case, is there a difference in swimming upstream versus downstream versus perpendicular to the flow direction). Each of these types of flow scenarios are common in biofluid mechanics in which cells, which exhibit fluid properties, are submerged within a moving fluid (e.g., red blood cells flowing through blood within the cardiovascular system). Additionally, stationary flow structures are concerned with the forces (drag, shear, pressure) that can be transmitted from a flowing fluid to the structure that is containing or bounding the fluid. This is a critical area of analysis for the design or evaluation of any fluid that flows through any “channel,” which includes blood flowing through blood vessels, lymph flowing through lymph vessels, and air flowing through the respiratory tract. Fluid mechanics principles can be used to describe all of these highlighted systems, among many others.

Also integral to the study of fluid mechanics is the design of fluid machinery. Fluid machinery includes pumps, turbines, and anything that has a lubrication layer between

two moving and usually solid parts. Typically, fluid machinery comes into play in the design of heating and ventilation systems, cars, airplanes, and a long list of other devices and systems, which include devices that interact with or within biological systems. Fluid mechanics is not an academic problem, but one that every engineer will face at some time during his or her career. This textbook is not going to replace a standard fluid mechanics text or a fluid mechanics course. Instead, we use fluid mechanics as a starting point to describe one particular application of fluid mechanics: biological fluid flows.

1.4 Scope of biofluid mechanics

So, why should we study biofluid mechanics? First, your body is composed of approximately 65% water. All cells have an intracellular water component, and each cell is immersed within an extracellular water compartment. Forces that are distributed and transmitted through this water layer act on each and every immersed cells. The fluid surrounding these cells can flow, possibly inducing variable forces on the immersed cells. In addition, some cells in your body are nonadherent cells under nonpathological conditions (i.e., red blood cells, white blood cells, platelets). These three highlighted cells are convected through your bloodstream (within the cardiovascular system) and experience many types of fluid forces (including shear forces and pressure forces), which can alter their functions. In fact, pathological flow conditions can “activate” these cells, initiating some disease processes. Gas movement (such as oxygen and carbon dioxide exchange within your lungs or air motion through the respiratory tree) also can be described by fluid mechanics principles. Joint lubrication, a major research area of biofluid mechanics, is critical to locomotion: with the degeneration of the lubrication layer, various everyday motions become difficult. Prosthetics cannot be designed without fluid mechanics. It is our hope that throughout this textbook, the readers will understand how fluid mechanics laws can be applied to biological systems and the significance of fluid mechanics laws to biological system as a whole.

Furthermore, the design of many implantable devices must consider fluid mechanics laws. Obvious examples are those devices that are directly implanted into the human body and are in contact with blood, such as stents and mechanical heart valves. However, a total artificial heart is a pump that will have a biological fluid flowing within it and this device replaces a portion of the cardiovascular system. This replacement, although it comes into contact with fluids, should replicate as accurately as possible the innate system it is replacing. Other examples of implantable devices that involve biofluid mechanics include extracorporeal devices that must maintain steady flow without aggravating cells or introducing harmful chemicals (for dialysis) and contact lenses that must consider the wetting of the eye, and gas diffusion to the eye, to function properly. Indeed, nearly every device intended for biological use will have to consider fluid mechanics laws, which are critical for proper design and functioning of the device.

Why is biofluid mechanics so critical to study? According to the American Heart Association’s 2019 Update, more than 115 million people in the United States had at least one cardiovascular disease. The majority of these cases are associated with high blood pressure (approximately 95 million people, which is approximately one-third of the United States

population; this number includes only people older than 20 years) or coronary heart disease (approximately 22 million people; note that some of these patients can overlap with the first group). In addition, cardiovascular diseases are the cause for approximately one of every three to four deaths in the United States, which is approximately 1.5 times more deaths than caused by cancer. For the complete statistics, which are divided into groups based on risk factors, age, race, etc. (see Ref. [1]). Coronary heart disease accounts for nearly 50% of these deaths and remains as the leading cause of death in the United States. One of the most telling statistics associated with cardiovascular diseases is that approximately every 30 s, one American will experience a coronary event and that approximately every 3.7 min, one American will die as a result of a stroke. Along with the American Heart Association, the Centers for Disease Control and Prevention generates national maps documenting the country-level heart disease death rates and the heart stroke death rates by county (see http://www.cdc.gov/dhdsdp/maps/national_maps/index.htm). Both of these maps include data only for people in the United States who are older than 34 years, and both provide evidence for where the highest incident rates of heart disease occur in the United States. It is clear that states along the lower Mississippi River have a higher rate of death associated with cardiovascular diseases than the majority of other states.

Biofluid mechanics is concerned not only with the cardiovascular system and diseases of the vascular system but also with lung diseases. Lung cancer is probably the first disease that comes to mind, and you are probably also considering that the most likely origin of lung cancer is exposure to cigarette smoke (either firsthand or secondhand). Indeed, approximately 85% of deaths associated with lung cancer are associated with cigarette smoking. Burning cigarettes emit close to 4000 different chemicals, with approximately 50 of these being known carcinogens. Interestingly, smoking cigarettes that have a reduced amount of tar does not significantly decrease the chances of developing lung cancer because of the plethora of other carcinogens within the cigarette. As a fact, tobacco companies are allowed to add approximately 600 chemicals to their product, including ammonia, 1-butanol, caffeine, cocoa, ethanol, 1-octanol, raisin juice, sodium hydroxide, and urea. In excess, some of the mentioned additives can lead to death, though perhaps not through cancer mechanisms. Furthermore, smoking is not just associated with lung cancer, but a smoker can succumb to other cancers as well, including oral, pharynx, larynx, bladder, kidney, stomach, and pancreatic cancer, because of the chemical additives that compose a cigarette, their combustion products, and the effects of these products of various organ systems. Interestingly, the rate at which e-cigarettes, which may contain some of the same chemicals that are within tobacco-based cigarettes, induce various cancers is currently unknown. Even though the inhaled products from tobacco smoke and e-vapor are fundamentally different, it is important to evaluate the risk associated with these exposures.

A third disease that is commonly investigated by people interested in biofluid mechanics is chronic kidney disease. Chronic kidney diseases are a group of diseases that alter the function of the kidneys and typically reduce their ability to remove toxins from the blood properly. Kidney diseases are linked to cardiovascular diseases, such as high blood pressure. Current statistics show that approximately 31 million American adults have some form of chronic kidney disease. The major cause of death for people with chronic kidney diseases is some form of cardiovascular event.

To bring us back to the cardiovascular system, we would like to highlight some of the major milestones that have transformed the study of cardiovascular diseases and the

management of pathologic cardiovascular conditions. This is clearly not an all-inclusive list, but just a list to describe some of the events that are important to our understanding of the cardiovascular system and may provide some motivation for studying biofluid mechanics.

- 1538: Andreas Vesalius published a new anatomy textbook, which contained two large and accurate anatomical charts dedicated to the heart.
- 1628: William Harvey concluded that the heart is a pump and that veins contain valves to prevent the backflow of blood.
- 1715: Raymond de Vieussens established that the heart consists of two chambers that isolate arterial and venous blood.
- 1733: Stephen Hales made the first blood pressure measurements, in a horse.
- 1816: René Laennec invented the earliest stethoscope to listen to blood moving through the heart.
- 1891: Cardiac chest compression was used to revive patients (reported by Friedrich Maass).
- 1902: Willem Einthoven invented the electrocardiograph and later received the Nobel Prize in physiology or medicine (1924) for this development.
- 1929: Werner Forssmann inserted a “catheter” into his own arm and passed it through his own cardiovascular system into his own right atrium. He then had colleagues take an x-ray of this procedure to document the catheterization. He later was awarded the Nobel Prize in physiology or medicine (1956) for his efforts.
- 1938: The first successful heart surgery was completed by Robert Gross.
- 1944: Alfred Blalock and Helen Taussig performed the first successful bypass surgery.
- 1947: The first successful defibrillation was completed.
- 1953: Charles Hufnagel implanted the first artificial heart valve.
- 1958: The first pacemaker and coronary angiography was completed.
- 1967: Christiaan Barnard successfully transplanted the first human heart.
- 1977: Andreas Grüntzig performed a balloon dilation of a stenosed coronary artery.
- 1970s–1980s: Robert Jarvik and Willem Kolff worked on and successfully designed a total artificial heart, which was first implanted in a patient in 1982.
- 1986: The first metal stent was implanted into an artery.
- 2000s Tissue engineering and stem cells used to improve the function of diseased cardiac tissue.

Clearly, we have not discussed all of the critical studies and findings that have helped to progress cardiovascular disease management, but this discussion highlights some of the major advances.

1.5 Dimensions and units

Dimensions and units are commonly confused, even though the solution to all engineering problems must include units. Dimensions are physical quantities that can be measured, whereas units are arbitrary names that correlate to particular dimensions to make the measurement relative to an agreed upon definition (e.g., a dimension is length, whereas a meter

is a relative unit that describes length). It is important to point out that there may be many units used to describe one dimension. Also, all units for the same dimension are related to each other through a conversion factor (e.g., 2.54 cm is exactly equal to 1 in by definition). There are seven base dimensions that can be combined to describe all of the other dimensions of interest in the various disciplines. In fluid mechanics, we generally pick length, mass, time, and temperature as base dimensions. Using this convention, force becomes a function of length, mass, and time (i.e., force is equal to mass multiplied by length all divided by time squared) and is not considered a base definition. However, others can choose to define force as one of their base dimensions. By making this choice, mass is defined (e.g., not a base dimension) by dividing force by the gravitational acceleration (which has dimensions of length divided by time squared). Readers are likely familiar with this concept as this is one of the major differences between the English system of units and the metric system of units. To continue this example, those who choose to use the metric system of units make use of the units kilogram, meter, and second to define the Newton. In contrast, those that choose to use the English system of units use of the units pound, foot, and second to define the slug.

Système International d'Unités (SI) units were the first international standard for units (this is also referred to as the *metric system*). English units followed later and are currently defined from the standard SI units. To define the seven base units within the SI system, scientists and engineers developed the following standards to quantify the associated seven base dimensions. The base unit for time is the second (s). One second was defined as the time for 9,192,631,770 periods of the radiation of a cesium-133 atom transitioning between two hyperfine ground states until 2019. Before this definition, an interestingly calculated hypothetical year and time were used to define the second, as the fraction $1/31,556,925.9747$ of the tropical year for 1900 January 0 at 12 h ephemeris time. In 2019, a new definition for the second has taken the form of taking a fixed numerical value for the cesium frequency as exactly $9,192,631,770 \text{ s}^{-1}$. This value is defined using the variable $\Delta\nu_{\text{Cs-133}}$. This allows one to then define the second as

$$1\text{s} = \frac{9,192,631,770}{\Delta\nu_{\text{Cs-133}}} \quad (1.1)$$

The base unit for length is the meter (m). One meter was defined as the distance traveled by light in a vacuum during $1/299,792,458$ of a second, until 2019. Before this definition, the meter was defined as the length of a pendulum with a half period of 1 s (1668), then one-ten-millionth of the length of the Earth's meridian (1791), followed by approximately 1.6 million wavelengths of krypton-86 radiation in a vacuum (1960). In 2019, a new definition was approved, and it is based on taking a fixed value for the speed of light in a vacuum (c). This value is defined as $299,792,458 \text{ ms}^{-1}$. From the defined value for the second, one can calculate the meter as

$$1\text{m} = \left(\frac{9,192,631,770}{299,792,458} \right) \frac{c}{\Delta\nu_{\text{Cs-133}}} \quad (1.2)$$

One inch (the English unit counterpart to the meter) is defined as exactly 0.0254 m (1 in = 2.54 cm). The standard unit for mass in the metric system is the kilogram (kg). Until 2019, a kilogram was defined by the mass of a platinum–iridium cylinder that is housed at the International Bureau of Weights and Measures (Paris, France). However it was found that the International Prototype Kilogram varied in mass over time with respect to reproductions made from this mass for various purposes. This mass of 1 g has been historically defined as the mass of 1 cm³ of water at 4°C, making a kilogram the mass of 1 L of water. However, the first prototype kilogram mass, which was in use until 2019, had the mass of 1.000025 L of water. The current agreed upon definition is based on the speed of light, the Planck constant, and the specific atomic transition frequency. The Planck constant and the atomic transition frequency are fundamental physical constants. With the new definition the Planck constant (h) is defined to be exactly $6.62607015 \times 10^{-34} \text{ kg m}^2 \text{ s}^{-1}$. From the known definitions of the meter and second, one can calculate the kilogram as

$$1\text{kg} = \left(\frac{(299,792,488)^2}{(6.62607015 \times 10^{-34})(9,192,631,770)} \right) \frac{h\Delta\nu_{\text{Cs}-133}}{c^2} \quad (1.3)$$

The base unit for temperature is the Kelvin (K). The Kelvin scale is defined from absolute zero (where no heat remains in an atom) and the triple point of water (the point at which a compound exists in the solid, liquid, and gaseous phases in equilibrium). From these four base units most of the parameters used in fluid mechanics can be derived. The three remaining base units are electric current (ampere (A)), amount of substance (mole (mol)), and luminous intensity (candela (cd)). In 2019, the definition of the ampere was changed to be based on a new fixed numerical value for the elementary charges (e) to be exactly $1.602176634 \times 10^{-19} \text{ C}$. From this definition the ampere becomes

$$1\text{A} = \frac{e\Delta\nu_{\text{Cs}-133}}{(1.602176634 \times 10^{-19})(9,192,631,770)} \quad (1.4)$$

The mole was defined when considerations on molecular mass, atomic mass, and Avogadro's number were under consideration. In 2019, the definition for mole was established to use Avogadro's number (N_A), which is $6.02214076 \times 10^{23} \text{ mol}^{-1}$. Using this fixed numerical value, the mole is defined as

$$1\text{mol} = \frac{6.02214076 \times 10^{23}}{N_A} \quad (1.5)$$

The candela is the luminous intensity of a source that emits a monochromatic radiation of frequency $540 \times 10^{12} \text{ Hz}$ and that has a radiant intensity of $1/683 \text{ watt/square radian}$ in that same direction. In 2019 these values were fixed as the luminous efficacy of monochromatic radiation at a frequency of $540 \times 10^{12} \text{ Hz}$ (K_{cd}) to be exactly $683 \text{ cd sr kg}^{-1} \text{ m}^{-2} \text{ s}^3 \text{ (W/sr)}$. The three last base units/dimensions are not as applicable to biofluid mechanics problems but may arise in problems throughout the textbook.

When converting between two different units, it is imperative to make sure that you track the units you are converting and that the quantities are being converted properly.

Engineering designs have failed because of miscalculations and misinterpretations in the units; thus we cannot stress the task of tracking units enough. For instance, if you are converting area, which is a length squared quantity, you must multiply by the conversion factor twice. If there is an addition or subtraction within your equation, you also need to make sure that the units are the same before the addition or subtraction operation. For instance, what is the solution to this subtraction: 3 meters minus 2 feet. We can ensure that the solution is not equal to 1 meter (or 1 foot). To complete the subtraction, you would first need to convert 2 feet to x many meters, and then you can proceed with the subtraction. This might seem trivial at this stage, but when your problem involves multiple dimensions, multiple quantities, and multiple algebraic steps, you must make sure that your units are correct before you complete the algebraic operations.

At this point, we would like to introduce a topic, the Buckingham Pi Theorem, which will be more fully discussed in [Section 15.3](#). This theorem is a mathematical approach that leads to the formation of a relationship between fluid mechanics quantities of interest. This theorem takes a dimensional analysis approach to relate quantities of interest. In principle, the theorem asks users to consider what dimensions are present in the quantities of interest and then takes an approach to eliminate all of the dimensions to come to a reduced relationship composed of the important variables. This approach has been very powerful in developing relationships and elucidating where constants of proportionality should exist. Although this was a very brief introduction to this powerful concept, please refer to [Section 15.3](#) to find a more thorough review of this topic, with examples. Note that this topic can be incorporated into the course at any time to help understand fluid mechanics relationships.

1.6 Salient biofluid mechanics dimensionless numbers

Dimensionless numbers tend to be very useful in characterizing many types of engineering systems. You may be familiar with this type of analysis from previous engineering courses. We will briefly introduce dimensionless numbers at this point, but more fully complete the analysis at a later time. For instance, you may have encountered the engineering parameter of strain, which is a dimensionless number that relates the percent of stretch that a material experiences to the resting length of that same material (note that some prefer to report strain in dimensions of length/length, e.g., mm/mm, but these dimensions do cancel out and thus you would remain with a dimensionless quantity). This type of dimensionless number helps us scale a parameter across multiple types of scenarios that engineers may come across, and typically these relationships become independent of other parameters (e.g., strain is largely independent of cross-sectional area geometry). In fluid mechanics, you may also encounter this type of dimensionless number to simplify the analysis. Some fluid mechanics engineers will report variables divided by some characteristics parameter or constant value to help relate the scale or parameters across various dimensions. For instance, some will divide the velocity (which can be a variable of space and time) by the inflow velocity (if it is uniform) or perhaps the centerline velocity at a given point of interest. Therefore, all of the velocity values become relative to this value and the velocity profile

will be scaled by this constant value. Fundamentally, this does not change the fluid properties or analysis of the problem; however, it may be easier to report, analyze, or interpret the data in this manner.

There is a second type of dimensionless number that exists in engineering fields. This second type of dimensionless number provides a measure of the importance of the phenomenon that plays a role in dictating how an event occurs. This type of dimensionless number also helps us to rescale problems as needed. Because this type of dimensionless number provides important information about the flow conditions, many different dimensionless quantities of importance to fluid mechanics and biofluid mechanics have been developed. We will discuss many of these dimensionless numbers and one method to derive these dimensionless numbers in [Section 15.3](#). However, because of the importance of two dimensionless numbers in biofluids mechanics phenomena, we will briefly discuss them here, while leaving a more thorough discussion for [Section 15.3](#).

The Reynolds number (Re) is the first dimensionless number that is important to nearly all biofluid mechanics flows. As stated earlier, dimensionless numbers relate two (or more) important phenomenon that play a role in the flow being analyzed. The Reynolds number relates the overall inertial forces that govern the flow to the viscous forces that may impede the flow. This is important because for any flow to occur, enough force must be present to overcome the fluid's resistance to flow. This does not mean that the Reynolds number must always be greater than 1, because the Reynolds number does not relate the driving forces to the resistance to flow; it only relates some of the inertial forces to some of the viscous forces (e.g., adhesion of the fluid to the bounding surface is not in this quantification).

Recall that inertia is defined as the object's resistance to change its velocity. Objects with a very large inertia resist changes to velocity very easily, whereas objects with a low inertia do not resist changes to velocity as strongly as high-inertia materials do. A simple experiment to observe inertia is to take a pen and hold it at its center between your forefinger and thumb. Now move your fingers to cause the ends of the pen to wiggle up and down. With a typical pen, these constant changes in motion are relatively easy to accomplish. Now conduct the same experiment, with the same pen, but hold the pen at one of the ends. The pen resists the changes in motion much greater under the second conditions. The moment of inertia of the pen in the second scenario is much larger than the first scenario. Fluid viscosity is simplistically defined as the internal resistance of a fluid to deform under shear loading conditions (we will discuss a more stringent definition of viscosity in later sections). A fluid with a large viscosity requires a large shearing force to deform the sample (or a small force applied for a very lengthy time), whereas a fluid with a lower viscosity requires a smaller shearing force to deform the sample. Another simple experiment can illustrate viscosity. Hold a glass of water and tip it at an angle (make sure not to spill the water!). Did the water deform? It should have, and the force was very low on the water. Now conduct the same experiment with syrup, toothpaste, or honey. Did the second fluid deform as easily; probably not. In this case water has a lower viscosity compared with the second fluid. A fluid that will experience a change in its velocity will have to balance changes to both the inertial forces and the viscous forces, which resist changes to velocity or deformation, respectively. This is true because when a fluid proceeds to a new velocity, the inertia will play a role in resisting this change and the viscous interactions will play a role in the deformation changes. Thus, the Reynolds number provides a measure of which forces

dominate changes to a fluids velocity. To relate these important parameters, the Reynolds number is defined as

$$\text{Re} = \frac{\text{inertial forces}}{\text{viscous forces}} = \frac{\rho v d}{\mu} \quad (1.6)$$

where ρ is the density of the fluid, v is some characteristic velocity (e.g., centerline velocity, max velocity, or other), d is a characteristic length of the flow (e.g., channel length, radius, diameter, or other), and μ is the dynamic viscosity of the fluid. Even though there are choices inherent within the Reynolds number formulation, there are some conventional choices for the characteristic velocity and length. If your flow can be approximated to be passing through a perfect tube with a constant cross section, v is conventionally chosen as the spatial mean flow velocity over the circular cross section and d is conventionally chosen as the diameter of the tube.

The Reynolds number also provides a measure of flow characteristics. For instance, low Reynolds number flows tend to be laminar whereas high Reynolds number flows tend to be turbulent. The transition between laminar and turbulent flows tends to be hard to strictly define, since there are many properties that affect the overall laminar versus turbulent flow properties. However, for perfect tubes with a constant cross-sectional area, the flow begins to transition to turbulence when the flow exceeds a Reynolds number of approximately 2300. However, true turbulence (as defined in [Section 2.12](#)) will only be found in flows with a Reynolds number of approximately 10,000. Flows in-between these two values are said to be transitioning and exhibit both laminar and turbulent flow properties. If the geometry of the flow changes, these transitioning values will also change; typical Reynolds number values, to describe laminar or turbulent flows can be found in fluid mechanics textbooks.

A second salient dimensionless number for biofluid mechanics flows is the Womersley number, which is related to the pulsatility of the flow. Flows that have regular oscillating time-dependent components (e.g., are not steady flows), are said to have pulsatility. The Womersley number is a ratio of the fluids oscillatory inertia to the viscous momentum. The oscillatory inertia is a measure of the forces that govern the pulsatile flow, whereas the viscous forces are again a measure of the fluids' overall resistance to changes in its velocity. The Womersley parameter can be defined as

$$\alpha = \frac{\text{oscillatory inertia}}{\text{viscous forces}} = \sqrt{\frac{\rho v \omega}{\mu \left(\frac{v}{d^2}\right)}} = d \left(\frac{\omega}{\nu}\right)^{\frac{1}{2}} \quad (1.7)$$

where ρ is the fluid density, v is a characteristic velocity, ω is the angular frequency associated with the oscillation, μ is the dynamic viscosity, d is a characteristic length, and ν is the kinematic viscosity. A fluid with a low Womersley number is characterized by having essentially no phase difference between the pulsatile pressure waveform that is driving the flow and the pulsatile velocity waveform associated with the flow. With increasing Womersley numbers, a phase difference between the pressure and velocity waveform can be observed, which is due to the inertia of the fluid resisting changes governed by the pressure waveform

and that the pulse frequency is relatively high. Other important dimensionless numbers and how dimensionless numbers can be used in various biofluid mechanics applications will be discussed in [Section 15.3](#).

Summary

1. This textbook will discuss basic fluid mechanics principles, flows within the macrocirculation, flows within the microcirculation, specialty circulations, and experimental techniques.
2. The National Institutes of Health working definition of biomedical engineering is “Biomedical engineering integrates physical, chemical, mathematical, and computational sciences and engineering principles to study biology, medicine, behavior, and health. It advances fundamental concepts; creates knowledge from the molecular to the organ systems level; and develops innovative biologics, materials, processes, implants, devices and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health.”
3. Fluid mechanics is useful for the analysis of anything that includes an interaction with a liquid or gas. This includes traditional engineering applications, as well as many biological applications.
4. Biofluid mechanics is focused on how biological systems interact with and/or use liquids/gases. For humans, this includes obtaining and transporting oxygen, maintaining body temperature, and regulating homeostasis. Cardiovascular diseases account for nearly one of three deaths in the United States; the highest prevalence regions of cardiovascular diseases are along the lower Mississippi River valley.
5. Dimensions are physical properties, whereas units are arbitrary names that correlate to a measurement. There are seven base dimensions, including time, length, mass, temperature, electric current, amount of substance, and luminous intensity. All other physical parameters can be related to these base units. Depending on which system of units are chosen, the base units can change, but again all dimensions/units can be defined from one another. The Buckingham Pi Theorem is a powerful mathematical tool that allows users to relate various quantities of interest and may lead to the development of important dimensionless numbers.
6. Dimensionless numbers are important for either scaling fluid properties, relating important parameters that govern fluid flows or both. Two of the most widely used biofluid mechanics dimensionless numbers are the Reynolds number.

$$\text{Re} = \frac{\rho v d}{\mu}$$

and the Womersley number

$$\alpha = d \left(\frac{\omega}{\nu} \right)^{\frac{1}{2}}$$

which relate the inertial forces to the viscous forces and the pulsatility to the viscous forces, respectively.

Reference

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Fundamentals of fluid mechanics

LEARNING OUTCOMES

- Describe fluid mechanics principles
- Identify the principle relationships and laws that govern fluid flow
- Specify different analysis techniques that can be used to solve fluid mechanics problems
- Describe the continuum principle
- Evaluate the pressures and stresses that act on differential fluid elements
- Define kinematic relationships for fluid flows
- Explain the relationships among shear rate, shear stress, and viscosity
- Define different classifications for fluids
- Describe fundamental changes at the microscale level
- Describe the relevance of turbulence in biofluid mechanics
- Identify the common features of turbulent flow and explain mathematical principles that can be used to describe turbulent flow

2.1 Fluid mechanics introduction

In the broadest sense, *fluid mechanics* is the study of fluids at rest and in motion. A *fluid* is defined as any material that deforms continually under the application of a *shear stress*. Shear stress is a particular mechanical load applied onto a surface (or assumed surface) of a material and is directed tangentially to the surface of the material. The surface can be a real surface or an assumed/imaginary surface used for calculations. Returning to the definition of a fluid, no matter how small the applied shear stress acting on a fluid surface is, that fluid will deform and appear to flow under the applied stress. (Note that for some fluids a yield stress must be met before the fluid flows; however, once this yield stress is met, the previous definition applies. See [Section 2.8](#) for more information about these and other special types of fluids.) Some define a fluid as any material that takes the shape of the container in which it is held. It is easily seen that any substance in the liquid or the gas phase would fall under all

of the definitions we have described and, therefore, can be defined as fluids. The distinction between a fluid and a solid is also clear from these definitions because solids do not take the shape of their containers; for instance, a shoe in a shoebox does not become a rectangular cuboid that takes the shape of a foot only when worn. In contrast, if you place a fluid in a shoebox, it would take the shape of a rectangular cuboid. Also, if you compare the action of solids and fluids under a shear stress loading condition, the distinction is clear: a solid will deform under shear, but this deformation does not continue when the shearing force is removed or held constant. However, as a caveat to this previous statement, some materials exhibit both solid and fluid properties. These materials are termed *viscoelastic* materials, and they deform continually under shear loading until some threshold deformation has been reached. In fact, all real solid materials must exhibit some fluid properties, but the fluid-like properties can be neglected in most practical situations for these materials.

We will begin our discussion with a review of shear loading, which should be familiar from a previous solid mechanics course. A typical manner to induce a shear loading condition on a solid material is through torsion. *Torsion* is defined as the twisting of a material when it is loaded by moments (or torques) that produce a rotation about an axis through the material. In solid mechanics courses, torsion analysis is typically introduced by applying a moment (M) at some location along the length of a solid bar, which is fixed on one end (see Fig. 2.1, which illustrates the loading at the free end of the bar). We will not define the appropriate equations of state for this loading condition. However, you can refer to a textbook on solid mechanics for an appropriate review. (Note that we suggest some textbooks in the Further Readings section.) For a more physiological example, the same analysis that is conducted for a fixed solid bar can be applied to a bone subjected to torsion. Imagine an athlete who plants a foot on a surface while making a quick rotation

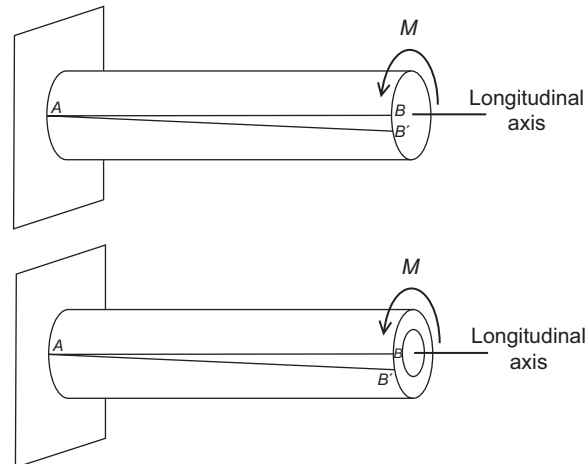


FIG. 2.1 A depiction of a method to model torsion throughout a solid material. Through the application of a moment at a location on the bar, a line AB would deform to the arc AB' . With removal of the moment, point B' would move back to B , assuming the induced stress did not exceed the materials yield stress. The second figure depicts a cylinder, which may be used for torsion analysis in bones.

about that foot. This would generate a moment throughout the bones in the leg and is a common cause for fractures in these athletes. To solve for the shear forces/stresses within the bone, we can assume that the foot is fixed to the surface and that the bone is modeled as a hollow cylinder (with a taper or variable cross-sectional area, if necessary, to make the solution more accurate) (see Fig. 2.1, which illustrates different modeling methods used in biomedical engineering). Clearly, as was the case in many introductory solid mechanics courses, this simplifying assumption ignores inhomogeneities (if any) in the bone material properties. We will see that this, or a similar, assumption is made in many biofluid mechanics examples that we will discuss because it is very difficult to mathematically quantify inhomogeneities within a fluid. We will typically assume a uniform distribution of molecules and cells throughout the fluid, although it has been shown that the distribution of these molecules is not homogeneous. The time-varying and spatially varying distribution of molecules is difficult to predict and quantify without intense computational methods.

To bring us back to the case of torsional analysis, under pure torsion loading conditions (e.g., there are no other external forces applied to the body), the shear forces throughout the material are dependent on the applied moment, the geometry of the material, and the load application position (radial and axial) within the material. Assuming that the elastic limit (in shear) of the material has not been surpassed and that the applied moment is constant in magnitude and direction, the material will deform to a certain extent (this would be seen as a twist of the bar and is illustrated in Fig. 2.1, in which line AB deforms to arc AB'). With removal of the moment, a solid material will return to its original conformation (e.g., the arc AB' will return to line AB , if we assume that the material does not experience any plastic deformations). We will learn that the shear stresses that are generated in a bar subjected to torsional loading are similar to what develops in a fluid subjected to shear loading; however, the mechanisms of the loading conditions and stress development are fundamentally different. We use the example of torsional loading on a bar because it should be familiar from previous courses and should highlight that some assumptions, such as geometry or material homogeneity, may need to be relaxed in physiological environments.

In contrast to the analysis just described for solid materials, any fluid subjected to a shearing force will deform continually assuming that the applied force exceeds the fluids yield stress (note that the fluid may have a yield stress equal to zero, approximated as zero or a value greater than zero). A typical example (from a fluid dynamics course) to depict a fluid under a shear loading condition is with a “parallel plate” design with a thin layer of fluid between the plates (Fig. 2.2). The plates on the top and bottom of the fluid are assumed

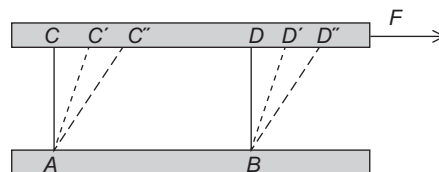


FIG. 2.2 Under a constant shearing force (F), a fluid will continually deform. Immediately after the application of a constant force to the top plate, a fluid element $ABCD$, deforms to $ABC'D'$. At a later time, the element will have deformed to $ABC''D''$ even though the force F is held constant and no additional force has been added to the system.

to be rigid solid materials that contain the fluid between them. Imagine that a constant horizontal force (F) is applied to the top plate, causing the top plate to move with some velocity in the positive X -direction to one particular fixed location. The fluid that is in contact with the top plate will move with the same velocity and move with the same displacement as the top plate because of a phenomena termed the *no-slip boundary condition*. The no-slip boundary condition dictates that a fluid layer in contact with a solid boundary must have the same velocity as that boundary. We will see later that the no-slip boundary condition can lead to the assumption that the fluid along the wall has a zero or negligible velocity, and this assumption is used in many fluid and biofluid mechanics solutions. Because of the constant horizontal force (F) that was applied to the top plate, a fluid element at time zero denoted by $ABCD$ will deform to $ABC'D'$ during the instantaneous application of the force. However, if one looks at a later time, the fluid element will continue to deform, even though the applied force has moved through its physical line of action, is no longer actively acting on the plate, and the top plate is no longer moving as a result of the applied force F . At the later time, the fluid element can then be depicted as the element $ABC''D''$. Although we did not discuss the mathematics associated with this phenomena, it is meant to illustrate that a fluid will continually deform under a constant loading condition, which is very different from what is observed with solid material deformations.

In biology, a condition depicted in Fig. 2.2 can occur in the lubrication of joints, where one solid boundary (a bone) moves in relation to another solid boundary (a second bone). One of these boundaries could be considered stationary through the use of a translating coordinate system fixed to that boundary. (This simplifies our analysis instead of having two moving boundaries and is a typical assumption used in engineering problems.) The second boundary will then move with some velocity relative to the stationary boundary (for now we will assume that the translating coordinate system does not accelerate). The deformation of the lubricating fluid between the joints can be depicted as in Fig. 2.2. Additionally, blood flowing through a vessel that is being deformed by some external force can be simplified to a similar parallel plate analysis, although this approximation may not be the best. The purpose of the discussion up to this point is to highlight one of the fundamental differences between solid and fluid materials: solids will deform to one particular conformation under a constant shearing force, whereas fluids continually deform under a constant shear force. Recall that an exception to this definition exists. There are viscoelastic materials that exhibit properties of both solids and fluids and, therefore, continually deform under constant loading (like a fluid) to some threshold deformation state (like a solid). In some instances, the deformation of viscoelastic materials is recoverable after removal of the loading conditions, which is similar to how solids respond to external loading.

Fluid mechanics can be divided into two main categories: static fluid mechanics and dynamic fluid mechanics. In static fluid mechanics, the fluid is either at rest or is undergoing rigid body motion. Under either of these conditions, the fluid elements are in the same arrangement at all times. This also suggests that the fluid elements do not experience any type of deformation (linear or angular) during their motion. Since a fluid element deforms continually under a shear force and there are no deformations in static fluid mechanics, the implication is that no shear stresses are acting on the fluid. Unfortunately, no true fluid can experience only rigid body motion, and at the microscopic level, fluid molecules are continually in motion (unless the fluid is at absolute zero). In general, the salient aspect of

static fluid mechanics is the pressure distribution throughout the fluid. Furthermore, this type of analysis can typically be applied to very special cases of fluid motions, but as we will show later in the text, the application of static fluid mechanics principles is typically limited. For dynamic fluid mechanics, the fluid may have an acceleration term (i.e., nonconstant velocity) and can undergo deformations. In the case of dynamic fluid mechanics, Newton's second law of motion can be used to evaluate the forces acting on the fluid. Generally, for this type of analysis, the pressure distribution and the velocity distribution throughout the fluid are of interest. From these calculated fluid parameters, any other parameter of interest, such as acceleration, wall shear stress, or shear rate, can be obtained.

2.2 Fundamental fluid mechanics equations

Determining the solution of any engineering problem should begin by writing down the known quantities (also termed *the givens*), including the equations that govern the system being addressed. In general, there are five fundamental relationships (Table 2.1) of interest in fluid mechanics. In no way do these relationships limit us to five solution methods or five problem types. Instead, they provide a foundation for solving a variety of complex problems. These possible solution routes also use a variety of different computational analysis methods. For instance, if one is interested in the velocity profile of the fluid, one would probably focus on kinematic relationships throughout the fluid. Yet conservation laws may be necessary to help with the calculations. However, if the stress distribution was of interest, one might start with kinetic relationships and use kinematics/conservation laws to help solve the problem. Algebra, trigonometry, and calculus techniques are some computational methods that may be needed to solve biofluid mechanics problems, although in practice, to solve more physiological and more accurate flow scenarios, computational methods and specific software packages might need to be employed, because simpler hand calculations may not be possible. Known variables in most fluid mechanics problems typically include geometrical constraints, fluid material properties (density, viscosity, heat transfer properties, etc.), and temperature of the system, among other inflow and outflow boundary conditions (e.g., the inflow velocity profile and the outflow pressure). Also, material properties of the bounding container and the temporal variations in fluid or flow properties (if any) are

TABLE 2.1 Useful relationships that are in fluid mechanics problems.

Kinematic	Velocities, accelerations, shear rates: Fluid properties
Stresses	Force intensities acting over a particular area: Flow properties
Conservation	Mass, momentum, and energy: Physical properties
Regulating	Initial and/or boundary conditions: Geometrical and/or limiting properties
Constitutive	Mathematically describes the fluid: Laws to describe flow

typically known. Even if each of these quantities are known, there are many interesting and important quantities that can be calculated to describe the fluid flow and its properties. Our goal as biofluid investigators would be to relate those fluid flow properties to physiological and/or pathological conditions.

The laws that govern fluid flow are common among other engineering disciplines and they should not be encountered for the first time in this textbook. These laws are described in detail in the following chapters, and the derivation of common fluid mechanics parameters and equations of state will be detailed in those chapters. Here we will briefly summarize the laws that fluid flow must obey.

1. *Conservation of Mass*: Stated simply, whatever mass flows into a system must flow out of the system or be accounted for by a change in the mass of the system or a change in density (ρ) of the fluid (Fig. 2.3). (Remember that *density* is defined as mass divided by volume [V]). This law is similar to Kirchhoff's current law, which is common in circuit analysis.

$$m_{\text{system}} = m_{\text{in}} - m_{\text{out}} - \frac{d(\rho V)}{dt} \quad (2.1)$$

2. *Conservation of Linear Momentum*: The time rate of change of momentum (mass multiplied by velocity) of a body is proportional to the net force acting on that body. This is a vector equation that can be divided into component directions as needed. If the mass

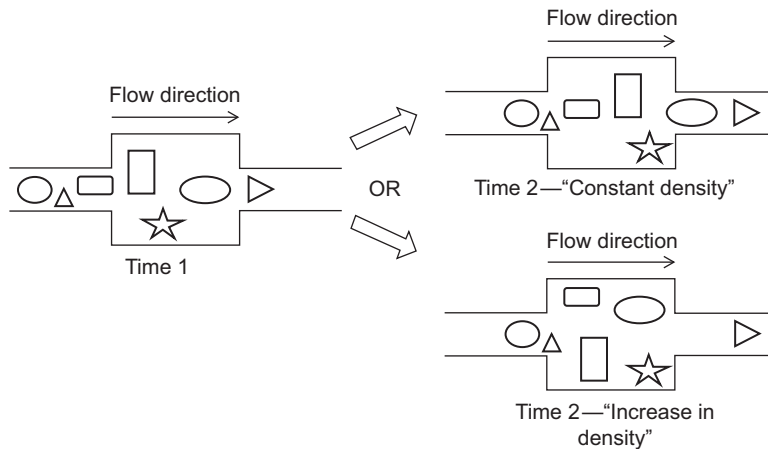


FIG. 2.3 Pictorial representation of the conservation of mass principle. At time 1, the density of the fluid within the square chamber is represented with approximately three shape elements within the square chamber. At some time later, the density of the fluid can either remain the same (“constant density” case) because the same quantity of elements is present or increase because one of the shape elements did not leave the volume of interest (“increase in density” case). We assume that each of the shapes has the same mass and volume to make the density calculations consistent with the discussion in the text.

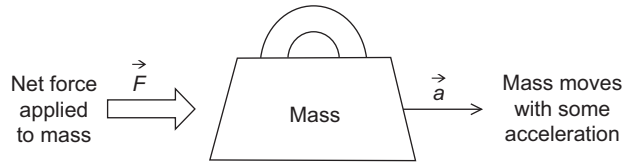


FIG. 2.4 When a force (F) is applied to a mass, the mass will move with an acceleration (a) that is proportional to the applied force and in the same direction as the net force. In this simple representation, we are not depicting all of the forces (such as friction or drag), just the net force that is acting on the mass.

of the body remains constant with time, the net force acting on a body is equal to the mass multiplied by the acceleration of the body (Newton's second law of motion, in simplified form, Fig. 2.4). Also, the acceleration of the body will proceed in the same direction as the direction of the net force. This is a common equation used in solid mechanics, engineering statics, and engineering dynamics.

$$\vec{F} = \frac{d(m\vec{v})}{dt} \quad (2.2)$$

3. *The First Law of Thermodynamics*: The change of the internal energy (δU) of a system is equal to the change of the amount of energy added to a system (through heat, δQ) minus the change in the amount of energy lost by the system because of the work (δw) done by the system on the surroundings (Fig. 2.5). Another relationship from this law states that an isolated system can hold or lose energy, but the total energy of the entire contained system remains constant. This law is dependent on the particular pathway in which energy is added/removed to/from the system and not just the difference between the beginning and end points (recall that for some energy changes, such as gravitational potential energy, it is typically assumed that the object's path does not

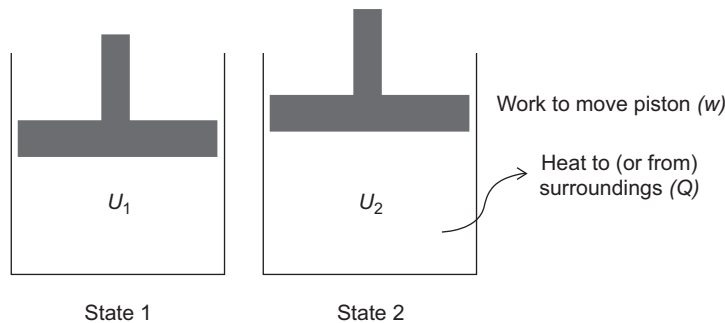


FIG. 2.5 Representation of the first law of thermodynamics in which the internal energy of a system is equal to the heat added to the system from the surroundings minus the work that the system conducts on its surroundings. In this example, a piston is moved up by the material within the system as heat is being lost to the surroundings.

play a role in the energy change; only the starting point of the material and the ending point of the material matter). This law should be familiar from a beginning thermodynamics course.

$$\delta U = \delta Q - \delta w \quad (2.3)$$

4. *The Second Law of Thermodynamics:* The entropy (S , disorder) of an isolated system will increase over time, until the system reaches equilibrium (Fig. 2.6). In physics, this law is used to determine the direction in which time moves and the total energy or efficiency of a system. The classic example of this law is that a mug that falls off a table and breaks will not mend unless external energy is put into the system. The same would be true in biological systems; if a bone breaks, it does not heal without the addition of energy (perhaps significant energy) into the system. This law also should be familiar from beginning thermodynamics courses.

$$\frac{dS}{dt} \geq 0 \quad (2.4)$$

5. *Conservation of Angular Momentum:* Unless acted upon by an external torque, a body rotating about an axis will continue to rotate about that axis. The mass moment of inertia of a body is the intrinsic resistance of that body toward changes in angular momentum (this is the second mass moment of inertia with units of mass multiplied by length squared). Moment of inertia is a state property of the material that is related to the geometry of the object and the material(s) that compose the object. An example of

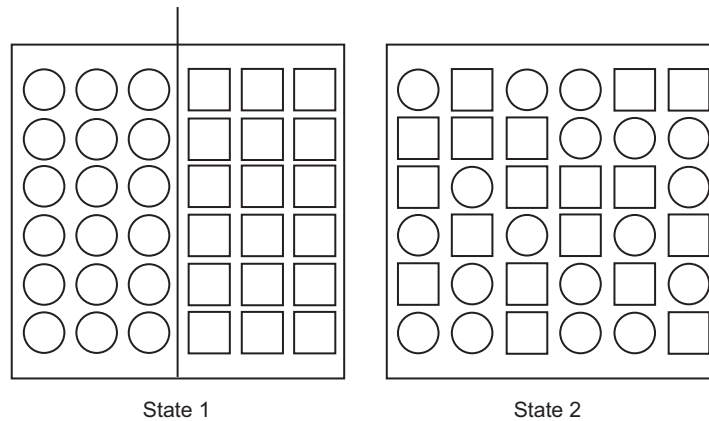


FIG. 2.6 The second law of thermodynamics states that the disorder of a system will increase with time. In this case there is a boundary between circular and square objects. Once this boundary has been removed, the system will tend to move from an orderly system to a disorderly system.

the conservation of angular momentum is as follows: a figure skater spinning around the centerline with arms outstretched will experience an increased angular velocity by bringing the arms into the body. Conversely, by stretching the arms back out, the angular velocity will decrease. This is due to changes in the body's moment of inertia (Fig. 2.7). Assuming that friction from the ice and drag from the surrounding air are negligible, the angular momentum is conserved under these motions. *Angular momentum* ($\vec{L}$) is defined by the cross-product between the position vector of a particle relative to the axis of rotation ($\vec{r}$, i.e., hands relative to the centerline) and the linear momentum of that particle ($\vec{p}$). *Conservation of angular momentum* is defined as no change in angular momentum with time as long as the mass moment of inertia remains the same. When the mass moment of inertia increases, the momentum decreases, and vice versa. Eq. (2.5) is the definition of angular momentum for discrete particles; for bodies, the angular momentum must be summated over the entire mass.

$$\vec{L} = \vec{r} \times \vec{p} \quad (2.5)$$

In most of the examples we will discuss in this textbook, not all of these governing laws will be required to solve the problem. However, they will all be applied to some extent as the reader progresses through the course and the material described in this textbook. Our goal is to allow the reader to realize how these laws affect different situations in biofluid mechanics. It is also true that problem solutions may require other relationships, such as constitutive or regulating rules, to solve the problem. However, the five laws listed previously are normally a good starting point for many biofluid mechanics problems. For example, the ideal gas law (which is a constitutive rule), $p = \rho RT$, is useful in solving many gas flow problems that might occur in biological systems but would not be as applicable in purely liquid flows when the changes in temperature or pressure are not significant (which is typically the case in biological systems). Furthermore, the ideal gas law assumes that the particles in the fluid have rare and inconsequential interactions but can exchange energy during any of the infrequent particle collisions. Liquid molecules interact with each other constantly and, therefore, this law would not be as useful for many liquid flow problems. In subsequent chapters, we will take the basic laws of mechanics and thermodynamics to derive constitutive

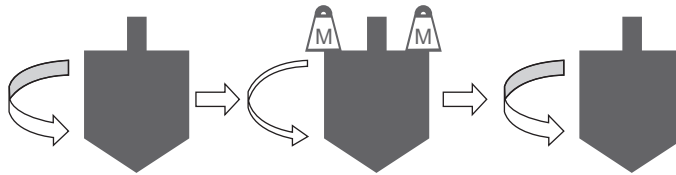


FIG. 2.7 The conservation of angular momentum states that a spinning body will have a particular angular velocity. As more mass (M) is added to the body at a larger radius from the axis of rotation, the angular velocity will decrease. If the added mass is removed, the angular velocity will return to the original angular velocity (the magnitude of angular velocity is represented by the width of the *curved arrow*). This assumes that there are no additional external forces acting on the body or that those forces are largely negligible.

equations that are useful for solving a variety of fluid problems. As a caveat, not all problems that we will encounter can be solved analytically. Chapter 15 will discuss some of the numerical methods that can be used to solve computationally complex problems, along with some of the current research topics that use computational approaches to understand a particular system of interest.

2.3 Analysis methods

The first step in solving a fluid mechanics problem is understanding the system that the problem addresses. In engineering mechanics, the laws that govern a system, normally represented by using a free body diagram, are used to analyze the problem. In thermodynamics, we generally discuss the system as being either open or closed to other neighboring/competing systems. Whatever approach is taken, governing equations are then written based on our system convention choices. In fluid mechanics, we will discuss similar parameters that should be familiar from engineering mechanics and thermodynamics. We define them in this textbook as the *system of interest* and the *volume of interest*. By properly defining these parameters and by choosing the proper laws that govern the entire system, the solutions to fluid mechanics problems typically become significantly easier. By choosing these parameters in a different way, the fluid mechanics problems still may be solvable but the process may become laborious. This is not to say that by choosing the system of interest and the volume of interest in the most ideal way, the solution will be computationally easy (e.g., algebra); the use of computational fluid dynamics still may be necessary to solve the problem (see Chapter 15). In addition, not choosing the ideal system of interest and volume of interest does not mean that you cannot arrive at a solution by hand, but it will generally be more difficult than the most ideal choice. A good analogy to reinforce this concept is from engineering mechanics courses. When drawing a free body diagram, an assumption must be made for the coordinate system association with the problem (in our example we will use the Cartesian coordinate system). If the problem consists of a mass on an inclined plane, there are two common ways to establish the coordinate system (Fig. 2.8). In the first, the x -axis of the coordinate system is aligned

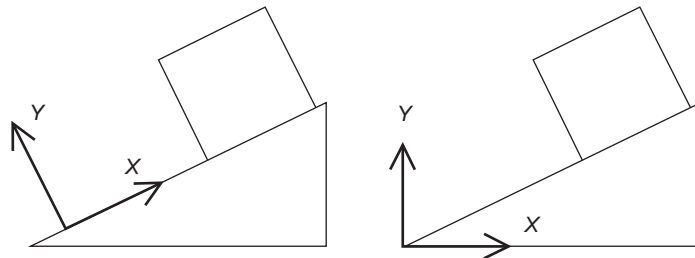


FIG. 2.8 Two common ways to set up the coordinate axes in a solid mechanics problem. Either convention can produce a solution, but the solution using the coordinate axis shown on the left would generally lead to a computationally easier solution than the right coordinate axis because many variables are aligned with that axis system.

with the slope of the inclined plane, and, in the second, the x -axis is horizontal. In either case, the y -axis is perpendicular to the defined x -axis. Using either of these coordinate conventions, we are able to reach a solution for typical properties of interest (e.g., acceleration of the mass); however, it is typically computationally easier to solve this problem when the coordinate axis is aligned with the inclined plane because the frictional forces, velocity, and acceleration terms all align with that coordinate system, whereas in the second configuration you must be careful regarding the decomposition of those same forces into the coordinate directions. The solution to fluid mechanics problems works in a similar manner; there is typically an “easier” way to define the system and volume of interest.

For fluid mechanics problems, a *system of interest* is defined for this textbook as a fixed quantity of mass and this typically encompasses the entire system of interest. The boundaries of this system separate the materials of interest and the surrounding materials that are not of interest. For instance, if our system is blood flowing through a blood vessel, the system of interest would be the blood vessel and everything within it and the boundaries of our system of interest would be the vessel wall. These boundaries are movable with time, but mass cannot cross this boundary (this is a good approximation of flow within the macrocirculation but would not be valid for flows within the microcirculation, as will be discussed in later sections). This is the key to defining the system of interest properly. For instance, if your system is an uninflated balloon, no mass (e.g., helium gas) can cross into this boundary; hence, the balloon would remain uninflated for the entire duration of the problem (Fig. 2.9A). However, if you choose your system to be the balloon plus the nearby helium tank, the balloon can be inflated during the example (see Fig. 2.9B) because by definition mass can pass between the tank and the balloon (note that the boundary is represented as the dashed box in Fig. 2.9A; mass from the helium tank cannot enter the balloon by crossing the imaginary dashed boundary). In this same situation, the system

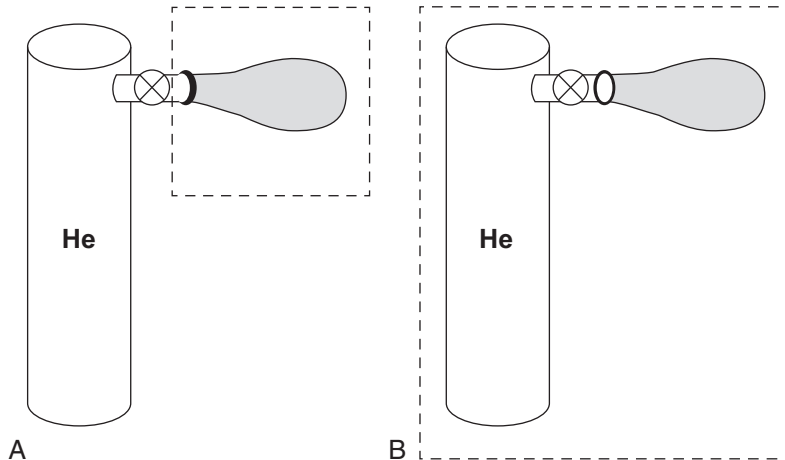


FIG. 2.9 Two choices for the system of interest (*dashed line*). With the first choice (A) the balloon will remain uninflated for the entire problem because no mass can transfer through the system boundary. For the second choice (B) the balloon can be inflated and the boundary would follow the balloon's wall in time.

boundary also will be variable with time. When the valve to the helium tank is closed (time 0) the system boundary is the flattened uninflated wall of the balloon. However, as you open the tank valve, the balloon gains mass and volume and the system boundary will follow the balloon wall. The same is true for biofluid problems that include the lungs; it is wise to include the atmosphere in the system of interest, if the problem deals with inspiration and exhalation, otherwise one could not solve a problem involving exchange with the atmosphere.

As stated previously, a free body approach is used extensively in mechanics of solids. This is an easy approach because a system can be chosen with a defined mass and this mass will generally not change with time (for general solid mechanics problems). However, in fluid mechanics, the flow of fluids through a system (pipe, turbine, blood vessel) is generally the most interesting problem, unless you are analyzing a static fluid dynamics problem. Therefore, it is not easy to define a finite mass that one is interested in because mass is exchanged with time as it flows through/along the containing surface. To circumvent this type of problem, a *volume of interest* is defined. This volume of interest is a volume in space through which fluid flows. The boundaries that define the volume of interest are the *surfaces of interest* (Fig. 2.10). These surfaces can experience motion with time, but this is not a requirement. For instance, large blood vessels on the arterial side and most air conduits in the lungs experience some form of translation and possibly changes in shape with time, whereas smaller vessels, such as capillaries, do not experience much translation and are generally considered to be stationary. Fig. 2.10 depicts a blood vessel with a fluid flowing through it. The dashed cylinder within the blood vessel is our choice of a volume of interest for a particular problem. The choice that was made in this figure depicts an example in which the volume of interest has both real and imaginary surfaces of interest. The real surface is the inside of the blood vessel wall, which surrounds our volume of interest. Real surfaces can be thought as the fluid boundaries, which prevent possible mass transfer. However, the vertical light gray circles, with which fluid will enter or exit our volume, are imaginary surfaces. These surfaces are solely chosen for convenience, so that we can solve the fluid mechanics problem more easily. Using these imaginary surfaces, we can impose boundary conditions or initial conditions with ease. Other choices for this surface of interest/volume of interest may make the boundary value and initial condition definitions more difficult

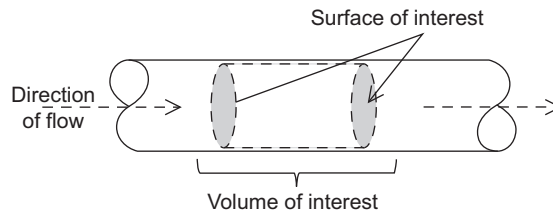


FIG. 2.10 Examples of a volume of interest and a surface of interest within a blood vessel. The two highlighted surfaces of interest are imaginary. The boundary of the dashed cylinder and the tube wall is a real surface. By choosing the surfaces in this manner the solution of fluid mechanics problem would be easier, compared with other choices for the surfaces/volumes of interest.

(remember problems depicted in Fig. 2.8 from engineering mechanics courses). It is of the upmost importance to choose these surfaces wisely because the methodology of fluid mechanics problems will change based on the choices made for the surface of interest and volume of interest. Some choices (as in Fig. 2.10) can make the solution easier, whereas other choices can make the problem computationally difficult to solve.

Depending on the particular application of the fluid mechanics problem, there are different approaches to take to reach a solution to the problem. First, if the point-by-point flow characteristics (an infinitesimal volume, i.e., one molecule of fluid) are of interest within the fluid, a differential approach to solve the governing equations should be used. This solution would be based on the differential equations of motion. This approach is useful in biofluid mechanics if one is interested in two-phase flows and the location of individual proteins or cells, etc., within the bloodstream and how these individual particles interact with other particles or the vessel wall. However, in some cases, this very detailed knowledge of the flow profile is unnecessary and too labor intensive to calculate (by hand and/or computationally). In this case one is most likely interested in the bulk properties of the fluid. Quantities of interest are most likely the velocity profile at a certain location and the pressure gradient across a particular length, among others. The solution to these types of problems takes the form of the integral equations of motion, and the volumes of interest are finite. An example of this approach is by looking at one particular section of a blood vessel (see the volume of interest in Fig. 2.10) and obtaining the overall velocity profile or other fluid property through the entire volume of interest. This method is generally easier to solve analytically and will be developed first in this textbook.

In general engineering mechanics, a number of methods can be used to describe the system that is being illustrated. The most common methods that are implemented in fluid mechanics are the Lagrangian method and the Eulerian method. When it is easy to record and solve for identifiable particles with a real mass and volume (e.g., cells, molecules, and other identifiable objects in the flow field) the Lagrangian method is the most applicable. This method of solution tracks each particle and continually solves the governing equations for each particle in the flow stream. This method is the point-by-point differential approach that we described previously. By using this method, Newton's second law of motion becomes a summation over all of the identified particles within the fluid. This summation leads to why the solution may become difficult computationally in biofluid mechanics problems. For example, in the blood, cellular matter constitutes approximately 40% of the total blood volume. To solve a Lagrangian biofluids problem, every cell within this 40% must be solved for and tracked individually. If your volume of interest is 1 μL of blood, your solution would consist of approximately 5×10^6 red blood cells, 6×10^3 white blood cells, and 2×10^5 platelets, along with all of the plasma proteins, sugars, ions, water molecules, and other compounds that constitute blood. To monitor each of these identifiable particles with a mass and volume properly, a lot of bookkeeping is required! With the Lagrangian approach, the acceleration, velocity, or position of interest is associated with the center of mass of the particle/molecule of interest, and this may not make sense in biological systems, in which the cell shape can and does change with time. Because of this shape change, there would most likely be a redistribution of mass and, at each time point, a new center of mass must be found for each particle.

The Lagrangian approach, however, is very useful in calculating particle trajectories in basic kinematic problems, if one can assume that the center of mass stays the same throughout the problem.

When considering a real fluid, which is composed of a large number of finite particles, the Eulerian method is more commonly used. This formulation is used because it is difficult (as described previously) to record all of the information about each particle within the fluid at every instant in time. The Eulerian method focuses on the overall flow properties within a certain volume over a certain time interval. Formulations that describe the flow are, therefore, spatially and temporally dependent. For instance, if one was interested in solving for the velocity profile 5 cm downstream of the aortic valve for every 5-ms interval during one cardiac cycle, the Eulerian approach is much more useful than particle tracking with the Lagrangian approach. This is because the solution for velocity or acceleration, among other fluid parameters, is associated with this particular volume and time but not with individual particles within the flow field. Using the Eulerian method leads to the assumption that a fluid can be considered as a continuous medium. If the fluid is a true continuum, the Lagrangian approach and the Eulerian approach will obtain the same solution. If the fluid is not a continuum, the solutions using these two methods may be and likely are different.

2.4 Fluid as a continuum

In our previous discussions about fluid characteristics, we did not discuss the molecular nature of a fluid. A fluid is composed of molecules in constant motion, within the fluid itself (random motion of particles or diffusion) and possibly within the constraining volume (i.e., is the flow static or dynamic?). In most applications, the bulk properties of the fluid are what we are interested in because this is what we can easily measure; however, to fully characterize the fluid, a point-by-point analysis must be undertaken. The bulk properties also can be considered as the time and/or spatially averaged values of the particular property for all of the fluid particles within the fluid element of interest. If we can assume that each fluid particle has the same properties as the bulk fluid properties and that these particles are uniformly distributed, our analysis will be simplified. Making this assumption allows us to consider a fluid as an infinitely divisible substance, which is the definition of a *continuum*. Therefore, the effects of individual molecules and the relative changes from the bulk fluids state properties induced by dividing the medium into very minute parts are ignored. If you have taken a course in mechanics of materials, the continuum principle should be familiar. In most mechanics examples when a deformation, stress, or strain is calculated within a certain material, the changes in the elastic modulus or deformities/inhomogeneities throughout the material are ignored. Under these cases, the material is assumed to be homogeneous throughout the section of interest. In biofluid mechanics, the assumption that a fluid is a continuum is normally legitimate when we consider flows within the macrocirculation (see Part II), but we must state the caveat that this is an assumption because blood is not homogeneous. However, when discussing the microcirculation (see Part III), molecular effects must be considered and the fluid should not be classified as a continuum, although we may make that assumption here to simplify some of the calculations. As a consequence of using the assumption that

a fluid is a continuum, properties such as density, viscosity, and temperature are continuous throughout the fluid. This is not necessarily a bad assumption on a large scale (i.e., bulk or average properties within the macrocirculation). Remember, though, that these properties can be a function of time and/or spatial location, but for the fluid to be defined as a continuum at a particular instant in time and in one particular location, the medium must be continuously divisible and the value of interest (e.g., viscosity) cannot change based on molecular interactions. Once again, this is very useful for general fluid mechanics problems, but this assumption breaks down in some biological systems.

A good illustration of this phenomenon is through the viscosity of a fluid. If we look at a particular volume of fluid (Fig. 2.11, light gray), which will be used to calculate the viscosity of the fluid, we obtain the average bulk viscosity for that volume. In general, the value for the bulk viscosity is similar to the individual viscosities of smaller sections within that same volume (i.e., dark gray section P). Imagine if we choose to divide the light gray section into 10 equal volumes. The quantified viscosity of these 10 parts should be similar to the average viscosity for the entire volume (light gray), and, if this is true, we can state that the fluid behaves as a continuum in terms of viscosity. However, if we choose our section to be on the order of a few picoliters (10^{-12} L) of a fluid taken from a 1-L volume of interest, the viscosity of the small section may be very different from the average bulk viscosity for the entire section. This is because viscosity itself is dependent on molecular interactions within the fluid (see Section 2.7). In our small volume, there may be a few fluid molecules that interact with each other to govern the viscosity of the solution within that

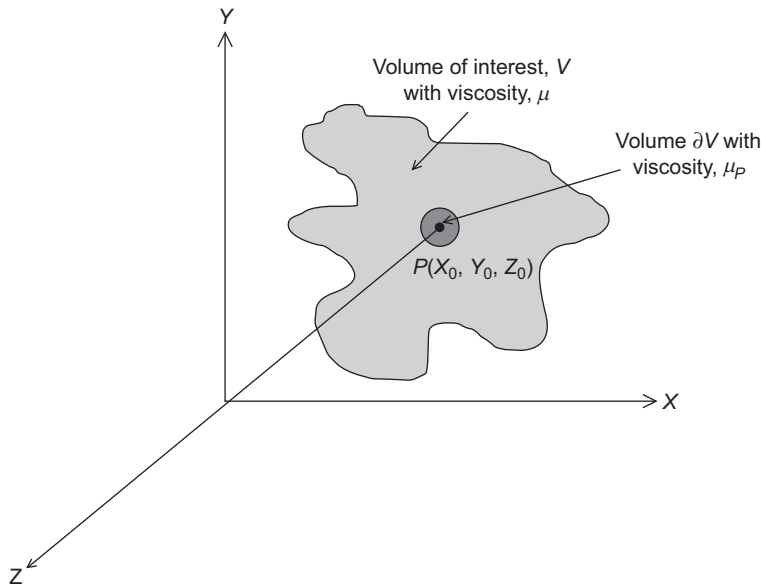


FIG. 2.11 The bulk viscosity (μ) of a fluid element can be described by the weighted average of the individual viscosities (μ_P) of differential elements (∂V). The viscosity within each differential element can be greater or lower than the bulk viscosity, but if we ignore these changes, we would assume that the fluid is a continuum.

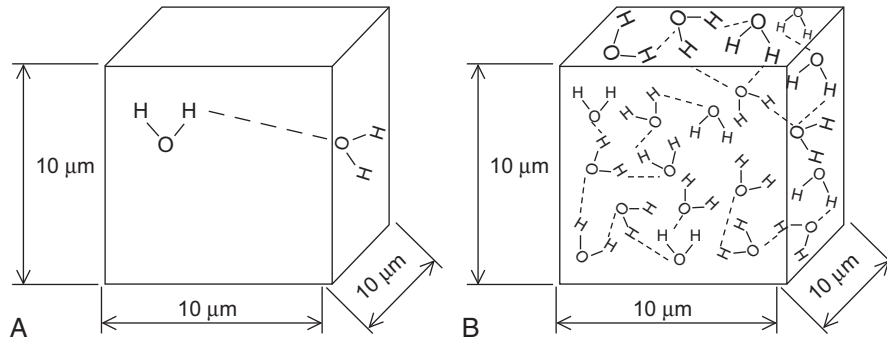


FIG. 2.12 If a noncontinuum fluid is divided into small volumes (e.g., 1 pL), the properties of the fluid may be different than the bulk property. In this figure, *panel A* shows a volume with a smaller viscosity compared with *panel B* because there are fewer intermolecular interactions (*dashed lines*) between the molecules in *panel A* than in *panel B*.

volume (Fig. 2.12). However, if there were many more fluid molecules within the same picoliter volume, there would be more interactions, which would alter the viscosity of that differential volume of fluid drastically compared with the volume with few molecules. The quantity of molecules per small volume may also differ as a function of time and space based on random molecular fluctuations within the fluid. Regardless of what the fluid viscosity is on this small scale, if the bulk viscosity is of interest, we can average each small section's viscosity to obtain the bulk viscosity. Once the bulk viscosity is known, if we can (or purposefully do) ignore the changes in viscosity between each of these small sections, we would by definition consider the fluid a continuum. Note that this same discussion can be used for any fluid property of interest; we are using viscosity as an example.

One way to think about the continuum principle is by considering the average height of adults in the United States. If you take the average height of the students in your biofluids class, will this be the same as the average U.S. height? Will this be close enough for an engineering approximation? The students in your class can be considered as a differential volume of the U.S. population. Would the average height of a different class be similar to the average height obtained from your biofluids class? A second, perhaps more difficult question is whether the average height of people living in the United States can even be obtained—meaning, can we actually collect the height of each individual person? Similar to the problem of the average height, can the true bulk viscosity (or any other fluid property) be quantified? It would be very difficult to measure the true viscosity because it is nearly impossible to quantify and average the true molecular viscosity of individual fluid volumes that are on the order of a few molecules in size. This problem is compounded when the properties can change with time and/or space. Imagine trying to obtain the viscosity of a differential element of fluid, to only have the fluid molecules continually move into and out of the differential element and have the molecules interact with other molecules, etc. If one single static snapshot of the bulk fluid can be obtained and used to quantify the viscosity of every differential element within that fluid, this would not be a concern; however, with current technology, this is not practical. Partially because of the difficulty of quantifying fluid

properties and the observation that fluid properties change with time, a quantity termed the apparent/effective *viscosity* has become popular (see [Section 7.7](#)) for flows within the micro-circulation. The apparent viscosity relates the bulk viscosity to the viscosity that we can calculate by measuring other flow parameters. Clearly, depending on the system that we are interested in, the bulk viscosity may be a good approximation; however, it may be more realistic to discuss the apparent viscosity. It is also true that viscosity is not only a function of space but also a function of time and temperature. Think about the oil in your car engine. On a cold winter morning when you start your car, the oil will initially be very viscous. However, after the car has been running for a few minutes, the oil heats up and the viscosity reduces. Over that short period, the viscosity decreased because of an increase in engine temperature. Most biological fluids in humans have an approximate constant temperature (approximately 37°C), but remember that physical property numerical values can change in time based on other physical or mechanical properties. For instance, an increase in shear rate between particular joints can decrease the viscosity of the fluid in the joint space (see Chapter 12). Sometimes, temperature can be critical to a particular problem, such that if you were to analyze the blood flow throughout your arm/hand when throwing snowballs barehanded at your classmates, you might want to include temperature changes. A second case could be taking a breath of air on a cold winter morning. The heat transfer properties combined with the fluid flow properties would need to be considered when modeling airflow through the nasal passageways. Be cautioned that temperature fluctuations can arise in biological problems, and these fluctuations can alter the fluid properties.

2.5 Elemental stress and pressure

You may recall from engineering mechanics that there are a number of different ways to define stress, including the Cauchy stress, the first Piola–Kirchhoff stress, and the second Piola–Kirchhoff stress. The most useful definition for stress in fluid mechanics is the Cauchy stress (σ), which is a measure of all of the forces acting on a differential volume oriented in space in the current configuration. This is in contrast to the Piola–Kirchhoff stress, which measures the forces on a differential element and relates them to a “static” reference configuration, which may be different from the current configuration. The reference configuration is normally a cube in space oriented along assumed Cartesian coordinate axes, whereas the current configuration could be that same cube rotated to any degree off any of the three Cartesian axes. In general, we can resolve the forces that act on a cube in three-dimensional (3D) space in terms of nine stress components, otherwise known as the stress tensor (Eq. (2.6)). The stress tensor is represented as a 3×3 matrix (σ), with subscript entries representing first the face (or surface) the force is acting upon and second the direction that the force acts. As an example, the first stress component σ_{xx} is the stress that acts on the x -face of the cube (the x -face is parallel to the yz -plane) and acts in the x -direction. The stress σ_{xz} acts on the x -face in the z -direction. Only six of the nine components in the stress tensor are independent because angular momentum must be conserved on each differential volume element.

The six independent values of stress are σ_{xx} , σ_{xy} , σ_{xz} , σ_{yy} , σ_{yz} , and σ_{zz} . To conserve angular momentum, σ_{yx} must be equal to σ_{xy} ; σ_{zx} must be equal to σ_{xz} ; and σ_{zy} must be equal to σ_{yz} .

$$\sigma = \begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix} \quad (2.6)$$

$\sigma_{(\text{face})(\text{direction})}$

Let us develop how to quantify stress on a surface. Any flowing surface is in contact with either another flowing surface (termed a *lamina of fluid*) or the bounding surface of the fluid volume. The movement of this flowing fluid surface will generate a net force on the neighboring surface (either fluid or boundary; please note that the bounding surface does not need to be a solid; for instance, it could be a free surface open to air) if it moves at a different velocity than that of the neighboring surface. The force that is generated on the two laminae of fluid must be in balance with each other so that conservation of momentum (Newton's laws) is satisfied (Fig. 2.13). Figure 2.13 illustrates that the areas in contact with each other from two adjacent laminae of fluid will have the same forces acting upon them (i.e., $\delta \vec{F}_2$), whereas the surfaces not in contact do not necessarily have the same forces acting upon them ($\delta \vec{F}_1$ and $\delta \vec{F}_3$). In addition, the actual forces on opposing surfaces within one lamina do not need to balance (e.g., $\delta \vec{F}_1$ and $\delta \vec{F}_2$) because elements within a dynamic fluid deform and the elements do not experience a uniform velocity profile across the differential height, δh . As a result of these deformations, the surfaces that are experiencing different forces within one lamina do not necessarily have the same surface area (as shown on the right-hand side of Fig. 2.13). However, the surface area of neighboring lamina in contact would equate to each other. Recall that forces of different magnitudes acting on surface areas of different sizes can still satisfy the conservation laws. Under many conditions, it is likely that these different stresses acting on different areas on opposing surfaces of a single lamina would end up balancing over the entire differential element satisfying the conservation laws. However, as the height of these laminae approaches the differential element size ($\delta h \rightarrow 0$), the forces on opposing surfaces of the same lamina will nearly be balanced, as described previously. Similarly, the surface areas of these opposing surfaces would also

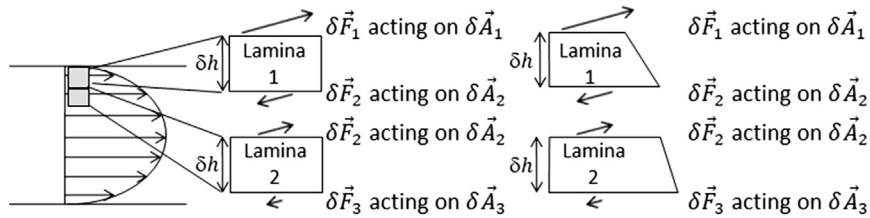


FIG. 2.13 Internal laminae of fluid exert forces on neighboring laminae. These forces must be balanced within the fluid. Areas in contact of the individual laminae are the same and are represented as δA_2 as in the text and figure.

nearly balance as $\delta h \rightarrow 0$. Let us define the surface area of the original lamina (lamina 2) in contact with a fluid lamina above it (lamina 1) as $\delta \vec{A}_2$. Lamina 1 is in contact with lamina 2 and the blood vessel wall in this example. Lamina 1 has the same surface area in contact with lamina 2 as lamina 2 has with lamina 1 (i.e., $\delta \vec{A}_2$). Because of this defined contact surface area and the motion of the fluid, there are some forces distributed over the surface area of each element. Consider a small element with a surface area, $\delta \vec{A}_2$, which has a force component acting on it ($\delta \vec{F}_2$). This force can be resolved into two elements; one that is normal to $\delta \vec{A}_2$ and one that is tangential to $\delta \vec{A}_2$. We will denote these forces as $\delta \vec{F}_n$ and $\delta \vec{F}_t$, respectively. The normal stress, σ_n (Eq. (2.7)), and the shear stress, τ_n (Eq. (2.8)), associated with these forces can then be defined as

$$\sigma_n = \lim_{\delta \vec{A}_n \rightarrow 0} \frac{\delta \vec{F}_n}{\delta \vec{A}_n} \quad (2.7)$$

$$\tau_n = \lim_{\delta \vec{A}_n \rightarrow 0} \frac{\delta \vec{F}_t}{\delta \vec{A}_n} \quad (2.8)$$

where n denotes the unit normal vector with regard to the differential area element. As the surface area approaches zero, the normal stress equation (Eq. (2.9)) and the shear stress equation (Eq. (2.10)) can be represented in differential form.

$$\sigma_n = \frac{d \vec{F}_n}{d \vec{A}_n} \quad (2.9)$$

$$\tau_n = \frac{d \vec{F}_t}{d \vec{A}_n} \quad (2.10)$$

To relate these equations to the stress tensor (Eq. (2.6)), you must define a coordinate system and define how the surface areas and forces relate to this system. In the most simplistic form, where a Cartesian coordinate system is used and the axes of this system are directly aligned with the fluid element, the normal stress σ_{xx} can be represented as Eq. (2.11) directly from Eq. (2.9) and the shear stress σ_{xy} can be represented as Eq. (2.12) from Eq. (2.10) (this is for a simplified 2D case):

$$\sigma_{xx} = \frac{d \vec{F}_x}{d \vec{A}_x} \quad (2.11)$$

$$\tau_{xy} = \sigma_{xy} = \frac{d \vec{F}_y}{d \vec{A}_x} \quad (2.12)$$

For our analysis, we will normally use an orthogonal coordinate system. In Cartesian coordinates, this is the standard x , y , and z directions, with which you should be familiar. When we begin to discuss flow through blood vessels, we will begin to adopt the cylindrical coordinate system for ease. Hopefully, the reader has some familiarity with the cylindrical coordinate system, in which each point is defined with a radial distance (r), an angular coordinate (θ), and a height (z). If you are asked to solve a problem involving 2D blood flow through a vessel, you may choose to solve the problem using the Cartesian system, if you assume that the flow is symmetrical about the centerline in the third direction (although this would mimic an infinitely wide rectangular channel solution instead of a circular cylinder, if this assumption is legitimate for your particular conditions).

If you consider a differential rectangular element in three dimensions, we can see how the components of the stress tensor are represented on this element (Fig. 2.14) giving us the standard nomenclature used within the Cartesian stress tensor. The components take the form of normal stresses and shear stresses (Eq. (2.13)), which is an extension of Eq. (2.6). Using this differential element and the Cartesian coordinate system, the stress tensor can be written as

$$\sigma = \begin{bmatrix} \sigma_{xx} & \tau_{xy} & \tau_{xz} \\ \tau_{xy} & \sigma_{yy} & \tau_{yz} \\ \tau_{xz} & \tau_{yz} & \sigma_{zz} \end{bmatrix} \quad (2.13)$$

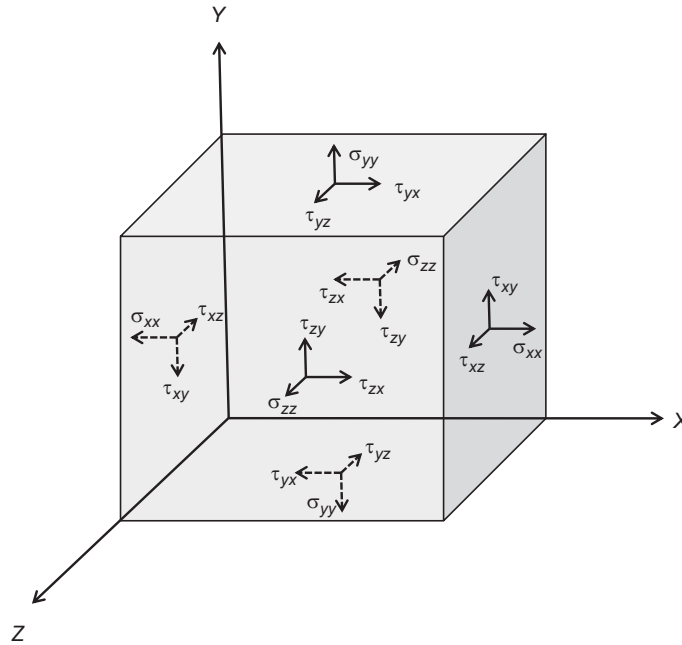


FIG. 2.14 The nine components of the stress tensor on a differential fluid volume. For momentum balance, only six of these values are independent. All stresses illustrated are positive stresses.

which has been reduced to its six independent values. As discussed previously, the shear stress values on opposing faces on a differential element must be equal so that momentum is conserved across the element. However, if one evaluates a nondifferential element, the stresses on opposing faces may not equate. It is important to point out that there is a sign convention for stress values. If the force acts in the positive direction on a positive face or a negative direction on a negative face, the numerical stress value is positive. If the force acts in a negative direction on a positive face or a positive direction on a negative face, the numerical stress value is considered negative. All stresses drawn in Fig. 2.14 are positive stresses. Note that in this figure, the stresses represented as dashed lines are the negative stresses acting on the negative faces. The stresses represented as solid lines are the positive stresses acting on the positive faces. Note that positive faces and negative faces are defined by the direction of the unit normal vector and is therefore dictated by your coordinate system definitions.

Two different types of forces can account for stresses within the stress tensor: surface forces and body forces. Surface forces act directly on the boundaries of the volume of interest, not internally within the volume. These forces also act by some form of direct contact with the substance that imparts forces directly onto our fluid element. These forces are normally constant (they can vary with time) at the point of contact. Contrary to this, body forces are developed without direct contact with the fluid element. These forces are normally distributed throughout the entire fluid and are normally variable depending on the spatial location within the volume of interest or even within the same fluid element. Examples of surface forces are the shear force induced by the fluid flow of a neighboring volume (i.e., neighboring fluid lamina) or the mechanical force that the elastic blood vessel applies onto the fluid. An example of a body force is the force resulting from gravity, which is dependent on the spatial location within the fluid.

Pressure has many functions in fluid mechanics and is a major constituent of forces that arise in the stress tensor. First, it can be the driving force for fluid motion. This is discussed as the inflow pressure head or the pressure gradient (change in pressure) across the volume of interest. However, at rest, fluids still exert an internal pressure. This is the *hydrostatic pressure*, which is defined partially by the weight of the fluid above a particular plane within the same fluid. This particular pressure is an example of a body force because it varies depending on the spatial location of the plane of interest within the fluid. For instance, the pressure on a free fluid surface (open to any atmosphere) must be equal to the atmospheric pressure at the free surface. However, a differential element of fluid below a free surface must be able to support the weight of the fluid above it as well as the atmospheric pressure. To think of this, consider walking around your campus grounds with 1 atmosphere of air pressure on your shoulders. If, however, you are carrying a heavy book bag while walking to your biofluid mechanics final examination, it might feel like the weight of the world is on your shoulders. However, in fact, the only added force is that of the book bag; you still are supporting the forces associated with the 1 atmosphere of pressure. Also, the pressure from the book bag is not added to your head (although again the final examination might seem weighty), but it is added to everything from your shoulders down (even the floor on which you are standing). One useful relationship between stress and pressure is that the hydrostatic pressure is equal to the average of the normal stress components at any differential location (Eq. (2.14)). The negative sign is added to the formulation to make sure that the

forces balance each other. For any other coordinate system (e.g., cylindrical) the hydrostatic pressure is equal to the average of the stresses along the main diagonal of the Cauchy stress tensor. (Remember to include the negative sign so that the forces can balance each other, i.e., an equivalent as represented in Eq. (2.13).) Eq. (2.14) is derived by realizing that hydrostatic pressures only act normal to surfaces, and, therefore, the hydrostatic pressure at a given location would need to equate to the average of the normal stresses.

$$p_{\text{hydrostatic}} = -\frac{1}{3}(\sigma_{xx} + \sigma_{yy} + \sigma_{zz}) \quad (2.14)$$

2.6 Kinematics: Velocity, acceleration, rotation, and deformation

Kinematics is the generalized study of motion. Using kinematic relationships you can describe the motion of any particle in space and time. In this section, we will develop the formulations for the motion of an infinitesimal area of fluid, $\delta x \delta y$, with a fixed identifiable mass, δm . (This derivation can be extended to three dimensions easily, by extending the area into a differential volume, denoted as $\delta x \delta y \delta z$.) As our differential mass moves throughout the fluid, it may experience translation, rotation, extension, pure shear, or any combination of these four movement classifications (Fig. 2.15). Translation and rotation are rigid body motions and should be familiar from engineering mechanics courses. *Translation* is defined when all

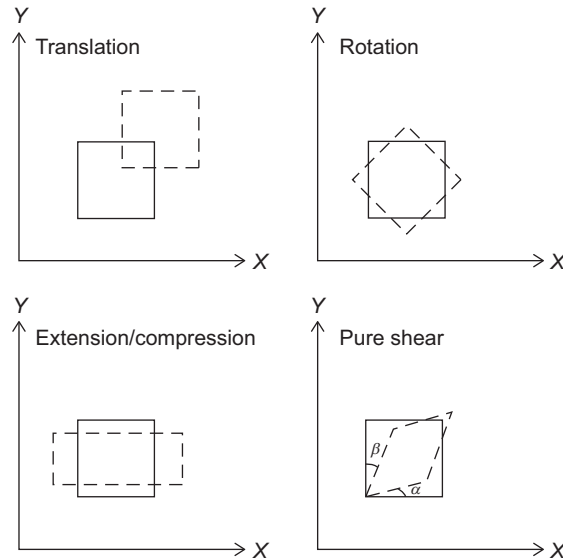


FIG. 2.15 Different motions that a fluid element can undergo. These include translation, rotation, extension/compression, and pure shear. In general, all of these motions can occur at the same time, which would be described as a general planar rotation/deformation.

of the particles within the mass move with the same displacement and there is maintenance of the relative orientation of these particles (note that translation can be linear or curvilinear). *Rotation* is defined when all the particles rotate about some point, maintaining the orientation among all particles. As depicted in Fig. 2.15, during pure rotation, particles experience different displacement based on their distance from the point of rotation. Particles along the point of rotation (axis of rotation in three dimensions) have a zero displacement, whereas those at the periphery of the rotating body have the largest displacement. In real fluid mechanics problems, it is extremely rare for fluid elements to experience only pure translation or rotation. However, in some cases these motions can be applied to approximate the flow scenario to make the calculations simpler, recognizing that the solutions may not be accurate. For most real fluid mechanics problems, when δm moves throughout the fluid, the internal organization of the particles is not conserved. When this is the case, the kinematic representation of the element will be a combination of extension/compression and pure shear and likely will include motions that can be described by translational and rotational. If the element is subjected to pure extension or compression, there are changes in the boundary lengths of the differential mass, δm . This requires some form of internal reorganization of the fluid particles to account for the changes in length; which is similar to compression or elongation in solid mechanics problems. Pure shear is observed when only the internal angles along the boundary of δm are altered. This occurs if the element is under a pure shearing force and there are no normal forces acting on the element. Please note that α and β do not need to be equal to each other when the body is under pure shear. Fig. 2.15 illustrates the kinematic movement of a mass in two dimensions. These movements can be extended to three dimensions to describe any motion that a differential volume $\delta x \delta y \delta z$ would experience.

Similar to previous courses in mechanics, *velocity* is defined as the time rate of change of the position vector of any particle. Here we will define the position vector of a particle in 3D Cartesian coordinates as

$$\vec{x}(t) = u_x(t) \vec{i} + u_y(t) \vec{j} + u_z(t) \vec{k} \quad (2.15)$$

which is defined relative to the origin of a fixed coordinate system. This particle has a position of (x_i, y_i, z_i) at time t . Using this formulation, the velocity vector would be defined as

$$\vec{v}(t) = \frac{d\vec{x}(t)}{dt} = \frac{du_x(t)}{dt} \vec{i} + \frac{du_y(t)}{dt} \vec{j} + \frac{du_z(t)}{dt} \vec{k} = v_x(t) \vec{i} + v_y(t) \vec{j} + v_z(t) \vec{k} \quad (2.16)$$

As in classic mechanics, *acceleration* is defined as the time rate of change of the velocity vector of the particle in 3D space. Thus it takes the form of

$$\begin{aligned} \vec{a}(t) &= \frac{d\vec{v}(t)}{dt} = \frac{d^2\vec{x}(t)}{dt^2} = \frac{dv_x(t)}{dt} \vec{i} + \frac{dv_y(t)}{dt} \vec{j} + \frac{dv_z(t)}{dt} \vec{k} \\ &= \frac{d^2u_x(t)}{dt^2} \vec{i} + \frac{d^2u_y(t)}{dt^2} \vec{j} + \frac{d^2u_z(t)}{dt^2} \vec{k} = a_x(t) \vec{i} + a_y(t) \vec{j} + a_z(t) \vec{k} \end{aligned} \quad (2.17)$$

Example 2.1

Given the following position vector, which describes the motion of a fluid element with respect to time, calculate the velocity and acceleration of the fluid particle as a function of time. This particle starts at the origin of the defined coordinate axis at time zero. Plot the fluid particle's position and velocity for time 0, 1, 2, and 4 s.

$$\vec{x}(t) = (3\text{ms}^{-1})\left(t + \left(\frac{5}{2}\text{s}^{-1}\right)t^2\right)\vec{i} + (2\text{ms}^{-1})t\vec{j}$$

Solution

The velocity of an element is calculated as the time derivative of the position vector.

$$\begin{aligned}\vec{v}(t) &= \frac{d\vec{x}(t)}{dt} = \frac{d}{dt} \left[(3\text{ms}^{-1}) \left(t + \left(\frac{5}{2}\text{s}^{-1} \right) t^2 \right) \right] \vec{i} + \frac{d}{dt} [(2\text{ms}^{-1})t] \vec{j} \\ &= [(3\text{ms}^{-1})(1 + (5\text{s}^{-1})t)] \vec{i} + [(2\text{ms}^{-1})] \vec{j}\end{aligned}$$

Acceleration is defined as the time rate of change of the velocity vector.

$$\vec{a}(t) = \frac{d\vec{v}(t)}{dt} = \frac{d}{dt} [(3\text{ms}^{-1})(1 + (5\text{s}^{-1})t)] \vec{i} + \frac{d}{dt} [(2\text{ms}^{-1})] \vec{j} = [(3\text{ms}^{-1})(5\text{s}^{-1})] \vec{i} = 15\text{ms}^{-2} \vec{i}$$

Fig. 2.16 and Table 2.2 depict the motion of the particle investigated. We would also like to note at this point, because this is the first example problem in the text, that it is critical to maintain units throughout calculations and to check whether the units of your final answer make sense within the constraints of the problem. This does make the computations a bit more labor intensive, but it is worth it as the calculations get more complex and confusing.

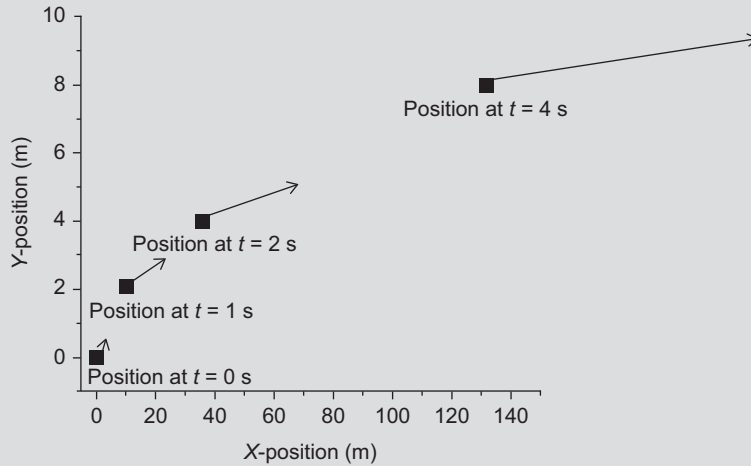


FIG. 2.16 The fluid particles position as a function of time. The *arrows* represent the magnitude of velocity at each time. Note that the *x* and *y* axes are not on the same scale.

Example 2.1 (*cont'd*)**TABLE 2.2** Kinematic properties of the particle as a function of time.

Time (s)	X-Position (m)	Y-Position (m)	X-Velocity (m/s)	Y-Velocity (m/s)	Velocity, magnitude, and direction	X-Acceleration (m/s ²)
0	0	0	3	2	3.61 m/s @ 33.7 degrees	15
1	10.5	2	18	2	18.11 m/s @ 6.34 degrees	15
2	36	4	33	2	33.06 m/s @ 3.47 degrees	15
4	132	8	63	2	63.03 m/s @ 1.82 degrees	15

The previously developed formulations for velocity and acceleration are based on the Lagrangian assumption that you can define discrete particles within the fluid. It is a requirement that each particle has a known position as a function of time; therefore, velocity and acceleration can be defined from this position vector (see Example 2.1). However, in fluid mechanics, it is sometimes more accurate to discuss the velocity as a property of the fluid as a whole, instead of the position of each fluid particle as a function of time. In this case the velocity vector of the fluid is defined prior to the position vector because it is probably difficult (if not impossible) to accurately describe each particle's position within the fluid (recall our earlier discussion on how many cells, proteins, fluid molecules, and other compounds would be included within a small volume of blood). In this Eulerian type approach, the velocity of the fluid becomes

$$\vec{v} = v(x, y, z, t) = v_x + v_y + v_z + v_t \quad (2.18)$$

The acceleration, which is the time derivative of the velocity, is defined by considering that a fluid element at time t has a velocity of

$$\vec{v}_{e|t} = v_{x|t} + v_{y|t} + v_{z|t} + v_{t|t} \quad (2.19)$$

where the added subscript for e indicates that it is the velocity for a particular fluid element. At a later time point the velocity of the same element can be defined as

$$\vec{v}_{e|t+dt} = v_{x+dx|t+dt} + v_{y+dy|t+dt} + v_{z+dz|t+dt} + v_{t+dt|t+dt} \quad (2.20)$$

assuming that the particle has moved to a new location of $(x + dx, y + dy, z + dz)$ from the initial position of (x, y, z) during the time interval of dt . From Eqs. (2.19) and (2.20), we can define the particle's change in velocity during the translation from (x, y, z) to $(x + dx, y + dy, z + dz)$ over the dt time interval as

$$d\vec{v}_e = \frac{\partial \vec{v}}{\partial x} dx_e + \frac{\partial \vec{v}}{\partial y} dy_e + \frac{\partial \vec{v}}{\partial z} dz_e + \frac{\partial \vec{v}}{\partial t} dt \quad (2.21)$$

where each term represents the differential change in velocity over a spatial or temporal dimension multiplied by the actual change in that dimension over the time interval dt , for a specific element e . We can obtain the acceleration of this particle over this particular time interval by taking the time derivative of Eq. (2.21). The acceleration can then be represented by

$$\vec{a}_e = \frac{d\vec{v}_e}{dt} = \frac{\partial \vec{v}}{\partial x} \frac{dx_e}{dt} + \frac{\partial \vec{v}}{\partial y} \frac{dy_e}{dt} + \frac{\partial \vec{v}}{\partial z} \frac{dz_e}{dt} + \frac{\partial \vec{v}}{\partial t} \frac{dt}{dt} = \frac{\partial \vec{v}}{\partial t} + v_x \frac{\partial \vec{v}}{\partial x} + v_y \frac{\partial \vec{v}}{\partial y} + v_z \frac{\partial \vec{v}}{\partial z} \quad (2.22)$$

$\frac{\partial \vec{v}}{\partial t}$ is termed the local acceleration of the fluid, and the remaining terms are the convective acceleration of the fluid. Eq. (2.22) is typically termed the total acceleration of a particle and is typically represented with the substantial derivative as follows

$$\frac{D\vec{v}}{Dt} = \vec{a}_e = \frac{\partial \vec{v}}{\partial t} + v_x \frac{\partial \vec{v}}{\partial x} + v_y \frac{\partial \vec{v}}{\partial y} + v_z \frac{\partial \vec{v}}{\partial z} \quad (2.23)$$

We should recognize that there are two ways in which a fluid particle can experience an acceleration. First, because of spatial constrictions (such as a nozzle) or dilations, the fluid elements may be convected into a region that has a higher or lower velocity. This type of acceleration is due to spatial changes and is termed the convective acceleration. If the flow is steady, meaning that the velocity profile at each spatial location is not a function of time, this is the only acceleration that fluid particles may experience. However, if the flow is unsteady, meaning that the velocity is a function of time, the particles can experience an added acceleration term, which is due to the temporal changes in the velocity profile. This arises when the flow is driven by an unsteady pump, such as the heart. Different types of temporal driving forces and spatial driving forces are shown in Fig. 2.17. We illustrate the pressure variation during one cardiac cycle as a temporal driving force and different types of constrictions as spatial driving forces. It is important to note that velocity and acceleration can be altered by spatial and temporal driving forces at the same time. Fluid velocity and acceleration are field quantities; that is, they are functions of the fluid itself.

Acceleration is itself a vector, and it can be divided into the following three component terms (in Cartesian coordinates)

$$\begin{aligned} a_x &= \frac{\partial v_x}{\partial t} + v_x \frac{\partial v_x}{\partial x} + v_y \frac{\partial v_x}{\partial y} + v_z \frac{\partial v_x}{\partial z} \\ a_y &= \frac{\partial v_y}{\partial t} + v_x \frac{\partial v_y}{\partial x} + v_y \frac{\partial v_y}{\partial y} + v_z \frac{\partial v_y}{\partial z} \\ a_z &= \frac{\partial v_z}{\partial t} + v_x \frac{\partial v_z}{\partial x} + v_y \frac{\partial v_z}{\partial y} + v_z \frac{\partial v_z}{\partial z} \end{aligned} \quad (2.24)$$

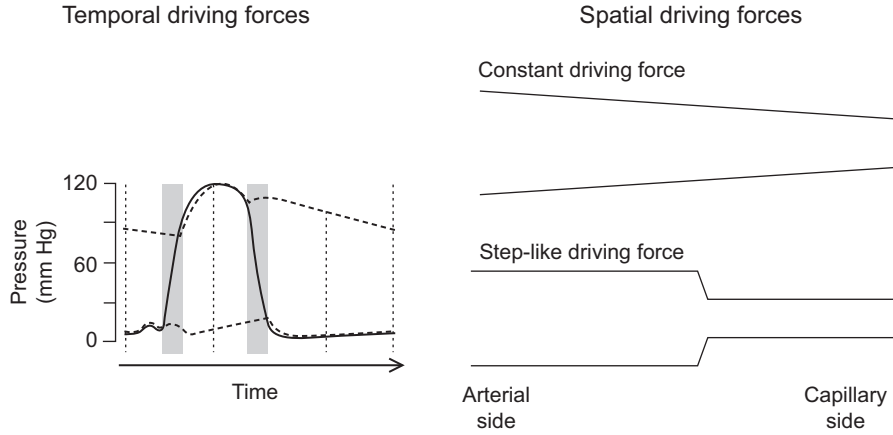


FIG. 2.17 Examples of temporal and spatial driving forces that may arise in the vascular system. In general, temporal and spatial driving forces can be coupled within the same problem.

As you will see later in the text, it is this acceleration formulation that is critical and serves as the foundation for many fluid mechanics problems. In summary, using the Eulerian approach to calculate velocity and acceleration, the main quantity of interest is a particular volume within the system, not a particular particle within the fluid. Again, this generally can make the computations significantly easier because one would solve for the entire fluid as an entity and not individual particles that compose the fluid.

To define the rotation of fluid particles, we must take a slightly different approach. Fig. 2.15 highlights the kinematic rotation of a fluid element at any time/space in the flow field. This can be described by rotation vectors, namely the angular velocity vector (in three dimensions, Eq. (2.25))

$$\vec{\omega} = \omega_x \vec{i} + \omega_y \vec{j} + \omega_z \vec{k} \quad (2.25)$$

where each Cartesian component is the rotation of the element about that particular Cartesian axis. For instance, ω_x is the angular velocity of the element about the x -axis. Rotation components can be described with linear velocity components by realizing that the rotation of a small fluid element (Fig. 2.18) can be represented as the mathematical limit (lim) as time approaches zero of the time rate of change of the angles (i.e., see α , Fig. 2.18) that the fluid element makes with the defined fixed coordinate system. As noted in the figure, the angle α is formed because of a difference in the magnitude of linear velocity along the line segment of the element (for 2D or face of the element for 3D). Hence, linear velocity changes can be directly related to angular velocity changes. From Fig. 2.18, ω_z (this figure illustrates rotations about the z -axis, even though the motion is in the xy -plane) would be defined as

$$\omega_z = \lim_{\Delta t \rightarrow 0} \frac{\Delta \alpha}{\Delta t} \quad (2.26)$$

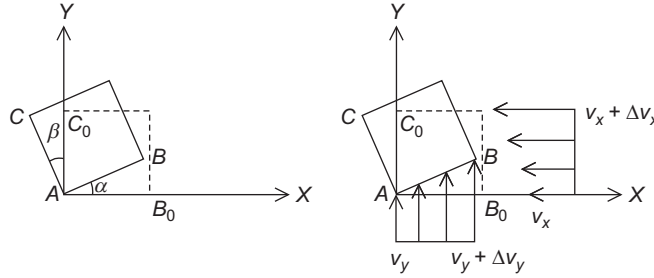


FIG. 2.18 Rotation of a rigid body used to calculate angular velocity, vorticity, and shear rate. The rate of change of the displacement of point B is defined from the change in velocity over time across line segment AB . The same analysis conducted on all other line segments in three dimensions would yield the angular velocity formula. Remember that α and β do not have to be the same.

Using this approach, the angular velocity about the z -axis also can be defined mathematically as the average of the angular velocity of two perpendicular line segments in the plane normal (x – y plane, for our example) to that axis system. This formulation will end up with fluid quantities that are more easily quantified and are typically used because the angle α does not typically equal the angle β (see Fig. 2.18). Additionally, the time rate of change of these two angles (and hence the angular velocity in one direction can become quite complex) does not need to be equal. The perpendicular line segments that will be used to define the changes in angular velocity are $\overline{AB_0}$ and $\overline{AC_0}$ (see Fig. 2.18). At some later time, points B_0 and C_0 will translate to a new location denoted as B and C , respectively (see Fig. 2.18), forming the angles α and β that were discussed previously (recall that these angles are not necessarily equal). To quantify the angular velocity, the difference in linear velocity at points A and B must first be determined. Since this element is a differential element, the velocity difference between A and B is defined as Δv_y . (This velocity acts in the y -direction even though the original line segment was in the x -direction because over a small time interval the velocity needed to initiate a rotation of this fluid element will only be in the y -direction.) Similarly, the difference in velocity from point A to point C would be Δv_x , making the same assumption regarding a small time interval. This discussion also makes the assumption that the x -velocity at A is defined as v_x and the y -velocity at A is defined as v_y . Using these definitions for velocity, the change in displacement for points A , B_0 , and C_0 to points A , B , and C would be 0 , $(v_y + \frac{\partial v_y}{\partial x} \Delta x - v_y) \Delta t$, and $-(v_x + \frac{\partial v_x}{\partial y} \Delta y - v_x) \Delta t$, respectively. To formulate these displacements (denoted as s), a change in velocity was multiplied by a change in time (i.e., $\Delta s = \Delta v \Delta t$). In addition, the change in velocity is defined as the velocity at B , $(v_y + \frac{\partial v_y}{\partial x} \Delta x)$, minus the y -velocity at A , (v_y) , or the velocity at C , $-(v_x + \frac{\partial v_x}{\partial y} \Delta y)$, minus the x -velocity at A , $-(v_x)$. The displacement of C is negative because the point moves in the negative x -axis direction and thus the velocity must be negative to initiate/induce this motion. Additionally, the partial derivative term for the velocity at B arises because

of the original Δv_y , but the assumption is made that $\Delta x \rightarrow 0$ for a differential element and thus the velocity changes can be represented with partial differential changes. Now we will take the limit as time approaches zero of the change in the angle (α or β) (from Eq. (2.26) to obtain Eq. (2.27)), providing us a formulation for the elements angular velocity.

$$\begin{aligned}\lim_{\Delta t \rightarrow 0} \frac{\Delta \alpha}{\Delta t} &\cong \lim_{\Delta t \rightarrow 0} \frac{\overline{BB_0}/\overline{AB_0}}{\Delta t} = \lim_{\Delta t \rightarrow 0} \frac{\left(v_y + \frac{\partial v_y}{\partial x} \Delta x - v_y\right) \Delta t / \Delta x}{\Delta t} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \left(\frac{\frac{\partial v_y}{\partial x} \Delta x \Delta t}{\Delta x} \right) = \frac{\partial v_y}{\partial x} \\ \lim_{\Delta t \rightarrow 0} \frac{\Delta \beta}{\Delta t} &\cong \lim_{\Delta t \rightarrow 0} \frac{\overline{CC_0}/\overline{AC_0}}{\Delta t} = \lim_{\Delta t \rightarrow 0} \frac{-\left(v_x + \frac{\partial v_x}{\partial y} \Delta y - v_x\right) \Delta t / \Delta y}{\Delta t} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \left(-\frac{\frac{\partial v_x}{\partial y} \Delta y \Delta t}{\Delta y} \right) = -\frac{\partial v_x}{\partial y}\end{aligned}\quad (2.27)$$

Therefore, angular velocity about the z-axis will equal the average of these two quantities for a differential area element and can be represented as

$$\omega_z = \frac{1}{2} \left(\frac{\partial v_y}{\partial x} - \frac{\partial v_x}{\partial y} \right) \quad (2.28)$$

A similar analysis conducted about the other two Cartesian axes (for a differential volume of fluid) would yield

$$\omega_x = \frac{1}{2} \left(\frac{\partial v_z}{\partial y} - \frac{\partial v_y}{\partial z} \right) \quad \text{and} \quad \omega_y = \frac{1}{2} \left(\frac{\partial v_x}{\partial z} - \frac{\partial v_z}{\partial x} \right) \quad (2.29)$$

Combining the terms for the angular velocity about each Cartesian direction into one angular velocity vector allows us to write an expression for the angular velocity of a fluid element as

$$\vec{\omega} = \frac{1}{2} \left[\left(\frac{\partial v_z}{\partial y} - \frac{\partial v_y}{\partial z} \right) \vec{i} + \left(\frac{\partial v_x}{\partial z} - \frac{\partial v_z}{\partial x} \right) \vec{j} + \left(\frac{\partial v_y}{\partial x} - \frac{\partial v_x}{\partial y} \right) \vec{k} \right] = \frac{1}{2} \text{curl } \vec{v} \quad (2.30)$$

Vorticity (ξ) is a measure of the rotation of fluid elements and is defined as $2\vec{\omega}$. An irrotational fluid has a vorticity of zero. Irrotational fluids simplify the governing equations of the fluid (to be derived later) and makes the computational analysis simpler. In most examples in this text, the vorticity will be zero. However, in biofluid mechanics, because of the large pressure and velocity gradients, recirculation zones, turbulence, and shed vortices can be generated that can cause a fluid to have a nonzero vorticity. Under these conditions, the fluid would be considered rotational. Some people think that an irrotational fluid is also inviscid; this is not necessarily true. However, an inviscid fluid that is initially irrotational will remain irrotational unless external forces are applied to the fluid element to induce rotation.

Example 2.2

Calculate the vorticity of the following velocity field. Is the flow rotational or not?

$$\vec{v} = [Cz\sin(xy) + Cxyz\cos(xy)]\vec{i} + Cx^2z\cos(xy)\vec{j} + Cx\sin(xy)\vec{k}$$

Solution

$$\begin{aligned}\xi &= \left(\frac{\partial v_z}{\partial y} - \frac{\partial v_y}{\partial z}\right)\vec{i} + \left(\frac{\partial v_x}{\partial z} - \frac{\partial v_z}{\partial x}\right)\vec{j} + \left(\frac{\partial v_y}{\partial x} - \frac{\partial v_x}{\partial y}\right)\vec{k} \\ &= \left(\frac{\partial(Cx\sin(xy))}{\partial y} - \frac{\partial(Cx^2z\cos(xy))}{\partial z}\right)\vec{i} + \left(\frac{\partial([Cz\sin(xy) + Cxyz\cos(xy)])}{\partial z} - \frac{\partial(Cx\sin(xy))}{\partial x}\right)\vec{j} \\ &\quad + \left(\frac{\partial(Cx^2z\cos(xy))}{\partial x} - \frac{\partial([Cz\sin(xy) + Cxyz\cos(xy)])}{\partial y}\right)\vec{k} \\ &= (Cx^2\cos(xy) - Cx^2\cos(xy))\vec{i} + (C\sin(xy) + Cxyz\cos(xy) - C\sin(xy) - Cxyz\cos(xy))\vec{j} \\ &\quad + (2Cxz\cos(xy) - Cx^2yz\sin(xy) - Cxz\cos(xy) - Cxz\cos(xy) + Cx^2yz\sin(xy))\vec{k} \\ &= 0\vec{i} + 0\vec{j} + 0\vec{k}\end{aligned}$$

The fluid is not rotational.

In solid mechanics, deformations are typically described by the change in length of a small element (i.e., strain). In contrast, for fluid mechanics, we discuss the rate of change of the extension/compression of fluid elements. Strain has nine components that make up the strain tensor (similar to stress components that comprise the stress tensor). Six of these components are independent of each other using the same assumptions that we made in developing the stress tensor. The rate of extension is defined by velocity changes through the flow field. If at a reference location at time t , the velocity of a fluid is v_x and this changes to $v_x + \Delta v_x$ at time $t + \Delta t$ and then the fluid elongates by $\Delta x + \Delta v_x \Delta t$. The first term in the elongation formulation arises from the original length between two points within the fluid. The second term is derived from the velocity component that may cause a change in the fluid element length. Similar to the angular velocity formulations, deformation in one dimension becomes

$$d_{xx} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \left(\frac{\Delta x + \Delta v_x \Delta t - \Delta x}{\Delta x} \right) = \frac{\partial v_x}{\partial x} \quad (2.31)$$

With a similar derivation, the other two normal deformations can be represented as

$$d_{yy} = \frac{\partial v_y}{\partial y} \text{ and } d_{zz} = \frac{\partial v_z}{\partial z} \quad (2.32)$$

The remaining six strain tensor components are derived in a similar manner using the relationship that these stress components arise from shear stress (or shear forces) on the fluid elements and not from velocity changes. These shear stresses cause a change in the angle of our fluid element (which is normally represented as a cube, in our assumed Cartesian coordinate system). Similar to our angular velocity calculations, the strain will be calculated as the average of the time rate of change of the two angles α and β that the element makes with the fixed coordinate axis (these angles are illustrated in Fig. 2.15).

$$\Delta\alpha \equiv \frac{\left\{v_y + \left(\frac{\partial v_y}{\partial x}\right)\Delta x - v_y\right\}\Delta t}{\Delta x} \quad \text{and} \quad \Delta\beta \equiv \frac{\left\{v_x + \left(\frac{\partial v_x}{\partial y}\right)\Delta y - v_x\right\}\Delta t}{\Delta y} \quad (2.33)$$

Eq. (2.33) assumes that the time interval is short enough that the angles do not change significantly and that the tangent of these angles is approximately equal to the angles themselves (this second assumption is typically termed the *small angle approximation*). Additionally, we want to point out that the angles represented in Eq. (2.33) are not the same angles as shown in Fig. 2.18, which illustrated a rigid body rotation about the z-axis. Using these formulas, the rate of deformation resulting from shear simplifies to

$$d_{xy} = d_{yx} = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \left(\lim_{\substack{\Delta x \rightarrow 0 \\ \Delta y \rightarrow 0}} \frac{1}{2} (\Delta\alpha + \Delta\beta) \right) = \frac{1}{2} \left(\frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} \right) \quad (2.34)$$

The remaining components of deformation resulting from shear are defined in a similar manner, in Cartesian coordinates, making the deformation tensor

$$d_{xz} = d_{zx} = \frac{1}{2} \left(\frac{\partial v_z}{\partial x} + \frac{\partial v_x}{\partial z} \right) \quad \text{and} \quad d_{yz} = d_{zy} = \frac{1}{2} \left(\frac{\partial v_z}{\partial y} + \frac{\partial v_y}{\partial z} \right) \quad (2.35)$$

$$\mathbf{d} = \begin{bmatrix} d_{xx} & d_{xy} & d_{xz} \\ d_{yx} & d_{yy} & d_{yz} \\ d_{zx} & d_{zy} & d_{zz} \end{bmatrix} = \frac{1}{2} \begin{bmatrix} 2\frac{\partial v_x}{\partial x} & \frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} & \frac{\partial v_z}{\partial x} + \frac{\partial v_x}{\partial z} \\ \frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} & 2\frac{\partial v_y}{\partial y} & \frac{\partial v_z}{\partial y} + \frac{\partial v_y}{\partial z} \\ \frac{\partial v_z}{\partial x} + \frac{\partial v_x}{\partial z} & \frac{\partial v_z}{\partial y} + \frac{\partial v_y}{\partial z} & 2\frac{\partial v_z}{\partial z} \end{bmatrix} \quad (2.36)$$

In fluid mechanics, the deformation tensor is known as the *shear rate* (similar to strain in solid mechanics). Again, this is the rate of change of the angles or changes in the element's geometry within a fluid and can be calculated from the velocity changes within the fluid.

Example 2.3

Calculate the shear rate of a fluid with the following velocity profile:

$$\vec{v} = Cxy \vec{i} + \sin(y) \vec{j} + Cz \vec{k}$$

Solution

$$d_{xx} = \frac{\partial v_x}{\partial x} = \frac{\partial(Cxy)}{\partial x} = Cy$$

$$d_{yy} = \frac{\partial v_y}{\partial y} = \frac{\partial(\sin(y))}{\partial y} = \cos(y)$$

$$d_{zz} = \frac{\partial v_z}{\partial z} = \frac{\partial(Cz)}{\partial z} = C$$

$$d_{xy} = d_{yx} = \frac{1}{2} \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) = \frac{1}{2} \left(\frac{\partial(Cxy)}{\partial y} + \frac{\partial(\sin(y))}{\partial x} \right) = \frac{Cx}{2}$$

$$d_{xz} = d_{zx} = \frac{1}{2} \left(\frac{\partial v_x}{\partial z} + \frac{\partial v_z}{\partial x} \right) = \frac{1}{2} \left(\frac{\partial(Cxy)}{\partial z} + \frac{\partial(Cz)}{\partial x} \right) = 0$$

$$d_{yz} = d_{zy} = \frac{1}{2} \left(\frac{\partial v_y}{\partial z} + \frac{\partial v_z}{\partial y} \right) = \frac{1}{2} \left(\frac{\partial(\sin(y))}{\partial z} + \frac{\partial(Cz)}{\partial y} \right) = 0$$

$$\mathbf{d} = \begin{bmatrix} Cy & \frac{Cx}{2} & 0 \\ \frac{Cx}{2} & \cos(y) & 0 \\ 0 & 0 & C \end{bmatrix}$$

2.7 Viscosity

Viscosity is a property of fluids that relates the shear stress acting on a fluid to the shear rate experienced by the fluid. Fundamentally, viscosity arises because of intermolecular interactions within the fluid. For instance, the intermolecular interactions in water are mostly hydrogen bonds (i.e., adhesion and/or cohesion; see [Fig. 2.12](#)). These bonds are relatively weak; therefore water does not have a high viscosity. Fluids that possess stronger intermolecular bonds will typically have a larger viscosity. Another way to consider viscosity is as the fluid's internal resistance to changes in motion that will result in deformations. (Recall from previous courses that rigid bodies have similar intrinsic resistive properties; for example, a body's resistance to linear acceleration changes is its mass and a body's resistance to rotational acceleration changes is its mass moment of inertia.) Fluids with a larger viscosity will resist motions that induce deformation more easily than those with a lower viscosity.

In solid mechanics, stress and strain are related by the modulus of elasticity. Fundamentally, viscosity is defined in the same way, as a value that completes the following proportionality

$$\tau_{xy} \propto 2d_{xy} = \frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \rightarrow \tau_{xy} = \mu \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) \quad (2.37)$$

In this formulation, the viscosity (μ) is the dynamic viscosity of the fluid. This is the internal resistance to motions that cause deformation that was discussed in the previous paragraph. A common unit for viscosity is Poise (where $1\text{P} \equiv 1\text{g}/\text{cm} \cdot \text{s}$). In fluid mechanics, the kinematic viscosity (ν) is a standardized version of the viscosity. The kinematic viscosity is defined as the dynamic viscosity divided by the fluid density. The unit for kinematic viscosity is Stoke (where $1\text{St} \equiv 1\text{cm}^2/\text{s}$).

Example 2.4

Calculate the shear stress on the upper and lower boundaries of the following fluid, given that the viscosity of the fluid is 3.5 cP. The distance between the two plates is 10 mm, and the velocity is 0 mm/s at the lower plate and 30 mm/s at the upper plate and assumed to vary linearly (Fig. 2.19).

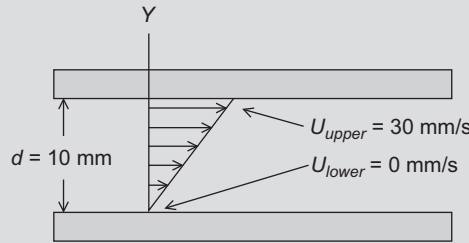


FIG. 2.19 Figure for the example problem 2.4.

Solution

$$\tau_{upper} = \mu \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) = \mu \frac{\partial v_x}{\partial y}$$

There is no velocity in the y -direction so the second term within the parenthesis is equal to zero, leaving the relationship shown. Because the velocity profile is assumed to be linear in the y -direction, the shear stress equation simplifies to

$$\begin{aligned} \tau_{upper} &= \mu \frac{\Delta v_x}{\Delta y} = \mu \frac{U_{upper} - U_{lower}}{d_{upper} - d_{lower}} = \mu \frac{U_{upper}}{d_{upper}} \\ \tau_{upper} &= 3.5 \times 10^{-2} \text{P} \left(\frac{1 \frac{\text{g}}{\text{cm}} \cdot \text{s}}{1\text{P}} \right) * \frac{30 \text{ mm}}{10 \text{ mm}} = 0.0105 \text{ Pa} = 0.105 \text{ dyne}/\text{cm}^2 \end{aligned}$$

Similarly, the shear stress on the lower plate can be calculated from (if we assume a linear velocity profile)

Continued

Example 2.4 (cont'd)

$$\tau_{lower} = \mu \frac{\Delta v_x}{\Delta y} = \mu \frac{U_{lower} - U_{upper}}{d_{lower} - d_{upper}} = \mu \frac{U_{upper}}{d_{upper}}$$

$$\tau_{lower} = 3.5 \times 10^{-2} P \left(1 \frac{\frac{g}{cm}}{1P} * s \right) * \frac{-30 \frac{mm}{s}}{-10 \frac{mm}{s}} = 0.0105 Pa = 0.105 \text{ dyne/cm}^2$$

Although the shear forces have the same magnitude, their lines of action are opposite. The force on the top plate is acting in the negative x -direction, and the force on the bottom plate is acting in the positive x -direction. Remember the sign convention for stress that was discussed in [Section 2.5](#), in which a positive shear stress can occur on a positive face in the positive direction or on a negative face in the negative direction (these conventions were used to determine the direction associated with the forces).

2.8 Fluid motions

Fluid motions is a concept that attempts to generalize and characterize how fluids respond to changes in shear rate. Many fluids under normal conditions can be considered as a Newtonian fluid. A Newtonian fluid is classified by a constant dynamic viscosity under any shear rate loading condition. Similar to a purely elastic material, these fluids are represented with a linear relationship between shear stress and shear rate. However, many fluids do not exhibit Newtonian properties and, therefore, are termed *non-Newtonian fluids* ([Fig. 2.20](#)). For example, ketchup will flow out of a bottle very slowly with only the gravitational force acting on the ketchup. However, if you squeeze the bottle slightly, the ketchup will flow out of the bottle more quickly. This is an example of a shear-thinning fluid (also termed *pseudoplastic*). Paints are a second example of a shear-thinning fluid; the shear forces created by a brush (or roller) causes the paint to thin evenly and cover the application surface. With removal of this shear force, the viscosity increases to prevent drips/bubbles from forming. These special fluids have a larger dynamic viscosity at low shear rates and a lower dynamic viscosity at high shear rates. Another non-Newtonian fluid is a sand–water mixture. When there is a large volume of water with a small amount of sand, this fluid will have a lower dynamic viscosity. Under a low shear rate, this type of mixture (large amounts of water to small amounts of sand, e.g., water to sand, 100:1) behaves as water. As the shear rate increases, water will flow out of the mixture more easily than the sand, leaving a similar quantity of sand and water (water to sand = 1:1). This 1:1 mixture will have a larger viscosity, at the higher shear rate, compared with the 100:1 water to sand mixture. At some time, most of the water will be removed from the mixture (water to sand = 1:100), and it will become very difficult to make this fluid flow, because the internal resistance to deformation will be high. Under very large stresses, the fluid will eventually deform because the internal resistance against motion is finite. This type of fluid is a shear-thickening fluid (also termed *dilatant*). Dilatant fluids have been used in body armor to allow the wearer normal mobility (when the shear forces

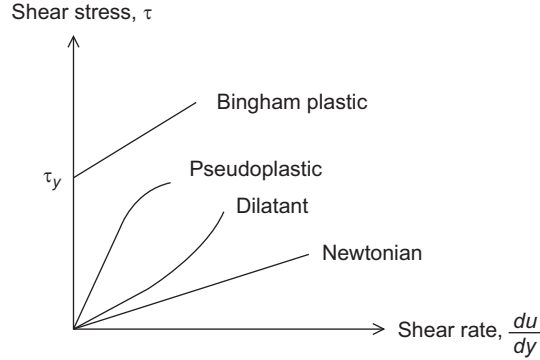


FIG. 2.20 Relationship between shear stress and shear rate for Newtonian and non-Newtonian fluids. Newtonian fluids have a constant viscosity as a function of shear rate. Non-Newtonian fluids have a nonconstant viscosity. Some fluids also may have a yield stress (τ_y), which must be overcome before the initiation of fluid flow.

are lower) and significant protection upon insult from a piercing object (such as a knife blade or bullet). In fact, composite body armor produced with dilatant fluids can outperform pure Kevlar in ballistic tests. To describe the motion of these fluids, the shear stress–shear rate relationship becomes (for 3D volume in a Cartesian coordinate system, as derived previously)

$$\tau_{xy} = k \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right)^n \quad (2.38)$$

where k is termed the consistency index and n is the flow behavior index. To maintain the sign convention for shear stress, this expression may also be written as

$$\tau_{xy} = k \left| \frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right|^{n-1} \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) = \eta \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) \quad (2.39)$$

where η is the apparent viscosity of the fluid. For Newtonian fluids, the apparent viscosity is the same as the dynamic viscosity because n is equal to 1. Pseudoplastic fluids can be described as having a value of n that is less than 1 and dilatant fluids can be described as having a value of n that is greater than 1. One more classification for fluids is a Bingham plastic fluid. These types of fluids do not flow when small stresses are applied to them. Under these scenarios, some threshold shear stress level (termed the yield stress) must be applied to the fluid so the fluid can begin to flow. An example of this type of fluid is toothpaste. When in the tube, small forces will not cause the toothpaste to flow out of the tube (e.g., gravity when the tube is held upside down). A certain yield stress (τ_y) must be applied to the tube for the toothpaste to come out. In the case of toothpaste, the yield stress must exceed the atmospheric pressure plus any additional internal adhesive forces (note that this fluid behavior is common in polymer solutions in which there is the potential for large adhesion forces between the polymer molecules). Bingham plastic fluids are modeled as

$$\tau_{xy} = \tau_y + \mu \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) \quad (2.40)$$

where τ_y is the yield shear stress, which again must be overcome to induce fluid motion (note that μ for Bingham plastic fluids is sometimes referred to as *the plastic viscosity*). All real fluids will have a minimal yield stress and will likely have a flow behavior index that is not equal to 1 and likely varies with the applied shear rate. However, for some fluids, such as water, the yield stress is so small and the variation of the flow behavior index away from 1 is negligible (even under large ranges of shear rate).

Blood is a non-Newtonian fluid that is a combination of a pseudoplastic fluid and a Bingham plastic fluid. This means that blood must surpass an initial yield stress to begin to flow and that, as the shear rate increases, once blood is flowing, the dynamic viscosity of blood decreases. Through numerical and experimental studies, it has been shown that using the assumption that blood behaves as a Newtonian fluid overestimates the actual shear stress values that can be found in the fluid flow field. This is significant because, as we will see in later chapters, shear stress is a significant mediator of cardiovascular diseases and can elicit many physiological/pathological cellular responses. Therefore, an accurate prediction of shear stress must be made by using the appropriate fluid relationships for blood's properties.

Another classification can be made for fluids that exhibit a time-dependent change in viscosity. If the apparent viscosity decreases under a constant shear stress, this fluid is thixotropic. Biological examples of thixotropic fluids include synovial fluid (found in joints), cytoplasm, and ground substance (extracellular matrix found in connective tissue). Similar, rheopectic fluids have a time-dependent increase in apparent viscosity, under a constant shear stress. Currently, no rheopectic fluids have been found occurring naturally in the human body; however, some printer inks can exhibit rheopectic behavior. The relationship between shear stress and shear rate for these fluids cannot be plotted in [Fig. 2.20](#) because the viscosity is dependent on time, which is not a variable in this figure.

Inviscid fluids have a zero (or negligible) viscosity. Although there is no such real fluid that exhibits these properties, some fluid mechanics analyses can be completed using this assumption and the obtained results would be still meaningful (e.g., gas flows may not involve viscosity considerations because the molecular interactions can be infrequent and when they occur they do not alter the flow conditions). Recall that under these conditions the fluid elements can only undergo rigid body motion. In most of the following examples in this textbook, we will use the no-slip boundary assumption. This means that the fluid at a boundary must have the same velocity as the boundary. (Refer to the previous parallel plate example [Example 2.4] in this textbook.) In most cases, when the boundary is stationary, the first lamina of fluid along the boundary will have a zero velocity. In some cases, the boundary can be moving and that first lamina will match the velocity of the boundary. However, this holds only for viscous fluids. Inviscid fluids do not resist flow internally, and, therefore, all of the fluid layers must have the same velocity, regardless of the boundary velocity. If you look at a velocity profile for blood modeled as an inviscid fluid versus that of a viscous fluid, it could be depicted as in [Fig. 2.21](#), assuming that all of the boundaries have a zero velocity component.

Flows also can be characterized as compressible or incompressible. If the density can vary throughout the fluid (because of geometry considerations or thermal consideration, among others) the fluid is considered compressible. Gases, for instance, are highly compressible. Incompressible fluids have negligible changes in density throughout the flow, suggesting that pressure and temperature (among other physical variables) do not affect the fluid density. Most liquids exhibit the property of being incompressible, and in this textbook we will



FIG. 2.21 The velocity profile for blood flowing through an artery that is modeled as an inviscid fluid (A) or a viscous fluid (B). An inviscid fluid has a uniform velocity profile because there is no internal resistance to motion. A viscous fluid has a nonuniform velocity profile, which can be idealized to a parabolic velocity profile for many conditions.

normally make the assumption that liquids are incompressible. However, please note that for most liquids, density can change as a function of temperature (e.g., the density of water at 5°C is 999.9 kg/m^3 , at 35°C is 994 kg/m^3 , at 55°C is 985.2 kg/m^3 , and at 95°C is 961.5 kg/m^3). If significant temperature fluctuations are a property of your flow, you must use compressible flow formulations to describe your flow conditions or approximate the fluid density changes with an appropriate manner of your choosing. However, in the human body, core body temperature is fairly constant at 37°C , so flow through internal organs may not need to account for blood density changes based on temperature. The temperature at your extremities can vary significantly from this, depending on the atmospheric temperature, so blood density changes may become a significant property of your particular problem. During problem solution, it is imperative to determine whether this possible density change is significant. Furthermore, cavitation is a phenomenon that occurs only in compressible fluids (and this phenomenon can occur behind implanted mechanical heart valves). *Cavitation* occurs when the fluid pressure is below the fluid vapor pressure and air pockets form within the fluid. These pockets can then burst when the pressure rises again.

Viscous fluids also can be characterized by laminar or turbulent flows. Laminar regions are characterized by smooth transitions in flow. Turbulent regions have time-dependent fluctuations in fluid properties such as velocity, acceleration, and viscosity. These fluctuations are random and cannot be quantified easily. In laminar flow, there is generally no mixing of fluid laminae. Because of the random fluctuations in turbulent flows, there is mixing of fluid laminae and, generally, there is a large increase in shear stress because of the transfer of fluid particles (mass and energy is transferred) between laminae. Turbulent flows typically have a non-zero vorticity. We will introduce some of the concepts of turbulent flows in [Section 2.12](#), but the majority of problems in this textbook will involve laminar flows.

2.9 Two-phase flows*

A two-phase flow is a fluid that is composed of either one fluid that is present in two discrete phases (e.g., water and steam in a turbine) or a mixture of fluids (e.g., water and oil). In principal, the two different fluid phases will have a different density and viscosity, among other fluid parameters. To describe a two-phase flow the same laws that will be

* This section is considered advanced and can be skipped without a loss of continuity.

developed in subsequent chapters of this text can be applied, but they must be applied separately to each phase. A similar process was used in solid mechanics courses, when you were asked to analyze an axial loaded solid bar composed of two materials: one material as a sheathing and a separate material as the core. If a single set of equations is used to quantify these conditions, this would introduce a statically indeterminate problem (e.g., one that could not be solved properly). However, by writing the equations independently for the two different material sections and then equating variables that must be the same (e.g., displacement at the boundary of the two materials), this type of problem could be solved. Under two-phase flow conditions, one must take a similar approach. In general, you must equate the pressure, velocity, and/or shear force at the phase boundary so that a solution can be reached. Without this approach, one would have a statically indeterminate problem. The difficulty with this type of fluid problem is whether the boundary between the two phases can be defined easily. For instance, a water and oil boundary may be easily defined, but if you are bubbling a gas through a fluid, there would be multiple boundaries that are transient with time as the bubbles move through the fluid.

One common two-phase (or multiphase) fluid is blood. The first phase to consider is the plasma, which contains water, salts, and proteins. The second phase is composed of the blood cells. (Note that these phases can be further divided; hence the comment about multiphase flows.) These cells can be considered fluid because they are mostly composed of water surrounded by an elastic membrane (cell membrane), which itself exhibits fluid properties (fluid-mosaic model). Currently, most blood simulations do not account for the difference in fluid properties that cells have exhibit compared with the fluid component(s) of blood. Furthermore, each cell type may have different fluid properties; however, for a more accurate solution, these cells and their fluid properties should be taken into account. This accounting is important because cells can transfer energy and momentum to the fluid and possibly absorb fluid (see Chapter 15). Blood cells make up approximately 40% of the blood volume and, in small blood vessels (see Part III), the cells can group together, forming a type of plug flow region. In microvessels, pockets of blood that are composed of only plasma followed by pockets of blood composed mostly of cellular matter are found. Although we will not develop solutions for general two-phase flows, a few examples will be used to illustrate this phenomenon later in this textbook.

One of the most applicable two-phase flow modeling approaches for biofluid mechanics scenarios is the dispersed particle flow, in which each fluid is analyzed separately but the fluids interact over the boundary surface(s). This type of analysis can be applied to blood flow and airflow into/throughout the lungs if particulate matter within the air is considered. Under these scenarios, the following definitions are critical to be able to quantify the flow conditions. The number of particles per unit volume is necessary to determine the density of the particles and which fluid should be considered the continuous phase and which the dispersed phase. The density of the dispersed phase can be represented as

$$n = \frac{\delta N}{\delta V} \quad (2.41)$$

where δN is the number of particles in a δV volume of interest. This density is limited by a specific value for the flow conditions in which the continuous phase can no longer be

considered as continuous. Using similar definitions, we can define the area that the particles occupy versus the area that the continuous phase occupies. The following relationships apply

$$\begin{aligned} A_p &= \frac{\delta V_p}{\delta V} \\ A_c &= \frac{\delta V_c}{\delta V} \\ A_p + A_c &= 1 \end{aligned} \quad (2.42)$$

where the subscript p denotes the particle phase and the subscript c denotes the continuous phase. Two other important definitions can be used to define the overall density (or other fluid parameter) of the two-phase flow and the loading ratio of the continuous phase and the particulate phase. In defining the overall density (and this would apply to any other fluid parameter), we make use of a simple weighted average formulation, which does not take into account any interactions that may occur between the phases. In this case the overall density can be defined as

$$\rho_t = A_p \rho_p + A_c \rho_c \quad (2.43)$$

and the mass loading ration can be defined as

$$l_r = \frac{\dot{m}_p}{\dot{m}_c} \quad (2.44)$$

where $\dot{m}$ is the mass flow rate of a particular phase. Assuming that the particle density is high enough that collisions occur between particles, the time between collisions must be known, because momentum and energy can be transferred during collisions. Without deriving all of the governing equations, it is important to highlight the momentum response time of particles, which is dependent on the fluid velocity and the particle velocity. This response time dictates how quickly changes in the fluid velocity will induce changes in the particle velocity. If we assume low Reynolds flow, we can obtain the following relationship for the momentum response time of the fluid particles

$$t_m = \frac{\rho_p d_p^2}{18\mu} \quad (2.45)$$

where d represents the particle diameter and μ represents the continuous phase viscosity. As briefly highlighted previously, the two different phases must be coupled in some manner to solve the two-phase flow scenario. Two major cases are currently under investigation in the literature. The first is when the particle density is relatively dilute compared with the total volume of the fluid. In this scenario, one would assume that the collision time between particles is negligible and that no momentum is exchanged during these infrequent collisions. The flow around each particle (if the continuous fluid and the particle have different velocities) or the flow of the particles within the fluid can be analyzed in discrete regions. However, in the cases in which the particle density is so large that collisions occur frequently,

momentum transfer between particles and the response time to momentum shifts becomes very important. Under these conditions, it is more likely that the entire flow field would be analyzed because the collision frequency would be so significant that the particles typically would not have time to respond to changes in continuous fluid momentum.

There has been a recent significant effort into determining the governing equations and developing simplified governing equations for two-phase flows. However, it has been somewhat difficult, since under most two-phase flow conditions, the particle density is not sparse enough to ensure that no collisions occur and is not dense enough to ensure that the momentum response time is smaller than the collision frequency. Under these “normal” conditions, the fluid behavior is much harder to predict and it appears to be a function of the fluid(s)/phase(s) involved.

2.10 Changes in the fundamental relationships on the microscale*

In the previous sections of this chapter, many relationships between various fluid mechanics parameters were described. These relationships still hold within the microcirculation; however, some of the parameters become more critical and can govern the blood flow throughout the vascular beds, more so than in the macrovasculature. Within the microcirculation, the viscosity of blood must be described by an apparent viscosity (η). This is because blood is no longer a homogenous fluid (or assumed to be homogeneous) and Newtonian flow rarely occurs within the microcirculation. In the microcirculation, the blood vessel diameter approaches the size of red blood cells (approximately $8\ \mu\text{m}$), and this causes a redistribution of the cells and the plasma components into distinct regimes. It is possible and likely to have a plasma-only region followed by a cellular region (with negligible plasma) within the capillary, and, therefore, different viscosities are associated with these two distinct phases (Fig. 2.22). Additionally, it is unlikely that the cellular regions will be composed of the same number of cells, and therefore, each cellular region may have its own distinct fluid parameters. The apparent viscosity would represent the overall viscosity of these distinct regions. It is not an average, or a weighted average, of these components, but a best estimate of the viscosity.

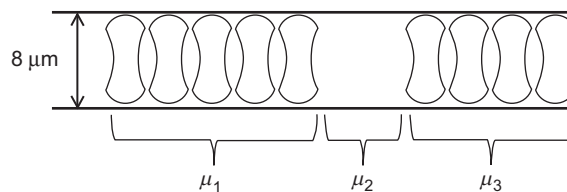


FIG. 2.22 The apparent viscosity within the microcirculation would represent the viscosity of the individual fluid and cell regions, which may have different nominal values for viscosity. The apparent viscosity could be considered a weighted average of these different viscosities but is realistically just an estimated value. Under most conditions, the apparent viscosity is not the same as the bulk viscosity.

*This section is considered advanced and can be skipped without a loss of continuity.

As shown in [Eq. \(2.1\)](#), conservation of mass within the microcirculation must now include the movement of fluid out of the blood vessel (one cannot define the system of interest as only the blood vessel). In the macrocirculation, we will typically consider that whatever fluid enters the inlet must leave by the outlet (unless there is an increase or decrease in volume/density of the system). In contrast, within the microcirculation, this assumption is not valid because we must include mass transfer across the blood vessel wall within the solution. Furthermore, in Chapter 3, we will develop the Navier–Stokes formula, which can be used to determine the characteristics of any flow field. In the microcirculation, this formula simplifies to the Stokes equations because the viscous effects dominate the flow, compared with the inertial effects (recall that the relationship between inertial and viscous effects make up the Reynolds number and thus flow within the microcirculation can be represented with low Reynolds flow equations). The Stokes equations will be described in detail in Parts III and IV of this textbook. It is also important to note that small changes in blood vessel diameter have large effects on the pressure and velocity distribution within the blood vessel (see [Sections 7.4 and 7.5](#)). The take-home message from this discussion is that all of the fundamental relationships described for the macrocirculation will still be accurate within the microcirculation. However, some of the critical parameters that govern flow will change, which can either simplify (Stokes flow) or complicate (fluid exchange) the problem we are describing. It is also critical to determine the appropriate value for viscosity within the microcirculation because we can no longer assume that the fluid is homogeneous and described by one viscosity value.

2.11 Fluid structure interaction*

The interaction of a flowing fluid and a deformable boundary is defined as a fluid structure interaction (FSI). As you can imagine, this should be a major consideration when solving biofluids mechanics problems. FSI examples can be found in many biological flow conditions. Deformation of the trachea and bronchi can cause changes in airflow. A narrowed airway may lead to snoring, which is a change in the vibration frequency of biological tissues. All blood vessels are flexible to some degree. The expansion and contraction of the aorta helps to continuously drive blood forward in the systemic circulation, even when the ventricles are experiencing diastole. The cardiac muscle contraction during systole can stop coronary blood flow because the coronary arteries collapse during heart muscle contraction. Proper muscular compression of leg veins is critical to return venous blood back to the heart. Disease conditions such as abdominal aortic aneurysm, coronary atherosclerosis, and venous valve dysfunction can change blood flow dynamics, which may potentially affect the functions of circulating blood cells and vascular wall endothelial cells. To mathematically describe the changes in structure (such as the trachea or a blood vessel), solid mechanics theories and modeling methods need to be used, to determine stress/strain distribution, deformation, and displacement of the structure. These types of models consider the material and mechanical properties of the structure (e.g., density, stiffness, dimension, etc.) only. The Navier–Stokes equations, which will be developed in Chapter 3, can still be used to solve for the fluid

*This section is considered advanced and can be skipped without a loss of continuity.

movement within the fluid domain. However, as the structure deforms or moves, fluid boundaries change accordingly and for every single change occurring in the structure, a new set of Navier–Stokes equations will need to be solved. These equations would need to consider new geometries and different force distributions from the vessel wall to the fluid. However, these highlighted equations can only represent the fluid movement. Thus, an FSI model couples the solid mechanics equations with the fluid mechanics equations. Results obtained from such models usually present different pressure-flow relationships as compared with solid-wall fluid models. This type of FSI modeling has been widely used to solve biomedical problems such as wave (pressure and velocity) propagation in flexible arteries or bypass grafts, wall stress calculation in various arteries, tearing and rupturing of diseased blood vessels, movement of natural or artificial heart valves, and even pressure variations in the spinal cord.

Another definition for FSI is based on the interaction of components within the fluid (e.g., particles) and the surrounding containing medium. By solving these particle–fluid interaction problems, particle transport within the fluid, air bubble movement, particle collision, droplet formation, etc., can be mathematically described. This could be helpful in solving certain biofluids problems, in which cells, especially platelets and white blood cells (e.g., these cells would be defined as the particles), can interact with each other and adhere to the cells that make up the vascular wall. Traditional numerical methods such as finite volume method and finite element method can be used to simulate particle movement and interaction with the flow. The immersed boundary method was reported to be more efficient to simulate flows with suspended particles. In this method, the outer surface of a particle could be defined as a deformable boundary, and the internal force induced by particle deformation and external forces induced by flow can be considered as body forces within the Navier–Stokes equations (see [Section 3.7](#)). However, when particles are considered, discrete phase (or multiphase) models are often used to describe phenomena such as particle movement, collision, binding, or dissociation mathematically. Note that although these methods are typically termed *particle–fluid interactions*, the “particle” has a definite mass and size with it that would potentially alter the flow field around the cell (thus we are not using the traditional definition of a particle from solid mechanics courses, in which particles have mass but no size).

In general, FSI problems are typically too complex to solve analytically, because of the complex 3D geometry change (such as blood vessels), large computational load of mesh/grid regeneration, and potential need to consider the suspending blood cells as a discrete phase. Just imagine the combined problem when the blood vessel wall is deformable, which alters the fluid flow properties, which in turn alters the deformation/movement of suspended cells. This is a very complex but very “real” scenario in physiological and pathophysiological flows. A large component of biofluids computational fluid dynamic research is currently concerned with FSI modeling (see [Section 15.2](#)). In this textbook, we will not develop the equations needed to solve these types of problems, but we will describe some of the applications associated with FSI and when it would be critical to use this analysis to accurately solve biofluids problems.

2.12 Introduction to turbulent flows and the relationship of turbulence to biological systems*

We highlighted earlier that viscous flows can be classified as either laminar or turbulent. Laminar flows are characterized by smooth, orderly flow in which no mixing exists between different lamina within the flow field. However, in some instances, this orderly flow breaks down and becomes unstable, disorderly, and fluctuating. These types of flow can no longer be described by the classic fluid mechanics formula, but instead need to be represented by a more complex statistical analysis that is continually evolving to describe the flow conditions. Turbulent flows begin to develop when the inertial forces far exceed the viscous forces. For internal flows in a smooth circular tube, flow remains laminar until the Reynolds number exceeds approximately 2000. When the Reynolds number exceeds 2000, the flow begins to transition to turbulence; however, enough viscous forces remain to impede the truly chaotic turbulent flow. Generally, although this varies with the surface properties of the tube, internal flows within a tube are considered transitional if the Reynolds number is between 2000 and 4000. True, fully developed turbulent internal flows within a circular tube can be observed when the Reynolds number exceeds 10^4 .

A number of ways exist to describe turbulent flows. We will discuss some of them for the remainder of this section; however, a more thorough discussion of these classifications can be found in some fluid mechanics textbooks. The primary classification for flows that have proceeded into the turbulent regime is time-dependent fluctuations in velocity, pressure, and temperature. Temperature fluctuations are found only if heat transfer is a component of the particular flow scenario (see Chapter 4 and [Section 8.6](#)). These fluctuations appear to be random and thus cannot be described well by mathematical formula. The random fluctuations in velocity and pressure cause mixing of fluid lamina, which is a second classification for turbulent flow. This mixing is much stronger than what is normally found because of the random molecular motions associated with the fluid. The mixing occurs in all dimensions, causing a rapid diffusion of mass, momentum, and energy throughout the fluid laminae. As a result of the mixing actions, the heat transfer and frictional forces associated with turbulent flows are significantly greater than with laminar flows, where there is negligible mixing between laminae. A third classification for turbulent flows is the presence of eddies, which are relatively small fluid sections that mix with each other. The size of eddies varies from the thickness of the shear layer (this is the layer that has significant shearing forces and is commonly discussed in non-fully developed flows and external flows but not internal flows) to the Kolmogorov length. The Kolmogorov length can be defined as

$$L_K = \left(\frac{\nu^3 \delta}{U^3} \right)^{\frac{1}{4}} \quad (2.46)$$

where ν is the kinematic viscosity of the fluid, δ is the shear layer thickness, and U is the mean inflow velocity. Finally, true turbulent flows are self-sustaining. Increased frictional forces experienced during turbulent flows, because of lamina mixing, will tend to reduce the

*This section is considered advanced and can be skipped without a loss of continuity.

random fluctuations, because extra energy would be needed to overcome these additional forces. The energy typically comes from the fluid itself, and thus this energy usage will tend to reduce the overall inertia of the fluid experiencing turbulence. Eventually, this reduces the fluid back toward lamina flows (without additionally energy input into the fluid system). A transitioning or laminar flow that generates localized turbulence will dissipate these fluctuations rather quickly. In contrast, a truly turbulent flow is maintained because new eddies are continually formed, which replace those lost by the viscous frictional dissipation described previously.

In the prior description, we have qualitatively described what can be observed during true fully developed turbulent flows. However, one of the goals of this textbook is to provide quantitative measurements for flow conditions. This is an immensely complicated situation because turbulent flows are random. Therefore, it is possible to observe and model turbulent flows but it is essentially impossible to predict turbulent flows. In the following discussion, we will highlight some of the important formulas, which can be used to describe turbulent flow characteristics. To quantitatively analyze turbulent flows, the fluid properties of interest must be subdivided into a time-averaged component and a fluctuating component. For example, it would not be possible to define a discrete function for velocity that is valid for all locations and times within the flow field. However, through experimental observations of turbulent flow, one can plot the velocity at given spatial locations, as a function of time. [Fig. 2.23](#) illustrates that the turbulence and hence the velocity vary with the location within the fluid field. [Fig. 2.23A](#) illustrates true self-sustaining turbulence that is typically found within the shear layer of an external flow (this layer is found close to the surface over which the fluid is flowing). The average speed at this particular location is 500 cm/s, but the flow velocity varies significantly about this number over time. [Fig. 2.23B](#) illustrates the fluid velocity at the boundary between the viscous flow regime and the free stream flow regime for an external turbulent flow (this layer is found to be significantly far from the surface that the fluid is flowing over). We can observe that the turbulent flow occurs for approximately 20% of the time, whereas for the remaining time the flow is largely steady (the average flow velocity was set at 500 cm/s as well for ease of understanding, but may vary from this number in a real turbulent flow scenario). The time associated with turbulent fluctuations can be quantified with an intermittency factor, which defines the percent of time that the flow is turbulent. The intermittency factor would be quantified by

$$\gamma = \frac{\text{turbulent time}}{\text{total time}} \quad (2.47)$$

Intermittency occurs because the viscous frictional force at the boundary between a free stream and the shear region may overcome the internal energy and dissipate the turbulent energy. When this occurs, the flow will appear laminar again. However, because the underlying shear region is characterized by true turbulence, that is, self-sustaining turbulence, the laminar boundary flow will sometimes become entangled with the turbulent flow. When this occurs, the flow will appear turbulent. If calculated, the intermittency factor for [Fig. 2.23A](#) would be 1, whereas for [Fig. 2.23B](#) it would be 0.2.

Turbulent flows are characterized by time-dependent fluctuations, so the fluid variables must be defined in a slightly different manner than what was introduced earlier in this

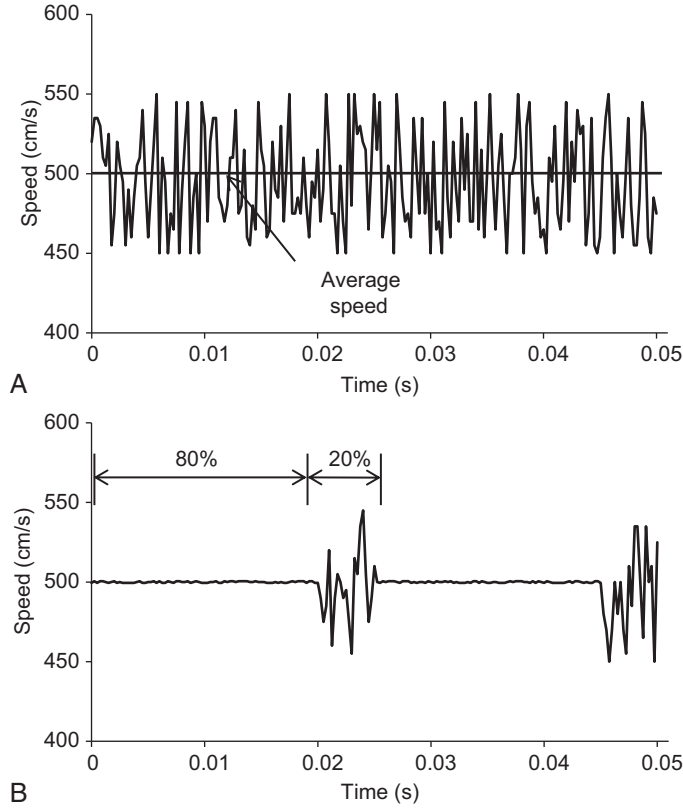


FIG. 2.23 Turbulent absolute velocity fluctuations in the shear layer (A) and at the boundary (B) of an external flow. Velocity fluctuations, in both instances, have a mean speed of 500 cm/s; however, the turbulence in the shear layer is self-sustaining, whereas the turbulence at the boundary can dissipate and reform. The reformation of the turbulence at the boundary is due to the ambient fluid becoming entrained within the turbulent fluid. However, the viscous forces can overcome this entrainment for approximately 80% of the time.

chapter. Since we have been using the example of velocity, we will continue with velocity here, but note that any of the fluid properties of interest can be used for this type of quantification and must be used to fully describe turbulent flow properties. The mean fluid velocity at a given location (x_0, y_0, z_0) in the flow field would be defined by

$$\bar{u} = \left(\frac{1}{T} \right) \int_{t_0}^{t_0+T} u dt \quad (2.48)$$

Therefore the velocity fluctuation (u') at any time at the same location (x_0, y_0, z_0) would be defined as

$$u' = u - \bar{u} \quad (2.49)$$

Unfortunately, the mean fluctuation $(\overline{u'})$ must be equal to zero over a sufficient period of time; therefore, to describe the fluctuations, we must work with the root mean square value of the fluctuation terms (the root mean square value is a common statistical method to describe varying fluctuations that summate to zero). The root mean square velocity fluctuation can be defined as

$$u'_{rms} = \sqrt{\overline{u'^2}} = \left(\frac{1}{T}\right) \int_{t_0}^{t_0+T} u'^2 dt \quad (2.50)$$

The study of turbulent flows has been and will be studied for many years in the fluid mechanics fields. The question remains: How do turbulent flows relate to biofluid mechanics scenarios? Blood flow through the circulation and airflow through the respiratory system rarely enter the turbulence regime. Reynolds numbers for blood flow in the systemic circulation rarely exceed 100, whereas true fully developed self-sustaining turbulent flows have a Reynolds number in the range of 10,000 (if we assume that the blood flows through a smooth circular tube). However, there are some conditions in which turbulent flows can develop transiently but dissipate nearly instantaneously in circulation. For instance, because of the complex geometry of the ascending aorta and the aortic arch, it is possible for random mixing to occur during the rapid jet deceleration phase associated with the end of systole. However, if this occurs, the turbulence is not fully developed and is also not self-sustaining. Thus this is not true turbulence. Additionally, it is common to find some mixing under pathological conditions; however, this would also dissipate quickly and would not be self-sustaining. Therefore, we would caution the reader that although some localized regions under very special conditions may experience turbulence, it is nearly impossible for true turbulence to develop in biological tissues. For completeness, we will discuss some of the mathematical formulas that can be used to describe turbulence in [Section 6.11](#); however, we will not make use of these formulas in any of the example problems in the text. The reader can skip the turbulence portion of [Section 6.11](#) without any loss of continuity to the textbook.

Summary

- 2.1. Fluid mechanics is the study of fluids at rest and in motion. A fluid is defined as a material that continuously deforms under a constant load.
- 2.2. Five relationships are useful in many fluid mechanics problems: kinematic, stresses, conservation, regulating, and constitutive. Five laws also govern most fluid flows

Conservation of Mass: $m_{system} = m_{in} - m_{out} - \rho \frac{d(\rho V)}{dt}$

Conservation of Linear Momentum: $\vec{F} = \frac{d(m\vec{v})}{dt}$

The First Law of Thermodynamics: $\delta U = \delta Q - \delta w$

The Second Law of Thermodynamics: $\frac{dS}{dt} \geq 0$

Conservation of Angular Momentum: $\vec{L} = \vec{r} \times \vec{p}$

- 2.3. The analysis of fluid mechanics problems can be significantly altered depending on the choice of the system of interest and the volume of interest. Mass that is not originally within the system of interest cannot enter the volume of interest during problem solution.
- 2.4. By assuming a fluid is a continuum, we can suppose that there are no inhomogeneities within the smallest division of the fluid that is made. Properties such as viscosity, density, and temperature, among others, must be constant throughout the entire fluid and are independent of the divisions made.

- 2.5. It is useful to use the stress tensor $\sigma = \begin{bmatrix} \sigma_{xx} & \tau_{xy} & \tau_{xz} \\ \tau_{yx} & \sigma_{yy} & \tau_{yz} \\ \tau_{zx} & \tau_{zy} & \sigma_{zz} \end{bmatrix}$ to define the various

stresses on fluid elements. Normal stresses are defined as $\sigma_n = \lim_{\delta \vec{A}_n \rightarrow 0} \frac{\delta \vec{F}_n}{\delta \vec{A}_n}$, whereas

shear stresses are defined as $\tau_n = \lim_{\delta \vec{A}_n \rightarrow 0} \frac{\delta \vec{F}_t}{\delta \vec{A}_n}$. Only six of these stresses are independent of each other to conserve momentum throughout the fluid element. A useful

relationship for the hydrostatic pressure as a function of the normal stresses is

$$p_{\text{hydrostatic}} = -\frac{1}{3}(\sigma_{xx} + \sigma_{yy} + \sigma_{zz}).$$

- 2.6. A fluid can undergo four general motions. These are useful in defining the position of fluid elements, the velocity, and the acceleration of the fluid.

$$\vec{x}(t) = u_x(t)\vec{i} + u_y(t)\vec{j} + u_z(t)\vec{k}$$

$$\vec{v}(t) = \frac{d\vec{x}(t)}{dt} = \frac{du_x(t)}{dt}\vec{i} + \frac{du_y(t)}{dt}\vec{j} + \frac{du_z(t)}{dt}\vec{k} = v_x(t)\vec{i} + v_y(t)\vec{j} + v_z(t)\vec{k}$$

$$\begin{aligned} \vec{a}(t) &= \frac{d\vec{v}(t)}{dt} = \frac{d^2\vec{x}(t)}{dt^2} = \frac{dv_x(t)}{dt}\vec{i} + \frac{dv_y(t)}{dt}\vec{j} + \frac{dv_z(t)}{dt}\vec{k} \\ &= \frac{d^2u_x(t)}{dt^2}\vec{i} + \frac{d^2u_y(t)}{dt^2}\vec{j} + \frac{d^2u_z(t)}{dt^2}\vec{k} = a_x(t)\vec{i} + a_y(t)\vec{j} + a_z(t)\vec{k} \text{ or} \end{aligned}$$

$$\vec{a} = \frac{d\vec{v}}{dt} = \frac{\partial \vec{v}}{\partial t} \frac{dt}{dt} + \frac{\partial \vec{v}}{\partial x} \frac{dx}{dt} + \frac{\partial \vec{v}}{\partial y} \frac{dy}{dt} + \frac{\partial \vec{v}}{\partial z} \frac{dz}{dt} = \frac{\partial \vec{v}}{\partial t} + v_x \frac{\partial \vec{v}}{\partial x} + v_y \frac{\partial \vec{v}}{\partial y} + v_z \frac{\partial \vec{v}}{\partial z}$$

Temporal and spatial driving forces can arise within the vascular system and appear in the substantial derivative equation for acceleration. The angular velocity of a fluid can be defined as

$$\vec{\omega} = \frac{1}{2} \left[\left(\frac{\partial v_z}{\partial y} - \frac{\partial v_y}{\partial z} \right) \vec{i} + \left(\frac{\partial v_x}{\partial z} - \frac{\partial v_z}{\partial x} \right) \vec{j} + \left(\frac{\partial v_y}{\partial x} - \frac{\partial v_x}{\partial y} \right) \vec{k} \right] = \frac{1}{2} \text{curl } \vec{v}$$

The deformation tensor takes the form of

$$\mathbf{d} = \frac{1}{2} \begin{bmatrix} 2\frac{\partial v_x}{\partial x} & \frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} & \frac{\partial v_z}{\partial x} + \frac{\partial v_x}{\partial z} \\ \frac{\partial v_y}{\partial x} + \frac{\partial v_x}{\partial y} & 2\frac{\partial v_y}{\partial y} & \frac{\partial v_z}{\partial y} + \frac{\partial v_y}{\partial z} \\ \frac{\partial v_z}{\partial x} + \frac{\partial v_x}{\partial z} & \frac{\partial v_z}{\partial y} + \frac{\partial v_y}{\partial z} & 2\frac{\partial v_z}{\partial z} \end{bmatrix}$$

- 2.7. Viscosity is a quantity that relates the shear rate of a fluid to the shear stress. This relationship takes the general form of $\tau_{xy} = \mu \left(\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right)$.
- 2.8. The definition of a fluid as Newtonian depends on whether the viscosity is constant at various shear rates. Newtonian fluids are classified with constant viscosities for a range of shear rates, whereas non-Newtonian fluids have a nonconstant viscosity. For most biological applications, we can assume that the fluid behaves as a Newtonian fluid. An inviscid fluid has no viscosity, and this is useful in some formula derivations or simple assumptions of fluid flow.
- 2.9. A two-phase flow consists of a fluid in both a gas and liquid phase or two fluids (with different viscosities) within the same flow conditions. Blood is a two-phase flow because the cellular matter may have a different viscosity than the plasma component (blood also can be considered a multiphase fluid). To analyze two-phase flow conditions, we must consider some form of coupling between the different phases and this is normally a function of the particle seeding density within the continuous fluid.
- 2.10. Many fundamental fluid relationships change on the microscale. One of the most applicable for biofluids problems is the viscosity, which is described by an apparent viscosity within the microcirculation.
- 2.11. Fluid structure interaction modeling is important if the fluid can affect and cause a deformation on the flow boundary. This is important in the cardiovascular system, in which the blood vessel wall is deformable and cellular matter can interact with the wall.
- 2.12. Turbulent flows are qualitatively described by time-varying, random fluctuations that cause mixing of the fluid lamina. Turbulent flows must be self-sustaining but can dissipate along the boundary between the turbulent flows and the nonturbulent flows. Turbulent flows must be characterized by time-dependent fluctuations

$$\bar{u} = \left(\frac{1}{T} \right) \int_{t_0}^{t_0+T} u dt$$

$$u' = u - \bar{u}$$

Additionally, statistical methods are needed to qualitatively describe the flow

$$u'_{rms} = \sqrt{\overline{u'^2}} = \left(\frac{1}{T}\right) \int_{t_0}^{t_0+T} u'^2 dt$$

In general, flows in biological systems never proceed into the turbulent regime, however, under very special circumstances, in very specific locations, turbulent flows may arise but they dissipate very quickly.

Homework problems

- 2.1. For a particle with a velocity distribution of $v_x = 5x$, $v_y = -5y$, $v_z = 0$, determine the particle's acceleration vector. Also, determine whether this velocity profile has a local and/or convective acceleration.
- 2.2. Consider a velocity vector $\vec{v} = (xt^2 - y)\vec{i} + (xt - y^2)\vec{j}$. (i) Determine whether this flow is steady (*hint*: no changes with time). (ii) Determine whether this is an incompressible flow (*hint*: check if $\nabla \cdot \vec{v} = 0$).
- 2.3. Given the velocity vector $\vec{v} = (2x - y)\vec{i} + (x - 2y)\vec{j}$, determine whether it is irrotational.
- 2.4. The velocity vector for a steady incompressible flow in the xy plane is given by $\vec{v} = \frac{4}{x}\vec{i} + \frac{4y}{x^2}\vec{j}$, where the coordinates are measured in centimeters. Determine the time it takes for a particle to move from $x = 1$ cm to $x = 4$ cm for a particle that passes through the point $(x, y) = (1, 4)$.
- 2.5. Flow in a two-dimensional channel of width W has a velocity profile defined by

$$v_x(y) = k \left[\left(\frac{W}{2}\right)^2 - y^2 \right]$$

where $y = 0$ is located at the center of the channel. Sketch the velocity distribution (with $k = 1$ and $W = 10$) and find the shear stress/unit width of the channel at the wall.

- 2.6. A velocity field is given by $\vec{v}(x, y, z) = 20xy\vec{i} - 10y^2\vec{j}$. Calculate the acceleration, the angular velocity, and the vorticity vector at the point $(-1, 1, 1)$, where the units of the velocity equation are millimeters per second.
- 2.7. Considering one-dimensional fluid (density, ρ ; viscosity, μ) flow in a tube with an inlet pressure of p_i and outlet pressure of p_o and tube radius of r and length l , the density of the fluid can be represented as ρ . Express the wall shear stress as a function of these variables (*hint*: balance Newton's second law of motion).
- 2.8. Data obtained from one experiment are presented in [Table 2.3](#). Plot the data and determine whether the fluid is pseudoplastic, Newtonian, or dilatant. Approximate the viscosity (or the apparent viscosity for this fluid).

Continued

Homework problems *(cont'd)*

TABLE 2.3 Shear stress versus shear rate data for Homework Problem 2.8.

Shear stress (dyne/cm ²)	5	9	23	48	95
Shear rate (s ⁻¹)	0.1	1	10	100	1000

- 2.9. Consider a red blood cell that originates from the origin of our xy -coordinate system. The velocity of the fluid is unsteady and is described by

$$v = \begin{cases} v_x = \frac{1cm}{s} & v_y = \frac{0.5cm}{s} & 0s \leq t \leq 2s \\ v_x = \frac{0.25cm}{s} & v_y = \frac{1cm}{s} & 2s < t \leq 5s \end{cases}$$

Plot the location of this red blood cell at time 0, 1, 2, 3, 4, and 5 s (enters from the origin at time 0). Also plot the location of the red blood cells that enter (from the origin) at time 1, 2, 3, and 4 s.

- 2.10. A flow is described by the velocity field

$$v = \left(\frac{y}{s}\right) \vec{i} + 0.75 \frac{m}{s^2} t \vec{j}$$

At $t = 2$ s, what are the coordinates of the particles that passed through the point (1,5) at $t = 0$ s. What are the coordinates of the same particle at $t = 3$ s?

- 2.11. The velocity distribution for laminar flow between two parallel plates can be represented as

$$\frac{u}{u_{max}} = 1 - \left(\frac{2y}{h}\right)^2$$

where h is the separation distance between the two flat plates and the origin is located half-way between the plates. Consider the flow of blood at 37°C ($\mu = 3.5$ cP) with maximum velocity of 25 cm/s and a separation distance of 10 mm. Calculate the force on a 0.25 m² section of the lower plate.

- 2.12 A biofluid is flowing down an inclined plane. The velocity profile of this fluid can be described by

$$u = \frac{\rho g}{\mu} \left(hy - \frac{y^2}{2} \right) \sin \theta$$

if the coordinate axis is aligned with the inclined plane. Determine a function for the shear stress along this fluid. Plot the velocity profile and shear stress profile, if the fluid density is 900 kg/m³ and viscosity is 2.8 cP. The fluid thickness h is equal to 10 mm and the plane is inclined at an angle of 40 degrees.

Homework problems (cont'd)

- 2.13.** A block with mass M_1 is in contact with a thin fluid layer of thickness h . The block is connected to a second mass M_2 via a cable that goes over an ideal pulley. Determine a relationship for the velocity of the block when the second mass is released from rest (Fig. 2.24).

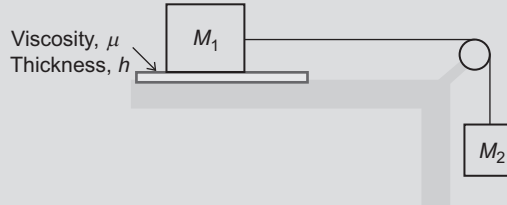


FIG. 2.24 Figure for Homework Problem 2.13.

- 2.14.** For the following velocity field:

$$\mathbf{v} = (xt^2 + 2y - z^2)\vec{i} + (xt - 2yt)\vec{j} + (3xt + z)\vec{k}$$

calculate the shear rate tensor, the vorticity, the hydrostatic pressure (use a viscosity of μ), and the acceleration of the fluid.

- 2.15.** A velocity field is given by

$$\mathbf{v} = 0.2s^{-1}x\vec{i} - 0.35(mm s)^{-1}y^2\vec{j}$$

where x and y are given in millimeters. Determine the velocity of a particle at point (2,4) and the position of the particle at $t = 6$ s of the particle that is located at (2,4) at $t = 0$ s.

- 2.16.** A fluid is placed in the area between two parallel plates. The upper plate is movable and connected to a weight by a cable. Calculate the velocity of the plate for (i) the fluid between the plates is water, (ii) the fluid between the plates is blood (assumed to have no yield stress), and (iii) the fluid between the plates is blood with a yield stress of 50 mPa. For all cases take the mass to be 10 g, the height between the plates to be 10 mm, and the contact area to be 0.5 m^2 (Fig. 2.25).

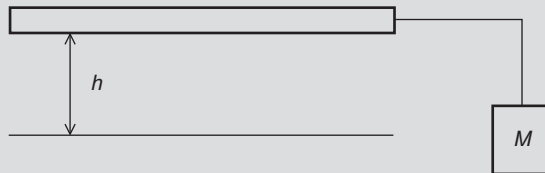


FIG. 2.25 Figure for Homework Problem 2.16.

- 2.17.** What type of fluid can be classified by the following shear stress–strain rate data? Plot the data and classify. Determine the viscosity of the fluid (Table 2.4).

Continued

Homework problems *(cont'd)*

TABLE 2.4 Shear Stress versus shear rate data for Homework Problem 2.17.

Shear stress (N/m^2)	0.4	0.82	2.50	5.44	8.80
Shear rate (s^{-1})	0	10	50	120	200

- 2.18.** A plate is moving upward through a channel filled with water, as shown in Fig. 2.26. The plate velocity is 10 cm/s, and the spacing is 50 mm on each side of the plate. The force required to move the plate is equal to 5 N. Determine the surface area of the plate.

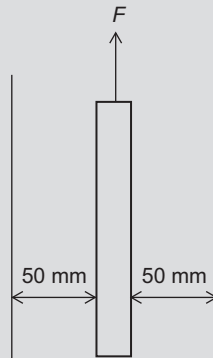


FIG. 2.26 Figure for Homework Problems 2.18 and 2.19.

- 2.19.** Use the same figure for Problem 2.18, except that the distance on the right-hand side is increased to 100 mm. The fluid on the right side is blood ($\mu = 3.5 \text{ cP}$). Determine the viscosity of the fluid on the left side. The plate is moving with a constant velocity.
- 2.20.** A conical shaft is turning within the conical bearing as shown in Fig. 2.27. The gap between the shaft and the bearing is filled with a fluid with a viscosity of 0.05 Ns/m^2 . Determine a symbolic expression for the wall shear stress that is acting on the shaft and determine the wall shear stress with using the values given in the figure.

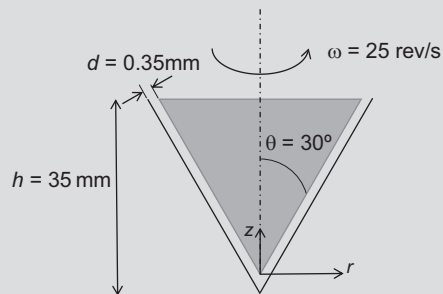


FIG. 2.27 Figure for Homework Problem 2.20.

Homework problems (cont'd)

- 2.21.** Two data points on the rheological diagram of a biofluid are provided. Determine the consistency index and the flow behavior index and the strain rate if the shear stress is increased to 3 dynes/cm². Assume that this is a two-dimensional flow.

$$\frac{dV}{dy} = 15 \frac{\text{rad}}{\text{s}}, \tau = 0.868 \text{ dynes/cm}^2$$

$$\frac{dV}{dy} = 30 \frac{\text{rad}}{\text{s}}, \tau = 0.355 \text{ dynes/cm}^2$$

- 2.22.** Given that the volumetric flow rate for a fluid within a circular cross-section tube can be represented by

$$Q = \frac{\pi r^4 \Delta P}{8\mu L}$$

where r is the tube radius, μ is the fluid viscosity, P is the pressure drop across the tube, and L is the tube length, calculate the pressure drop across a tube of length 1 m and diameter of 23 mm. The fluid is blood ($\mu = 3.5 \text{ cP}$) and has a volumetric flow rate of 4.5 L/min. Assuming the same conditions, what would the required pressure drop be for water ($\mu = 1 \text{ cP}$) and chocolate syrup ($\mu = 15,000 \text{ cP}$).

- 2.23.** At a stenosis, the energy in the flowing fluid is skewed from potential energy to kinetic energy. Why? What effect may this have on locations downstream of the stenosis.
- 2.24.** The no-slip boundary wall condition for Newtonian fluids has been well established. No known exceptions to this condition exist for Newtonian fluids. Blood is a non-Newtonian fluid. What should the boundary condition for blood and a solid surface be.

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Conservation laws

LEARNING OUTCOMES

- Develop equations that govern pressure variation within a static fluid
- Determine the buoyancy forces that act on objects immersed within a fluid
- Develop a general relationship for the time rate of change of any fluid system property
- Apply the generalized formula for the time rate of change of a system property to the conservation of mass, conservation of momentum, and conservation of energy of a fluid system
- Describe the conservation of momentum principle with acceleration
- Derive and apply the Navier–Stokes equations
- Explain the Bernoulli principle and the assumptions inherent in this principle

3.1 Fluid statics equations

Fluid statics problems deal with fluids that either are at rest or are only undergoing constant velocity rigid body motions. This implies that the fluid is subjected to normal stresses only because by definition a fluid will continually deform under the application of a shear stress. Recall that shear stress acting on a fluid element would induce angular deformations within the fluid (see Fig. 2.15) and therefore particular regions of the fluid element would experience some form of acceleration (either angular and/or linear). Another way to think about static fluid problems is that the relative position of all fluid elements remains the same after loading and the relative position of all components that make the complete fluid would also remain the same. Therefore each fluid element and the larger fluid as a whole would experience only pure translation or pure rotation about the same axis of rotation. These types of problems fall under the class of hydrostatics, and the analysis methods for these problems are typically simpler than for fluid dynamics problems. Newton's second law of motion, simplified to the sum of the forces acting on the fluid is equal to zero

($\sum \vec{F} = 0$), is the primary governing equation that is used to solve these types of problems (we assume that there are no changes in mass/density and that the fluid element does not experience any form of an acceleration).

Although fluid statics problems make the assumption that the fluid elements are not undergoing deformation, it is still possible to gain important information from this type of “simplified” analysis of fluids that are actually undergoing some form of dynamic motion. Normal forces can be transmitted by fluids, and these forces can then be applied to devices within a biological system. For instance, by inserting a catheter into a patient, there will be some hydrostatic forces that the blood transmits onto the device. While the catheter is moved throughout the cardiovascular system, the hydrostatic forces change, and it may be critical to determine these forces or the total force acting on the device. Under this condition, it is typical that the pressure forces are more critical than the shearing forces of the fluid on the catheter. Imagine undergoing balloon angioplasty (in which a small balloon attached to the end of a catheter is inflated within the cardiovascular system) and not knowing the hydrostatic pressure that is being applied to the end of the catheter from the fluid. If the physician does not overcome this pressure, the balloon will not inflate and the procedure will not be completed to remedy the pathologic condition being experienced by the patient. Therefore, it is critical to understand these principles (among others) to conduct balloon angioplasty. Hydrostatic pressure arises because of the weight of the fluid above the section of interest and the surrounding atmospheric pressure or other pressure that is induced by the containing surface (e.g., the elastic recoil of the blood vessels can locally increase the hydrostatic pressure). Therefore, the hydrostatic pressure is different at various locations throughout the body. When a person is standing upright, the hydrostatic pressure at the top of the head is lower than that at the heart, and the hydrostatic pressure at the feet is greater than that of the heart. One way to remember this principle is when you have been standing in the same position for a long time, without moving significantly, blood will tend to pool in your lower extremities. Typically, this would eventually lead to a “cramping” feeling followed by a “pins and needles” feeling when blood begins to move again through the vascular system. The reason that the blood pools in your lower limbs is that the blood in the legs cannot overcome the hydrostatic pressure to return back to the heart. In addition, after sleeping, if you stand up too fast, the heart cannot overcome the new hydrostatic pressure difference and you may get light headed (while sleeping supine the hydrostatic pressure is effectively the same at the heart, head, and toes). When we discuss venous return and heart mechanics, we will show how the body can compensate for rapid changes in pressure difference. Another way to recall this phenomenon is that after donating blood, the nurse will typically tell you to raise your arm. Why is this? This increases the hydrostatic pressure difference between your heart and your arm and will minimize the blood loss while a clot is forming at the venipuncture location. In this case, blood would have a hard time overcoming the new hydrostatic pressure gradient to enter the arterial circulation of the arm and the blood within the venous circulation of the arm will return quickly back to the heart.

As stated in the previous chapter, the primary quantity of interest for fluid statics problems is the pressure field throughout the fluid. Here we will develop the equations used in fluid statics analysis. To accomplish this, Newton’s second law of motion will be applied to a differential element of fluid (Fig. 3.1). Recall that Newton’s second law of motion states

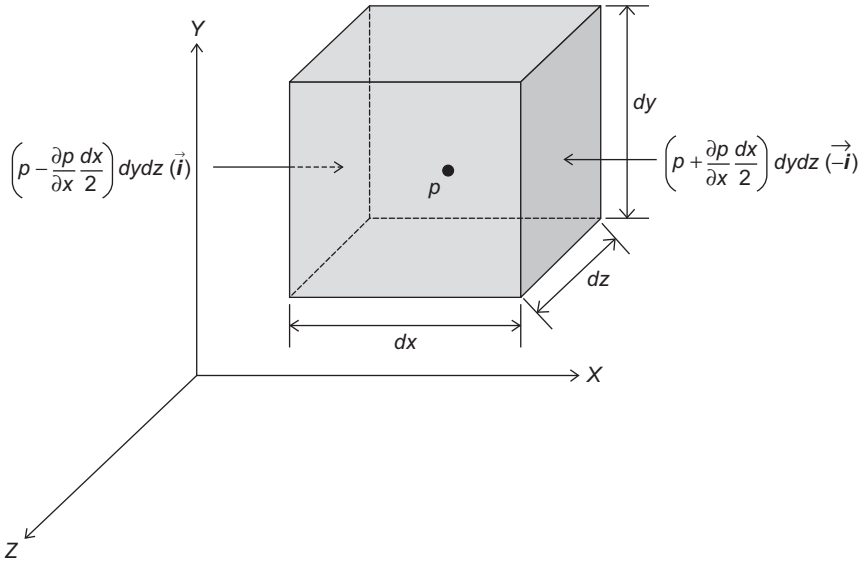


FIG. 3.1 X-direction pressure forces that act on a differential fluid element. Similar pressure forces can be derived for the other Cartesian directions.

that the sum of all of the forces acting on an element (body forces and surface forces) is equal to the element's mass multiplied by the element's acceleration (if we can assume that the density is a constant). We will assume here that the only body force acting on the element is due to gravity. In most biofluid mechanics problems in this textbook, this will be the only body force that is considered. However, be cautioned that other body forces can be applied by a magnetic field (blood flow of a patient undergoing magnetic resonance imaging) or by an electric field. Although these may be less common body forces, they may need to be considered for your particular problem. The mass of the differential element, dm , is equal to the fluid density multiplied by the differential volume of the element ($dm = \rho dV = \rho dx dy dz$, in Cartesian coordinates; for other coordinate systems the analysis is similar; note that $V \equiv \text{volume}$ and $v \equiv \text{velocity}$, for this textbook). Therefore, the force resulting from gravity becomes

$$d\vec{F}_b = \vec{g} dm = \vec{g} \rho dx dy dz \quad (3.1)$$

where $\vec{g}$ is the gravitational constant.

Since the fluid is under static flow conditions, there are no shear forces applied to the fluid element. Therefore, the only surface force acting on the element is the pressure force. As we will see, pressure varies with position throughout the entire fluid, but the total pressure acting on a differential element can be symbolically represented with the summation of the pressure acting on each face of the differential element. Let us define the pressure at the center of the differential element to be p (see Fig. 3.1). Using this definition, the pressure acting on each face of the differential element would be equal to p plus or minus the particular directional pressure gradient multiplied by the distance between the center of the element and the

face. For instance, in the x -direction, the pressure on the right face of the differential element in the current orientation, shown in Fig. 3.1, would be

$$p + \frac{\partial p}{\partial x} \frac{dx}{2}$$

This pressure will act in the negative x -direction. In contrast, the pressure on the left face would be

$$p - \frac{\partial p}{\partial x} \frac{dx}{2}$$

This pressure will act in the positive x -direction (the pressure gradient is defined as $\frac{\partial p}{\partial x}$ in the x -direction, and the total length of the element in the x -direction is dx). Remember that pressure has the same units as stress. To determine the force that the pressure exerts on each face, one must multiply the stress by the area over which it acts (again, for ease of viewing, only the two forces that act in the x -direction are shown in Fig. 3.1). For the case of the x -direction pressure values, the area over which this pressure acts can be represented as $dydz$. In Fig. 3.1, the pressure force is also multiplied by a unit vector to indicate the direction of the force. Remember, for pressure there is a sign convention; a positive pressure is a compressive normal stress, and these are the forces that are shown on the differential element in Fig. 3.1. For force balance, the illustrated differential element would produce an equal and opposite force on the adjacent fluid elements (or surfaces).

The four remaining pressure forces (e.g., those that act in the y - and z -directions) can be obtained through a similar analysis method. By summing all of these six forces, the total surface force acting on the fluid element can be obtained. It would be represented as

$$\begin{aligned} d\vec{F}_s = & \left(p - \frac{\partial p}{\partial x} \frac{dx}{2} \right) (dydz) (\vec{i}) + \left(p + \frac{\partial p}{\partial x} \frac{dx}{2} \right) (dydz) (-\vec{i}) + \left(p - \frac{\partial p}{\partial y} \frac{dy}{2} \right) (dxdz) (\vec{j}) \\ & + \left(p + \frac{\partial p}{\partial y} \frac{dy}{2} \right) (dxdz) (-\vec{j}) + \left(p - \frac{\partial p}{\partial z} \frac{dz}{2} \right) (dxdy) (\vec{k}) + \left(p + \frac{\partial p}{\partial z} \frac{dz}{2} \right) (dxdy) (-\vec{k}) \end{aligned} \quad (3.2)$$

Combining terms in the previous equations yields

$$\begin{aligned} d\vec{F}_s = & \left(p - \frac{\partial p}{\partial x} \frac{dx}{2} \right) (dydz) (\vec{i}) + \left(-p - \frac{\partial p}{\partial x} \frac{dx}{2} \right) (dydz) (\vec{i}) + \left(p - \frac{\partial p}{\partial y} \frac{dy}{2} \right) (dxdz) (\vec{j}) \\ & + \left(-p - \frac{\partial p}{\partial y} \frac{dy}{2} \right) (dxdz) (\vec{j}) + \left(p - \frac{\partial p}{\partial z} \frac{dz}{2} \right) (dxdy) (\vec{k}) + \left(-p - \frac{\partial p}{\partial z} \frac{dz}{2} \right) (dxdy) (\vec{k}) \\ = & -2 \left(\frac{\partial p}{\partial x} \frac{dx}{2} \right) (dydz) (\vec{i}) - 2 \left(\frac{\partial p}{\partial y} \frac{dy}{2} \right) (dxdz) (\vec{j}) - 2 \left(\frac{\partial p}{\partial z} \frac{dz}{2} \right) (dxdy) (\vec{k}) \\ = & - \left(\frac{\partial p}{\partial x} \vec{i} + \frac{\partial p}{\partial y} \vec{j} + \frac{\partial p}{\partial z} \vec{k} \right) dxdydz \end{aligned} \quad (3.3)$$

From a previous class in calculus, you may recall that the final term in the parentheses (right-hand side of the equation) of Eq. (3.3) is the gradient (denoted as grad or ∇) of the pressure force in Cartesian coordinates. Therefore, the total surface forces acting on a differential fluid element can be mathematically represented as

$$d\vec{F}_s = -\nabla \vec{p} dxdydz \quad (3.4)$$

Returning to Newton's second law, the sum of the forces acting on a differential fluid element can then be represented as

$$d\vec{F} = d\vec{F}_b + d\vec{F}_s = \vec{g} \rho dxdydz - \nabla \vec{p} dxdydz = (\vec{g} \rho - \nabla \vec{p}) dxdydz \quad (3.5)$$

If one divides the summation of the force acting on a differential element of fluid by the unit volume (Eq. (3.5)), one gets a relationship that holds for fluid particles and is in terms of density.

$$\frac{d\vec{F}}{dxdydz} = \frac{d\vec{F}}{dV} = \vec{g} \rho - \nabla \vec{p} \quad (3.6)$$

For a static fluid flow case ($\vec{a} = 0$), Newton's second law of motion for a fluid element with a finite volume simplifies to

$$\frac{d\vec{F}}{dV} = \vec{g} \rho - \nabla \vec{p} = \rho \vec{a} = 0 \quad (3.7)$$

where density multiplied by the differential volume has been substituted for the differential mass, because the fluid density is typically known compared with a differential mass. The significance of this equation is that the gravitational force must be balanced by the pressure force at each individual point within the fluid. Remember that this is true only if the fluid does not experience acceleration and the only body force is the gravitational acceleration (one would need to check if these assumptions are valid for your particular conditions). In terms of the vector component equations, which must independently summate to zero in each direction, for fluid static problems, Eq. (3.7) can be represented as

$$\begin{aligned} -\frac{\partial p}{\partial x} + \rho g_x &= 0 \\ -\frac{\partial p}{\partial y} + \rho g_y &= 0 \\ -\frac{\partial p}{\partial z} + \rho g_z &= 0 \end{aligned} \quad (3.8)$$

It is conventional to choose a coordinate system in a particular way, so that the gravitational force acts in only one direction. For the sake of a convention, we will typically align the gravitational force with the z -direction of the Cartesian coordinate system (although it is possible to align this with another direction or in multiple directions). With this definition, Eq. (3.8) simplifies to

$$\begin{aligned}\frac{\partial p}{\partial x} &= 0 \\ \frac{\partial p}{\partial y} &= 0 \\ \frac{\partial p}{\partial z} &= -\rho g_z = \rho g\end{aligned}\tag{3.9}$$

because $gx = gy = 0$ and $gz = -g$. Using these assumptions, the pressure is only a function of one coordinate variable (z) and is therefore independent of the other two coordinate variables (x and y). Note that pressure can act in the x/y directions; however, the pressure must be constant in those directions. The assumptions made in this analysis are that the fluid is under static flow conditions (has no acceleration term), the only body force is the gravitational force, and that gravity is only aligned with the z -axis (using the Cartesian coordinate system). Combined, this allows the use of a total derivative instead of a partial derivative in Eq. (3.9). Therefore,

$$\frac{dp}{dz} = -\rho g_z\tag{3.10}$$

Eq. (3.10) relates the pressure within a fluid to the vertical height of the fluid; if the assumptions made are valid or are within a reasonable estimate of the flow conditions. Eq. (3.10) can be integrated to calculate the pressure distribution throughout a static fluid if the correct boundary conditions are applied. In general, you would need to know if the fluid's density or gravity varies with changes in vertical distances.

Example 3.1

Calculate the static fluid pressure in the cranium at the end of systole and at the end of diastole. Assume that the cranium is 30 cm above the aortic valve and that the pressure at the end of systole and end of diastole is 120 mmHg and 80 mmHg, respectively, at the aortic valve (Fig. 3.2). The density of blood is 1050 kg/m^3 and can be assumed to be constant.

Solution

$$\begin{aligned}dp &= -\rho g_z dz \\ \int_{p_0}^{p_1} dp &= -\rho g_z \int_{z_0}^{z_1} dz\end{aligned}$$

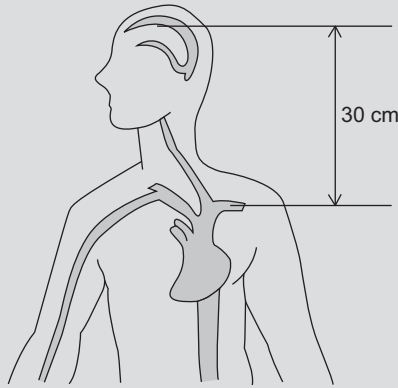
Example 3.1 (cont'd)

FIG. 3.2 Difference in fluid static pressure between the aortic valve and the cranium based on height.

Because the fluid density and gravity is not a function of height, these variables can be removed from the integral.

$$\begin{aligned} p|_{p_0}^{p_1} &= -\rho g_z z|_{z_0}^{z_1} \\ p_1 - p_0 &= -\rho g_z (z_1 - z_0) \\ p_1 &= p_0 - \rho g_z (z_1 - z_0) \end{aligned}$$

End of systole

$$\begin{aligned} p_1 &= p_0 - \rho g_z (z_1 - z_0) \\ p_1 &= 120 \text{ mmHg} - \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(9.81 \frac{\text{m}}{\text{s}^2}\right) (30 \text{ cm} - 0 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}}\right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}}\right) \\ p_1 &= 96.83 \text{ mmHg} \end{aligned}$$

End of diastole

$$\begin{aligned} p_1 &= p_0 - \rho g_z (z_1 - z_0) \\ p_1 &= 80 \text{ mmHg} - \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(9.81 \frac{\text{m}}{\text{s}^2}\right) (30 \text{ cm} - 0 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}}\right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}}\right) \\ p_1 &= 56.83 \text{ mmHg} \end{aligned}$$

Notice that in Example 3.1, the absolute change in pressure remains the same at the end of systole and at the end of diastole ($\Delta p = -23.17 \text{ mmHg}$). This change in pressure is constant because we assumed that the vertical height difference and the blood density did not change. Again, this is valid only if the three assumptions we made to derive this formula (as shown in the example problem) can be applied to the particular example.

Example 3.1 brings us to an important distinction in fluid statics situations. All pressures must be referenced to a specific reference value. For instance, we may have chosen to call the pressure at the aortic valve 0 mmHg, and this choice would make the cranium pressure

exactly -23.17 mmHg for each of the two cases in Example 3.1. This is true even when the aortic pressure is variable because the aortic pressure is our reference and is defined as 0 mmHg at all times. Two types of pressures are generally discussed in engineering. The first is the absolute pressure, and the second is the gauge pressure. Absolute pressure is referenced to a vacuum; this also would be the absolute (or exact) pressure of the system at your particular point of interest. Gauge pressure is the pressure of the system related to some other reference pressure, which is conventionally local atmospheric pressure (which is variable). Therefore, gauge pressure is actually a pressure difference and is not the actual pressure of the system. In our in-text Example 3.1, 120 mmHg and 80 mmHg are gauge pressures. This means that the actual pressure at the aortic valve would be 120 mmHg plus 1 atm (which would be equal to an absolute pressure of 880 mmHg). In this textbook, we will refer all gauge pressures to atmospheric pressure, so that

$$p_{\text{gauge}} = p_{\text{absolute}} - p_{\text{atmospheric}}$$

Eq. (3.10) describes the pressure variation in any static fluid. Changes in the pressure force are only a function of density, gravity, and the height location, assuming that the gravitational force acts only in the z -direction. In Example 3.1, we made the unstated assumption that changes in gravity are negligible. For most practical biofluid mechanics problems, the variation in the gravitation force with height is insignificant. Assuming that gravity is 9.81 m/s^2 at sea level, for every kilometer above sea level gravity reduces by approximately 0.002 m/s^2 . Therefore, when the height changes being described are on the order of meters or centimeters (which will be typical in this textbook), the change in gravity with height is somewhat negligible. This is a reasonable assumption and used in many engineering examples (e.g., it is atypical for gravity changes to be accounted for in introductory engineering mechanics courses). However, in some biofluid situations, it may not be a good assumption that the density is constant, so be careful when applying the equation that we have been discussing.

Remember our definition for incompressible fluids; the fluid density is constant under all conditions. In this situation, it would be appropriate to use Eq. (3.10), in the form shown in Example 3.1. The pressure variation in a static incompressible fluid would then become

$$p = p_0 - \rho g_z(z - z_0) \quad (3.11)$$

A useful instrument to measure pressure variations solely based on height differences is a manometer. In classical fluid mechanics examples, manometers are used extensively to determine the pressure of a fluid compared with atmospheric pressure (Fig. 3.3). Relating this to a biological example, manometers have been coupled to catheter systems to measure the intravascular pressure relative to atmospheric pressures. Even though the blood is flowing within the blood vessel, the blood that was diverted into the catheter system would not be flowing (or can be assumed to be relatively static). Importantly, it would maintain the same pressure of the adjacent flowing blood within the vascular system. These systems, however, are not very accurate when quantifying pressure because of the effects they may induce on the patient. Most likely, blood flow within the vessel would be shunted or the vessel would be ligated to insert the catheter. Therefore, the pressure being measured by the manometer system is not necessarily the exact physiological pressure, under normal conditions, but is the hydrostatic pressure under some modified conditions.

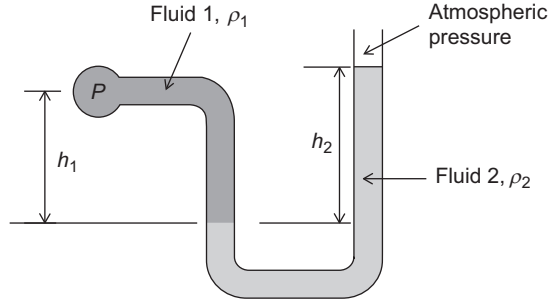


FIG. 3.3 Schematic of a classical fluid mechanics manometer for measuring the pressure of a fluid at P . By measuring the differences in height, with a known open pressure, the hydrostatic pressure at P can be calculated.

Example 3.2

Blood is flowing through point P (Fig. 3.4), which is connected to a catheter tip manometer system. Blood enters the manometer and equilibrates the pressure of the various fluids within the system (as denoted in the figure). Calculate the pressure within the blood vessel assuming that blood density is 1050 kg/m^3 and that atmospheric pressure is 760 mmHg .

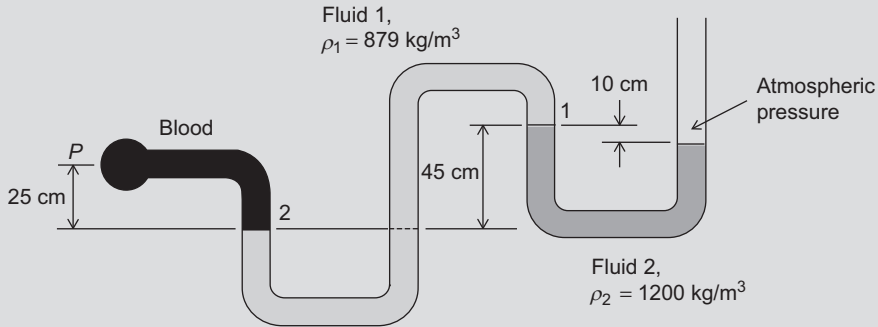


FIG. 3.4 Schematic of a catheter-tip manometer to measure intravascular blood pressure.

Solution

$$\begin{aligned}
 p_1 &= p_{atm} - \rho_2 g (z_1 - z_0) \\
 p_1 &= 760 \text{ mmHg} - \left(1200 \frac{\text{kg}}{\text{m}^3} \right) \left(9.81 \frac{\text{m}}{\text{s}^2} \right) (10 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}} \right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}} \right) = 751.17 \text{ mmHg} \\
 p_2 &= p_1 - \rho_1 g (z_2 - z_1) \\
 p_2 &= 751.17 \text{ mmHg} + \left(879 \frac{\text{kg}}{\text{m}^3} \right) \left(9.81 \frac{\text{m}}{\text{s}^2} \right) (45 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}} \right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}} \right) = 780.28 \text{ mmHg} \\
 p_{\text{blood}} &= p_2 - \rho_{\text{blood}} g (z_p - z_2) \\
 p_{\text{blood}} &= 780.28 \text{ mmHg} - \left(1050 \frac{\text{kg}}{\text{m}^3} \right) \left(9.81 \frac{\text{m}}{\text{s}^2} \right) (25 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}} \right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}} \right) = 760.96 \text{ mmHg}
 \end{aligned}$$

Example 3.2 illustrates a few principles that should be remembered when working on fluid statics problems. The first is that the pressure at an interface between two different fluids is always the same. This is how we can equate the pressure at locations 1 and 2 and 2 and P . If the fluid is continuous (same density), any location at the same height has the same pressure. Therefore, you can move around the bends without calculating each pressure change around those bends. In addition, the dashed line through fluid 1 has the same pressure as location 2. Finally, pressure should increase as the elevation decreases and pressure should decrease as the elevation increases.

There are many biofluid problems in which the fluid density will vary. These types of fluids are compressible fluids, and the density function of these particular fluids would need to be stated within the problem (or experimentally determined in a laboratory setting). In general, the density function would need to be given as a function of pressure and/or height; however, there are other relevant engineering variables that can alter density, such as temperature. Once this function is known, Eq. (3.10) can be used to solve for the pressure distribution throughout the fluid, assuming that gravity aligns with one direction. As an example, the density of most gases depends on the pressure and the temperature of the system. The ideal gas law represents this relationship and should be familiar to most students. The ideal gas law states that

$$p = \rho RT \quad (3.12)$$

where R is the universal gas constant (8.314 J/(g mol K)) and T is the absolute temperature (in Kelvin). A concern with using the ideal gas law is that it introduces a new variable, T , into the equation, which may vary with height as well. We will typically make the assumption in this textbook that temperature fluctuations within the body can be neglected. This means that for humans, the temperature will be assumed to be 310.15 K (37°C), unless stated otherwise. Using the ideal gas law, the pressure variation in a compressible fluid, with a constant temperature and with negligible changes in gravity with respect to height, is

$$\begin{aligned} \frac{dp}{dz} &= -\rho g_z = -\frac{p}{RT} g_z \\ \frac{dp}{p} &= -\frac{g_z}{RT} dz \\ \int_{p_0}^{p_1} \frac{dp}{p} &= -\frac{g_z}{RT} \int_{z_0}^{z_1} dz \\ \ln(p)|_{p_0}^{p_1} &= -\frac{g_z}{RT} z|_{z_0}^{z_1} \\ \ln(p_1) - \ln(p_0) &= \ln\left(\frac{p_1}{p_0}\right) = -\frac{g_z}{RT} (z_1 - z_0) \\ \frac{p_1}{p_0} &= e^{-\frac{g_z}{RT} (z_1 - z_0)} \\ p_1 &= p_0 e^{-\frac{g_z}{RT} (z_1 - z_0)} \end{aligned} \quad (3.13)$$

Depending on the particular application of the problem, the differential equation that relates pressure variations to height changes (Eq. (3.10)) can be solved for any fluid that has a density or temperature variation with height.

There is one important point to remember about hydrostatic pressure. Most students should be familiar with the concept that a pressure gradient acts as a driving force for fluid flow (e.g., the fluid will flow from high pressure to low pressure). Hydrostatic pressure is not this driving force; otherwise, it would be easier for blood to flow from the heart to the head than from the heart to the feet (when standing upright). Hydrostatic pressure is more similar to a friction concept; that is, to move an object, enough force must be applied to overcome the frictional forces. In fluid mechanics examples, there must be enough force applied to the fluid to overcome a hydrostatic pressure gradient to have the fluid accelerate in that direction. Also, in some instances, hydrostatic pressure can aid in fluid movement, whereas in other instances it can hinder movement.

3.2 Buoyancy

Buoyancy is defined as the net vertical force acting on an object that is either floating on a fluid's surface or immersed within the fluid. To determine the net force acting on an immersed object, the same relationship for pressure variation within a static fluid can be applied. Starting from Eq. (3.10), the net pressure on a three-dimensional (3D) object would need to take into account the quantity of material that is in the z -direction (Fig. 3.5, or the direction(s) that align with the direction of gravity). Again, by taking a differential element, the net force in the z -direction would be

$$dF_z = (p + \rho g h_1) dA - (p + \rho g h_2) dA = \rho g (h_1 - h_2) dA \quad (3.14)$$

For our example, the forces acting on the sides of the cylinder would balance each other (e.g., the forces in the radial and angular directions), so they do not need to be considered

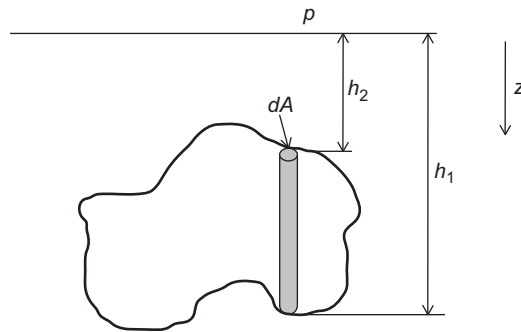


FIG. 3.5 A body immersed in a static fluid. dA describes the cross-sectional area of the body at the location of h_1 or h_2 (which are measured in the z -axis). Various cross-sectional areas would be used to determine the buoyancy forces on an immersed object.

in the following formulation. Please note that our formulation assumes that gravity acts only in the z -direction for this case. Recall from a calculus course that

$$(h_1 - h_2)dA = dV$$

which is the volume of the element of interest (in Fig. 3.5 this would be the shaded cylinder), assuming that the cross-sectional area is uniform through the geometry. Therefore, the summation of all of the forces that act on the immersed body would be

$$F_z = \int_V dF_z = \int_V \rho g dV = \rho g V$$

where V is the immersed volume of the element and gravity and density are not a function of the fluid volume of interest. This pressure force is equal to the force of gravity on the liquid displaced by the object. For biomedical applications, this is useful for designing any probe, which would be immersed within a biological fluid. Any cardiovascular implantable device would fall within this category as well.

Example 3.3

Determine the maximum buoyancy of a catheter that is inserted into the femoral artery of a patient and is passed through the cardiovascular system to the coronary artery (Fig. 3.6). The location where the catheter is inserted into the femoral artery is 50 cm below the aortic arch. The coronary artery is 5 cm below the aortic arch. Assume that the maximum buoyancy would occur at peak systole for a normal healthy individual (120 mmHg; this pressure is assumed to be measured at the aortic arch). Also assume that the catheter is perfectly cylindrical with a diameter of 2 mm.

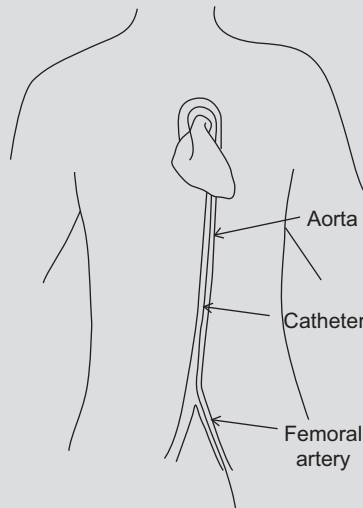


FIG. 3.6 Catheter inserted at the femoral artery that is passed to the coronary artery. These catheters are commonly used during surgeries to remedy atherosclerotic lesions.

Example 3.3 (cont'd)**Solution**

Pressure at incision:

$$p_1 = 120 \text{ mmHg} + \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(9.81 \frac{\text{m}}{\text{s}^2}\right) (50 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}}\right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}}\right) = 158.63 \text{ mmHg}$$

Pressure at coronary artery:

$$p_1 = 120 \text{ mmHg} + \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(9.81 \frac{\text{m}}{\text{s}^2}\right) (5 \text{ cm}) \left(\frac{1 \text{ m}}{100 \text{ cm}}\right) \left(\frac{1 \text{ mmHg}}{133.32 \text{ Pa}}\right) = 123.86 \text{ mmHg}$$

Volume of catheter from femoral artery to aortic arch:

$$V = \pi \left(\frac{2 \text{ mm}}{2}\right)^2 (50 \text{ cm}) = 1.57 \text{ cm}^3$$

Volume of catheter from aortic arch to coronary artery:

$$V = \pi \left(\frac{2 \text{ mm}}{2}\right)^2 (5 \text{ cm}) = 0.157 \text{ cm}^3$$

Buoyancy force on catheter:

$$F = \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(9.81 \frac{\text{m}}{\text{s}^2}\right) (1.57 \text{ cm}^3) + \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(9.81 \frac{\text{m}}{\text{s}^2}\right) (0.157 \text{ cm}^3) = 0.0178 \text{ N}$$

Note that the force acting on the catheter was not affected by the absolute pressure in the system because these values cancel when adding the pressure terms (see Eq. (3.14)).

3.3 Conservation of mass

The previous two sections described the pressure distribution in static fluids. However, in most biofluid mechanics problems, the fluid that we are interested in will be in motion (and possibly be described by at least one acceleration component), and therefore the previous analysis may not be applicable or may not be the most accurate. Recall that you may be able to obtain some meaningful information from static fluid analyses. In the following four sections, we will develop relationships that govern general fluid motion. Our analysis for each of these four sections will use a volume of interest (sometimes called a *control volume*) formulation, because it is normally quite difficult to identify the same mass of fluid throughout time. Remember that fluids under accelerated motion will deform and, therefore, some identifiable volume must be defined so that the laws of motion can be applied (Fig. 3.7 illustrates different ways a defined fluid volume of interest may deform at later times; the

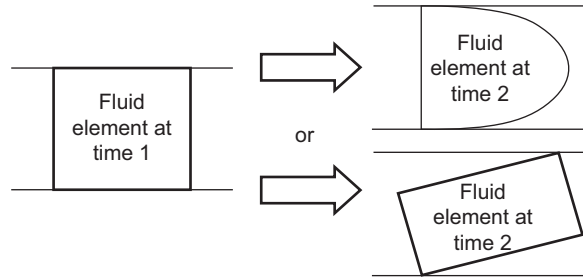


FIG. 3.7 Two possible arrangements for a fluid element after the fluid experienced some form of accelerated motion. It is typically easier to maintain the same control volume (represented as a square at time 1) than to identify and alter the volume of interest at a later time. This image shows that there are multiple possible arrangements for fluid elements after deformation, depending on the boundary conditions (although these are approximated for the figure and are not intended to relate to a physical property). It is critical during the analysis of biofluid mechanics problems to simplify these issues of fluid deformability by choosing control volumes wisely and those that are easily used in the formulations.

intention of this figure is to illustrate that it may not be the most beneficial to follow one discrete fluid volume, but instead we may want to track what is occurring within a general region within the flow profile. Furthermore, we may not know a priori what the deformation will look like for a given fluid element and because our calculations are dependent on this knowledge, we would need to incorporate additional somewhat unnecessary assumptions into the analysis). If you are interested in particular fluid elements and how those particular fluid elements move with time, you must take a differential approach to Newton's laws. The laws that govern a system should be familiar from earlier courses in mechanics/thermodynamics. We will extend these principles to a volume in the following formulations.

First we will develop the conservation of mass principle for fluid mechanics. The basis for this principle is that mass can neither be created nor destroyed within the volume/system of interest. If the inflow mass flow rate is not balanced by the outflow mass flow rate, there will be a change in volume or density within the volume of interest. If the inflow mass flow rate exceeds the outflow mass flow rate, mass will accumulate within the system. When the outflow mass flow rate exceeds the inflow mass flow rate, mass will be removed from the system. As an example, under normal conditions (e.g., not under strenuous activity), the blood volume within the heart remains constant from beat to beat. Stated in other words, the mass ejected from the aorta and the pulmonary arteries is recovered from the superior vena cava, the inferior vena cava, and the pulmonary veins. However, you can imagine a case in which the residual fluid mass within the heart decreases from beat to beat. As an example, a patient who is experiencing severe blood loss from a laceration would initially continue to eject the normal amount of blood from the heart, but at some later point the venous return would not be equal to this ejection volume. Therefore the blood volume in the heart would likely decrease. At some later time, under these conditions, the ejection volume would likely decrease as well. No matter what the case is regarding mass changes within the volume of interest, mass must be conserved within the system of interest.

Before we move forward into the derivation of the conservation of mass of a system, we will derive a general relationship for the time rate of change of a system property as a function of the same property per unit mass of the volume (inherent property). This is sometimes

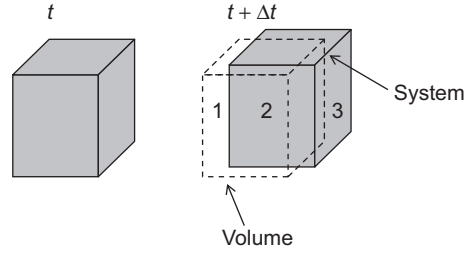


FIG. 3.8 System and volume of interest used to derive the formula for conservation laws. The system of interest is shown by the *gray shaded cube*, and the volume of interest is the *dashed cube*. To use this formulation, one would need to know the change in time between the two states shown in this figure.

referred to as the *Reynolds Transport Theorem (RTT) formulation*. For mass balance, the system property is mass and the inherent property is 1 (i.e., mass divided by mass). For balance of linear momentum, the system property is momentum ($\vec{P}$) and the inherent property is velocity ($\vec{v}$) (i.e., momentum divided by mass). For energy balance, the system property is energy E (or entropy, S), and the inherent property is energy per unit mass e (or entropy per unit mass, s). The system and volume of interest that we will use for the derivation of the RTT will be a cube, but this same analysis technique can be applied to any shape (Fig. 3.8). We will also assume that the shape remains the same over our time interval, but this analysis also holds for deformation. (Please note that during the derivation, we will take the mathematical limit of the time interval as the system property approaches a numeric value of zero; thus for very small, “differential,” time intervals it is a reasonable assumption that the shape remains the same.) The system and volume have been chosen so there is a region that overlaps at some later time, Δt , during the motion (area 2 represents the region that overlaps at the two time points). Mass from area 1 enters the volume of interest during Δt and mass from area 3 exits the volume of interest during Δt .

The following derivation will relate the time rate of change of any general system property (W) to its inherent property (w). W and w are arbitrary representations that are used only as a placeholder during formula derivation (RTT). This formulation starts by using the definition of a derivative.

$$\frac{dW}{dt} = \lim_{\Delta t \rightarrow 0} \frac{W|_{t+\Delta t} - W|_t}{\Delta t}$$

At any time t , the system is defined by the volume of interest, which keeps the same shape at all times. At time $t + \Delta t$, the system occupies areas 2 and 3, instead of areas 1 and 2 (for time t). Again, regardless of the area encompassed by the volume of interest, the total volume (and its dimensions) remains constant at all times. Therefore, the following definitions apply for the system properties at time t and at time $t + \Delta t$.

$$\begin{aligned} W_t &= W_{\text{volume of interest}} = W_{VI} \\ W_{t+\Delta t} &= W_2 + W_3 = W_{VI} - W_1 + W_3 \end{aligned}$$

Note that the numeric subscripts relate to the specific sections of the total volume denoted in Fig. 3.8. Using these definitions in the derivative formulation

$$\frac{dW}{dt} = \lim_{\Delta t \rightarrow 0} \frac{(W_{VI} - W_1 + W_3)_{t+\Delta t} - (W_{VI})_t}{\Delta t} \quad (3.15)$$

which is equal to

$$\frac{dW}{dt} = \lim_{\Delta t \rightarrow 0} \frac{(W_{VI})_{t+\Delta t} - (W_{VI})_t}{\Delta t} + \lim_{\Delta t \rightarrow 0} \frac{(W_3)_{t+\Delta t}}{\Delta t} - \lim_{\Delta t \rightarrow 0} \frac{(W_1)_{t+\Delta t}}{\Delta t} \quad (3.16)$$

The first term in Eq. (3.16) is equal to

$$\lim_{\Delta t \rightarrow 0} \frac{(W_{VI})_{t+\Delta t} - (W_{VI})_t}{\Delta t} = \frac{\partial W_{VI}}{\partial t} = \frac{\partial}{\partial t} \int_V w_{VI} \rho dV \quad (3.17)$$

Eq. (3.17) is developed by recognizing that the left-hand side term and the middle term represent the definition of a derivative and an alternative way to represent said derivative, respectfully. The middle term is represented as a partial derivative because the general system property can be a function of space or time, and here we want to focus on the changes of the property with time. The right-hand side term (Eq. 3.17) represents a third way to represent this derivative. Here, the general inherent property is multiplied by density and volume (which is equal to mass) to obtain the time rate of change of the general system property, integrated over the entire volume of interest. This formulation is typically more applicable, since the inherent property and/or density can be a function of volume, which is the variable that we typically define in biofluid mechanics. For the remaining two terms in Equation (3.16), a similar analysis can be conducted to obtain

$$\begin{aligned} dW_3|_{t+\Delta t} &= w_3 \rho dV|_{t+\Delta t} = w_3 \rho \Delta x dA|_{t+\Delta t} \\ dW_1|_{t+\Delta t} &= w_1 \rho dV|_{t+\Delta t} = w_1 \rho \Delta x (-dA)|_{t+\Delta t} \end{aligned} \quad (3.18)$$

For this formulation (Eq. 3.18), the variables cannot be described with the definition of a derivative. Also, remember that dV can be described as the change in length (i.e., from area 2 to area 3) multiplied by the differential area (in general, the cube can move in 3D space). Also, recall that a negative sign is included in the differential area term for the system property associated with the area 1 formulation to take care of the direction that the normal area vector is facing. For this section of the volume of interest, the mass is moving to the right (as shown in Fig. 3.8), but the area vector for area 1 is oriented toward the left. Additionally, the change in length (Δx) can be considered the fluid path for any deformation that the fluid element experiences during the time interval that is being observed. If we integrate the two equations in (3.18), we get

$$\begin{aligned} \int_{\text{area 3}} dW_3|_{t+\Delta t} &= W_3|_{t+\Delta t} = \int_{\text{area 3}} w_3 \rho \Delta x dA|_{t+\Delta t} \\ \int_{\text{area 1}} dW_1|_{t+\Delta t} &= W_1|_{t+\Delta t} = \int_{\text{area 1}} w_1 \rho \Delta x (-dA)|_{t+\Delta t} \end{aligned} \quad (3.19)$$

Substituting these values into Eq. (3.16)

$$\begin{aligned}\lim_{\Delta t \rightarrow 0} \frac{(W_3)|_{t+\Delta t}}{\Delta t} &= \frac{\int_{\text{area } 3} w_3 \rho \Delta x dA}{\Delta t} = \int_{\text{area } 3} w_3 \rho \vec{v} \cdot d\vec{A} \\ \lim_{\Delta t \rightarrow 0} \frac{(W_1)|_{t+\Delta t}}{\Delta t} &= \frac{\int_{\text{area } 1} w_1 \rho \Delta x (-dA)}{\Delta t} = - \int_{\text{area } 1} w_1 \rho \vec{v} \cdot d\vec{A}\end{aligned}\quad (3.20)$$

The previous equation uses the following equalities

$$\begin{aligned}\lim_{\Delta t \rightarrow 0} \frac{\Delta x}{\Delta t} &= \vec{v} \\ dA &= d\vec{A}\end{aligned}\quad (3.21)$$

to change the quantities between scalar and vector forms. Combining Eqs. (3.17) and (3.20) into Eq. (3.16)

$$\frac{dW}{dt} = \frac{\partial}{\partial t} \int_{V1} w_{V1} \rho dV + \int_{\text{area } 3} w_3 \rho \vec{v} \cdot d\vec{A} + \int_{\text{area } 1} w_1 \rho \vec{v} \cdot d\vec{A} \quad (3.21)$$

The entire system of interest consists of areas 1, 2, and 3, and we can make the assumption that there is no change in flow within region 2 during the time interval of Δt (this is why we choose to overlap the systems from the two time intervals). Therefore $\vec{v}$ is zero for area 2, and we can combine the two area integrals in Eq. (3.21) into a general form, where “area” is defined to be equal to area 1 plus area 3.

$$\frac{dW}{dt} = \frac{\partial}{\partial t} \int_V w \rho dV + \int_{\text{area}} w \rho \vec{v} \cdot d\vec{A} \quad (3.22)$$

When developing the formulation for the time rate of change of a system property, we took the limit of the generic system property (W) as time approaches zero. This forces the relationship to be valid at the instant when the system and the control volume completely overlap, even though we developed the formulations as if the volume of interest has moved slightly in space. The first term of Eq. (3.22) is the time rate of change of any arbitrary general system property (W). The second term in Eq. (3.22) is the time rate of change of the inherent property within the volume of interest (w). The third term in Eq. (3.22) is the flux of the property out of the surface of interest or into the surface of interest, considering any possible flux from area 1 or 3. From this relationship, all of the conservation laws can be derived by substituting the appropriate system property and inherent property, which were described previously.

In Chapter 2, we defined conservation of mass as

$$m_{\text{system}} = m_{\text{in}} - m_{\text{out}} - \frac{d(\rho V)}{dt}$$

In a more concise form, mass balance can be stated as

$$\left. \frac{dm}{dt} \right|_{\text{system}} = 0 \quad (3.23)$$

The mass of a system can be defined as

$$m_{\text{system}} = \int_{m\text{-system}} dm = \int_{V\text{-system}} \rho dV$$

Substituting the appropriate system property values for mass into [Eq. \(3.22\)](#)

$$\left. \frac{dm}{dt} \right|_{\text{system}} = \frac{\partial}{\partial t} \int_V \rho dV + \int_{\text{area}} p \vec{v} \cdot d\vec{A} = 0 \quad (3.24)$$

The previous equation ([Eq. \(3.24\)](#)) describes the changes in mass within a system of interest. The first term (right-hand side of [Eq. \(3.24\)](#)) describes the time rate of change of the mass within the volume of interest. This includes any possible change in density within the volume or changes with the volume itself. The second term (right-hand side) describes the mass flux into/out of the surfaces of interest. Mass that is entering into the volume of interest would be considered a negative flux (because the velocity vector acts in the opposite direction to the area normal vector), whereas mass leaving the volume of interest would be a positive flux (the velocity and the area vectors are acting in the same direction). By the conservation of mass principle, the time rate of change of mass within the volume of interest has to be balanced by the flux of mass into/out of the volume of interest.

[Eq. \(3.24\)](#) can be simplified for specific special fluid cases. Under incompressible flow conditions or conditions that are assumed to be incompressible, there is no change in fluid density with time/space. This simplifies [Eq. \(3.24\)](#) to

$$\left. \frac{dm}{dt} \right|_{\text{system}} = \rho \frac{\partial V}{\partial t} + \rho \int_{\text{area}} \vec{v} \cdot d\vec{A} = 0 \quad (3.25)$$

because the volume integral of dV is simply the volume of interest. By canceling out the density terms and making a further assumption that the volume of interest does not change with time, [Eq. \(3.25\)](#) becomes

$$\left. \frac{dm}{dt} \right|_{\text{system}} = \int_{\text{area}} \vec{v} \cdot d\vec{A} = 0 \quad (3.26)$$

A volume that does not change with time would be considered nondeformable or rigid. This is not always a good assumption in biofluids because some blood vessels change shape when the heart's pressure pulse is passed through it, but the question would remain whether the change in the blood vessel shape significantly alters the fluid properties. If the change in

volume significantly changes the fluid properties, it should be included within the calculations; however, if the fluid properties are not altered significantly, volume changes may be ignored. In addition, the lungs make use of a shape change (and hence volume change) to drive the flow of air into or out of the system (e.g., the volume of the lungs is altered, and this translates into a change in pressure to drive air movement). In this textbook, we will assume that our volume of interest is nondeformable unless stated otherwise. Eq. (3.26) does not make an assumption on the flow rate (i.e., is it steady or does it change with time?), so this equation is valid for any incompressible flow through a nondeformable volume. Remember that by definition, steady flows can have no fluid property that changes with time. Therefore, in the case of a steady flow, the first integral term in Eq. (3.24) would be equal to zero. For a general compressible steady flow situation, Eq. (3.24) would simplify to the mass flux equation.

$$\int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = 0 \quad (3.27)$$

In fluid mechanics, the integral represented in Eq. (3.26) is commonly referred to as the volume (or volumetric) flow rate, Q . For an incompressible flow through a nondeformable volume, the volume flow rate into the volume must be balanced by the flow out of the volume. However, because the volume is nondeformable, the volume flow rate can be calculated at any one location at any time within the system of interest. The definition for volume flow rate is

$$Q = \int_{\text{area}} \vec{v} \cdot d\vec{A} \quad (3.28)$$

The volume flow rate divided by area is defined as the average velocity at a particular section of interest within the flow field.

$$v_{\text{avg}} = \frac{Q}{A} = \frac{1}{A} \int_{\text{area}} \vec{v} \cdot d\vec{A} \quad (3.29)$$

From the special cases that we have discussed and the general formula, we can now use the conservation of mass to solve various fluid mechanics problems.

Example 3.4

Determine the velocity of blood at cross-section 4 of the aortic arch schematized in Fig. 3.9. Assume that the diameter of the blood vessel is 3 cm, 1.5 cm, 0.8 cm, 1.1 cm, and 2.7 cm at cross-sections 1, 2, 3, 4, and 5, respectively. Branches 2, 3, and 4 make a 75-degree, a 85-degree, and a 70-degree angle with the horizontal direction, respectively. The velocity is 120, 85, 65, and 105 cm/s at sections 1, 2, 3, and 5, respectively. There is inflow at 1 and outflow at all of the remaining locations. Assume steady flow at this particular instant in time and that the volume of interest is nondeformable.

Continued

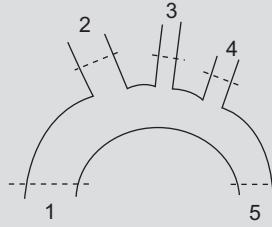
Example 3.4 (*cont'd*)

FIG. 3.9 Schematic of the aortic arch.

Solution

Fig. 3.10 highlights the given geometrical constraints in this problem. The gray dashed box shown on this figure represents one of the possible choices for the volume of interest. We will also make the assumption that blood density does not change and has a value of 1050 kg/m^3 .

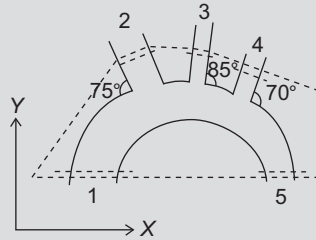


FIG. 3.10 Figure depicting our choice for the control volume around the aortic arch. Note that the area of interest at each location (1 to 5) is perpendicular to the mean velocity direction.

We can directly apply Eq. (3.26) because we have made the assumption that the density does not change with time, that the volume is not deformable, and that the flow is steady.

$$\int_{\text{area}} \vec{v} \cdot d\vec{A} = 0 \quad (3.26)$$

Eq. (3.26) will further simplify to the volume flow rate at each location because of the assumptions that the velocity is constant with respect to area at the one particular time that we are interested in (e.g., the velocities that were provided in the prompt represent the peak velocity or the average velocity at each cross-section of interest). Therefore, Eq. (3.26) can be represented as

$$-v_1 A_1 + v_2 A_2 + v_3 A_3 + v_4 A_4 + v_5 A_5 = 0$$

The negative sign occurs with the first quantity in the preceding equation because the velocity at location 1 opposes the area normal vector at 1. The remaining quantities are positive because at these locations the velocity is in the same direction as the area normal vector (also, as a rule of thumb, inflow is generally negative and outflow is generally positive in these types of calculations).

Example 3.4 (cont'd)

The area at each location is

Location	Area
1.	$\pi \left(\frac{3 \text{ cm}}{2} \right)^2 = 7.069 \text{ cm}^2$
2.	$\pi \left(\frac{1.5 \text{ cm}}{2} \right)^2 = 1.767 \text{ cm}^2$
3.	$\pi \left(\frac{0.8 \text{ cm}}{2} \right)^2 = 0.503 \text{ cm}^2$
4.	$\pi \left(\frac{1.1 \text{ cm}}{2} \right)^2 = 0.950 \text{ cm}^2$
5.	$\pi \left(\frac{2.7 \text{ cm}}{2} \right)^2 = 5.726 \text{ cm}^2$

Substituting the known values for area and velocity into the previous equation

$$v_4 = \frac{v_1 A_1 - v_2 A_2 - v_3 A_3 - v_5 A_5}{A_4}$$

$$v_4 = \frac{(120 \text{ cm/s})(7.069 \text{ cm}^2) - (85 \text{ cm/s})(1.767 \text{ cm}^2) - (65 \text{ cm/s})(0.503 \text{ cm}^2) - (105 \text{ cm/s})(5.726 \text{ cm}^2)}{0.950 \text{ cm}^2}$$

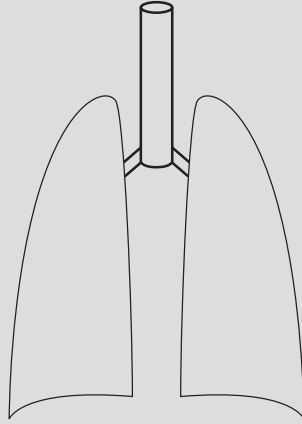
$$= 67.54 \frac{\text{cm}}{\text{s}}$$

This velocity would flow at a 75-degree angle off the positive x -axis. Density was not used in any of the formulations because it is constant and thus would cancel out in each term. This problem also illustrates that it does not matter which direction (x or y) the velocity is acting at the inflow and outflow locations, because all of the mass needs to be conserved. We provided information regarding the branching angles of the vessels off of the aorta, but they were not used in the calculations to determine the velocity.

Example 3.5

Calculate the time rate of change of air density during expiration. Assume that the lung (Fig. 3.11) has a total volume of 6000 mL, the diameter of the trachea is 18 mm, the airflow velocity out of the trachea is 20 cm/s, and the density of air is 1.225 kg/m³. Also assume that lung volume is decreasing at a rate of 100 mL/s.

Continued

Example 3.5 (*cont'd*)**FIG. 3.11** Schematic of the lung.**Solution**

We will start from Eq. (3.24) because we are asked for the time rate of change of density. We are asked to find the time rate of change of air density; this suggests that Example 3.5 conditions are representing a nonsteady flow scenario. In addition, we were told what the rate of change in the lung volume is during this procedure, further supporting the use of Eq. (3.24).

$$\frac{\partial}{\partial t} \int_V \rho dV + \int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = 0 \quad (3.24)$$

Assume that at the instant in time that we are measuring the system, density is uniform within the volume of interest. This allows us to remove density from within the first integral. Since no information was provided about how density varies within the volume, we would be unable to solve this problem without making the assumption.

$$\frac{\partial}{\partial t} \rho \int_V dV + \int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = 0$$

The volume integral of the volume of interest is just the volume of interest. Therefore, Eq. (3.24) can be represented as

$$\frac{\partial}{\partial t} (\rho V) + \rho \vec{v} \cdot A = 0$$

if we also assume that the density and velocity are not functions of the outflow area of interest (the second integral obtains a positive solution because we are representing an outflow velocity and this velocity aligns with the area vector). Using the product rule

$$V \frac{\partial \rho}{\partial t} + \rho \frac{\partial V}{\partial t} = -\rho \vec{v} \cdot A$$

Example 3.5 (cont'd)

Solving this equation with the known values

$$\begin{aligned}\frac{\partial \rho}{\partial t} &= \frac{-\rho \vec{v} \cdot \vec{A} - \rho \left(\frac{\partial V}{\partial t} \right)}{V} \\ &= \frac{-\left(1.225 \frac{\text{kg}}{\text{m}^3}\right) \left(20 \frac{\text{cm}}{\text{s}}\right) \left(\pi \left(\frac{18 \text{ mm}}{2}\right)^2\right) - \left(1.225 \frac{\text{kg}}{\text{m}^3}\right) \left(-100 \frac{\text{mL}}{\text{s}}\right)}{6000 \text{ mL}} = 0.01 \frac{\text{kg}}{\text{m}^3 \text{s}}\end{aligned}$$

Note that the change in volume is negative because we were told that the lung volume is decreasing at the given rate.

We would like to point out that although gas flow generally can be considered by using compressible fluid flow properties (as done for Example 3.5), under some conditions the significance of this compressibility may be ignored. A general engineering rule of thumb is that if the Mach number is less than 0.3, the flow can be considered incompressible. However, we would like to point out that this rule should be applied sparingly and only when one knows the accuracy required from the solution. Under many normal biological gas flow examples, the effects of gas compressibility on the flow conditions is minimal; however, these effects may translate to significant biological functions. We would like to warn the readers to know how and when to apply simplifying assumptions.

3.4 Conservation of momentum

Newton's second law of motion can be written in terms of linear momentum, which is a general form of the equation.

$$\vec{F} = \frac{d(\vec{P})}{dt} = \frac{d(m\vec{v})}{dt} \quad (3.30)$$

For this analysis, we want to develop a relationship for the linear momentum within a volume of interest. We will follow a similar technique as that used to develop a relationship for the conservation of mass within a volume of interest. As we alluded to earlier, before developing Eq. (3.22) for the linear momentum case, we need to define the applicable system and inherent property. In this case the system property is momentum and the associated inherent property is velocity ($\vec{v}$). We will take some space to define linear momentum and how it relates to fluid mechanics to help orient the reader.

Linear momentum is defined as

$$\vec{P} = \int_{\text{system mass}} \vec{v} dm = \int_V \vec{v} \rho dV \quad (3.31)$$

for a volume of interest. In writing Newton's law, we had to consider and define the forces that act on the fluid element. Recall from our earlier discussion that the summation of the forces that act on a fluid element must include all body forces (denoted as $\vec{F}_b$) and all surface forces (denoted as $\vec{F}_s$). Thus, in considering the conservation of linear momentum, we may need to quantify all of the forces that act on the volume/surfaces of interest. Physically, linear momentum is a force of motion, which is conserved (and thus remains constant) unless other forces are applied to the system during its motion. By substituting the system property and the inherent property into Eq. (3.22), we can obtain the formulation for conservation of linear momentum using the RTT:

$$\frac{d\vec{P}}{dt} = \frac{\partial}{\partial t} \int_V \vec{v} \rho dV + \int_{\text{area}} \vec{v} \rho \vec{v} \cdot d\vec{A} \quad (3.32)$$

Using Newton's relationship for momentum, Eq. (3.32) can be represented as

$$\frac{d\vec{P}}{dt} = \sum \vec{F} = \vec{F}_b + \vec{F}_s = \frac{\partial}{\partial t} \int_V \vec{v} \rho dV + \int_{\text{area}} \vec{v} \rho \vec{v} \cdot d\vec{A} \quad (3.33)$$

We make use of forces in lieu of the time rate of change of momentum because it is typically easier to quantify forces acting on a fluid element of interest. Eq. (3.33) states that the summation of all forces acting on a volume of interest is equal to the time rate of change of momentum within the control volume and the summation of momentum flux through the surface(s) of interest. To solve conservation of momentum problems, the first step will be to define the volume of interest and surfaces of interest and label all of the forces that are acting on this system (note though that some of the forces may cancel out and thus they may not be included in the final calculations). This becomes especially important when making the choice on how to define the coordinate system; for ease of quantification the coordinate system should typically align with the majority of the forces. For the other forces, you will need to know the trigonometric relationships between the forces and the chosen coordinate axes. If a standard Cartesian coordinate system is chosen, gravity typically aligns with one of the axes and gravity will typically be the only body force that acts on the system. Surface forces are due to externally applied loads and are normally denoted through a pressure acting on the system. In this case the generalized surface force will be represented as

$$\vec{F}_s = \int_{\text{area}} -\vec{p} \cdot d\vec{A}$$

The negative sign in this formulation is added to maintain the sign convention for forces that are acting on the system of interest (Fig. 3.12). In Fig. 3.12, the pressure is positive, but because the pressure and the area vectors act in opposite directions, their vector product would be a negative force, which does not correspond with the positive directions chosen for the coordinate system—thus the inclusion of a negative sign to allow for the forces to align with the coordinate directions appropriately.

Unlike the conservation of mass formula, the formulas derived for the conservation of linear momentum are vector equations (compare with aortic arch example [Example 3.4]

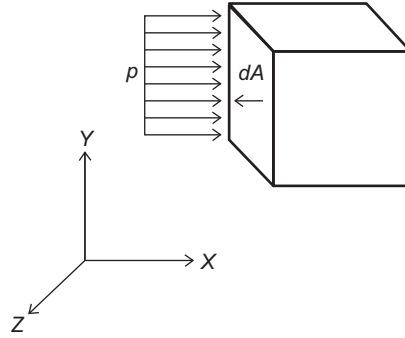


FIG. 3.12 Pressure force acting on a surface of interest. Recall that the area vector for this surface would act in the negative x -direction, whereas the pressure forces are acting in the positive x -direction.

for conservation of mass, where the direction of the velocities did not matter for the completed calculations). Eq. (3.33) written in component form is

$$\begin{aligned}
 F_x &= F_{bx} + F_{sx} = \frac{\partial}{\partial t} \int_V u \rho dV + \int_{\text{area}} u \rho \vec{v} \cdot d\vec{A} \\
 F_y &= F_{by} + F_{sy} = \frac{\partial}{\partial t} \int_V v \rho dV + \int_{\text{area}} v \rho \vec{v} \cdot d\vec{A} \\
 F_z &= F_{bz} + F_{sz} = \frac{\partial}{\partial t} \int_V w \rho dV + \int_{\text{area}} w \rho \vec{v} \cdot d\vec{A}
 \end{aligned} \tag{3.34}$$

where u , v , and w are the velocity components in the x -, y -, and z -directions, respectively. As before, the product of $\rho \vec{v} \cdot d\vec{A}$, is a scalar whose sign depends on the directions of the normal area vector and the velocity vector (the sign of u , v , and w are solely defined by the velocity component directions). If these two vectors (e.g., direction of velocity and area normal vector) act in the same direction, the scalar product of the vectors is positive; if they act in opposite directions, the scalar product is negative. Remember that the velocity vector ($\vec{v}$) in this product is not a component of velocity but is the entire velocity vector. In scalar notation, the entire form of the product would be represented as $\pm |\rho v^2 A \cos \alpha|$, where α is defined by the coordinate system of choice and the positive or negative sign is defined through the velocity/normal area vectors relationship and the direction of the velocity component. The angle α appears to define the u , v , and w directional velocities (note that we have assumed that none of the variables are a function of the area normal vector). Some students find this type of overall formulation easier to understand; however, when applying this relationship, one must take significant care in determining the sign. Regardless of how you choose to calculate the momentum flux, remember that the product of $\vec{v} \rho \vec{v} \cdot d\vec{A}$ is a vector, and the sign of this product depends on the coordinate system chosen (this defines the sign associated with the velocity vector) and the sign of the scalar product. We hope that the application of these sign conventions will become apparent in some of the example problems. To determine the sign of the momentum flux through a surface, first determine the sign (e.g., direction) associated with $|\rho v A \cos \alpha|$, and then determine the sign of each velocity component (u , v , and w). By knowing the signs of these two parts, the sign of the overall product can be determined relatively easily.

Example 3.6

Determine the force required to hold the brachial artery in place during peak systole (schematized in Fig. 3.13). Assume that at the inlet the pressure is 100 mmHg and at the outlet the pressure is 85 mmHg (these are gauge pressures). The diameter of the brachial artery is 18 mm at the inflow and 16 mm at the outflow. The blood flow velocity at the inlet is 65 cm/s. For simplicity, neglect the weight of the blood vessel and the weight of the blood within the vessel.

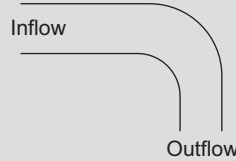


FIG. 3.13 Brachial artery schematic for Example 3.6.

Solution

Figs. 3.13 and 3.14 depict what is known about this flow situation. The problem statement asks to solve for F_x and F_y . Remember that the weight of the blood vessel and the weight of the blood in the vessel can be incorporated as an additional force in the y -direction (the mass of blood would typically be obtained through the volume of the blood vessel and the density of blood).

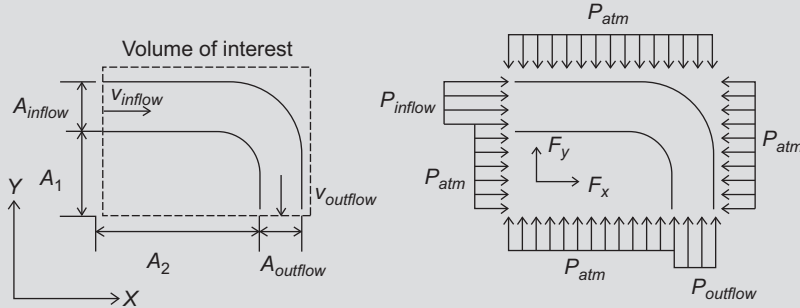


FIG. 3.14 Free body diagram for the brachial artery in Example 3.6.

To solve this problem, assume that there is steady flow at the instant in time that we are interested in, that 1 atm = 760 mmHg, that the blood vessel does not move and is not deformable, and that the flow is incompressible. First, we will need to solve for the outflow velocity using the equations for conservation of mass.

$$\left. \frac{dm}{dt} \right|_{\text{system}} = \frac{\partial}{\partial t} \int_V \rho dV + \int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = 0 \quad (3.34)$$

Because this is a steady flow problem, none of the variables change with time. Thus, the conservation of mass can be rewritten as

$$\int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = 0 \rightarrow \rho_1 v_1 A_1 = \rho_2 v_2 A_2$$

Example 3.6 (cont'd)

if we can assume that density and velocity are not a function of the inflow or outflow area.

$$\frac{\left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(65 \frac{\text{cm}}{\text{s}}\right) \left(\pi \left(\frac{18 \text{ mm}}{2}\right)^2\right)}{\left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(\pi \left(\frac{16 \text{ mm}}{2}\right)^2\right)} = v_2 = 82.27 \text{ cm/s} (-\vec{j})$$

Note that the velocity accelerates because of the step-down nature of the geometry. This is not necessarily representative of what occurs in the actual physiology, but this problem illustrates how to use conservation of mass and momentum together. In addition, we added the direction vector so we can use it in the momentum calculation. Conservation of mass does not provide any information regarding the directionality; this information was gained from the figure and the choice of the “standard” Cartesian system.

First, let us solve for the x -component of the force needed to hold the brachial artery in place.

$$F_x = F_{bx} + F_{sx} = \frac{\partial}{\partial t} \int_V u \rho dV + \int_{\text{area}} u \rho \vec{v} \cdot d\vec{A}$$

$$F_{bx} = 0, u_2 = 0$$

$$F_{sx} = p_{\text{inflow}} A_{\text{inflow}} + p_{\text{atm}} A_1 - p_{\text{atm}} (A_{\text{inflow}} + A_1) + F_x = A_{\text{inflow}} (p_{\text{inflow}} - p_{\text{atm}}) + F_x$$

$$A_{\text{inflow}} (p_{\text{inflow}} - p_{\text{atm}}) + F_x = A_{\text{inflow}} (p_{\text{inflow-gauge}}) + F_x = \int_{\text{area}} u \rho \vec{v} \cdot d\vec{A} = u_1 * (-\rho v_{\text{inflow}} A_{\text{inflow}})$$

Note that the u component of the velocity is positive, but the overall flux is negative because the velocity vector and the normal area vector act in opposite directions. In addition, note that atmospheric pressure is acting on all of the surfaces of the blood vessel, but they cancel out and leave the gauge pressure at the inflow, which was provided in the prompt.

$$F_x = -u_1 \rho v_{\text{inflow}} A_{\text{inflow}} - A_{\text{inflow}} (p_{\text{inflow-gauge}})$$

$$F_x = -\left(65 \frac{\text{cm}}{\text{s}}\right) \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(65 \frac{\text{cm}}{\text{s}}\right) \left(\pi \left(\frac{18 \text{ mm}}{2}\right)^2\right) - \left(\pi \left(\frac{18 \text{ mm}}{2}\right)^2\right) (100 \text{ mmHg}) = -3.5 \text{ N}$$

This means that this force acts toward the left because the flow/pressure is pushing toward the right. Also note that in this case, the total velocity and the x -velocity component are the same because (1) we assumed that the flow is only in the x -direction and (2) the coordinate system aligns with the flow direction. Now solve for the y -component of force.

$$F_y = F_{by} + F_{sy} = \frac{\partial}{\partial t} \int_V v \rho dV + \int_{\text{area}} v \rho \vec{v} \cdot d\vec{A}$$

$$F_{by} = 0, v_1 = 0$$

$$F_{sy} = p_{\text{outflow}} A_{\text{outflow}} + p_{\text{atm}} A_2 - p_{\text{atm}} (A_{\text{outflow}} + A_2) + F_y = A_{\text{outflow}} (p_{\text{outflow}} - p_{\text{atm}}) + F_y$$

Continued

Example 3.6 (*cont'd*)

$$\begin{aligned}
 A_{\text{outflow}}(p_{\text{outflow}} - p_{\text{atm}}) + F_y &= A_{\text{outflow}}(p_{\text{outflow-gauge}}) + F_y = \int_{\text{area}} v \rho \vec{v} \cdot d\vec{A} \\
 &= v_2 * (\rho V_{\text{outflow}} A_{\text{outflow}})
 \end{aligned}$$

Again, we are assuming that none of the flow variables change with time and that velocity and pressure are not functions of the outflow area of interest. Note that the v_2 -velocity component is negative (this will be accounted for later) and the flux term is positive because the area and the velocity vectors act in the same direction.

$$\begin{aligned}
 F_y &= v_2 * (\rho v_{\text{outflow}} A_{\text{outflow}}) - A_{\text{outflow}}(p_{\text{outflow-gauge}}) \\
 F_y &= \left(-82.27 \frac{\text{cm}}{\text{s}}\right) \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(82.27 \frac{\text{cm}}{\text{s}}\right) \left(\pi \left(\frac{16 \text{ mm}}{2}\right)^2\right) - \left(\pi \left(\frac{16 \text{ mm}}{2}\right)^2\right) (85 \text{ mmHg}) \\
 &= -2.42 \text{ N}
 \end{aligned}$$

This means that this force acts downward. Note that because the chosen coordinate system aligned with the inflow in the x -direction and the outflow with the y -direction, we did not need to account for angles in either formulation. The overall net force is 4.25 N acting at an angle of 214 degrees from the positive x -axis.

3.5 Momentum equation with acceleration

In deriving [Eq. \(3.33\)](#), we made an assumption that the volume of interest (and therefore the fluid within the volume) had no acceleration at the instant in time that we were evaluating the system. The acceleration of interest that we are discussing is not the possibility of the fluid to accelerate (or decelerate) within the containing volume because of volume changes. Instead we are discussing the acceleration that is associated with the volume of interest itself (e.g., if the containing volume is moving at a nonconstant velocity). Therefore, [Eq. \(3.33\)](#) does not hold for a volume of interest or system of interest that itself is accelerating during the time of interest. This is the case because typically when evaluating an accelerating system, you would use an inertial or fixed coordinate system (normally denoted as XYZ) instead of a reference (or relative) coordinate system, which follows the moving, possibly accelerating volume (normally denoted as xyz). With a nonaccelerating volume of interest, it is convention for the inertial and the relative reference system to be the same. In the previous derivations, a relative coordinate system was used for simplicity and this relative system was either fixed or moving with a constant velocity. Furthermore, [Eq. \(3.33\)](#) does not hold for an inertial reference frame because the relative momentum for an inertial coordinate system is generally not the same as the relative momentum for a reference coordinate system. That means that the sum of the forces that act on the system of interest equals the time

rate of change of momentum of the reference coordinate system but it does not have to equal the time rate of change of momentum of the inertial coordinate system (again, this is true only if the volume is accelerating). This can be represented mathematically as

$$\sum \vec{F}_{system} = \frac{d\vec{P}_{xyz}}{dt} \neq \frac{d\vec{P}_{XYZ}}{dt}$$

To develop an equivalent formulation, as Eq. (3.33), for an accelerating control volume, a relationship between the inertial momentum ($\vec{P}_{XYZ}$) and the control volume momentum ($\vec{P}_{xyz}$) must be found. To start, let us define Newton's second law of motion in terms of momentum and a system of interest.

$$\sum \vec{F}_{system} = \frac{d\vec{P}_{XYZ}}{dt} = \frac{d}{dt} \int_{system-mass} \vec{v}_{XYZ} dm = \int_{system-mass} \frac{d\vec{v}_{XYZ}}{dt} dm \quad (3.35)$$

Eq. (3.35) makes use of the standard momentum equations. To define the inertial velocity component in terms of the system velocity, use the following relationship.

$$\vec{v}_{XYZ} = \vec{v}_{xyz} + \vec{v}_r \quad (3.36)$$

where $\vec{v}_r$ is the velocity of the volume of interests reference frame relative to the inertial reference frame. Making the assumption that the fluid is irrotational,

$$\frac{d\vec{v}_{XYZ}}{dt} = \vec{a}_{XYZ} = \frac{d\vec{v}_{xyz}}{dt} + \frac{d\vec{v}_r}{dt} = \vec{a}_{xyz} + \vec{a}_r \quad (3.37)$$

These equations should be familiar from a classical engineering dynamics course. In Eq. (3.37), the first acceleration term ($\vec{a}_{XYZ}$) is the acceleration of the system relative to the inertial frame, the second acceleration term ($\vec{a}_{xyz}$) is the acceleration of the system relative to the system reference frame, and the third acceleration term ($\vec{a}_r$) is the acceleration of the system reference frame relative to the inertial reference frame. Please note that a rotational system would have multiple acceleration terms (see our brief discussion at the end of this section about the added complexity of a rotational system). Substituting the acceleration terms into Eq. (3.35)

$$\begin{aligned} \sum \vec{F}_{system} &= \int_{system-mass} \frac{d\vec{v}_{XYZ}}{dt} dm = \int_{system-mass} \frac{d\vec{v}_{xyz}}{dt} dm + \int_{system-mass} \vec{a}_r dm \\ \sum \vec{F}_{system} - \int_{system-mass} \vec{a}_r dm &= \int_{system-mass} \frac{d\vec{v}_{xyz}}{dt} dm = \frac{d\vec{P}_{xyz}}{dt} \end{aligned} \quad (3.38)$$

In this formulation, we leave the reference coordinate system velocity as a velocity (instead of an acceleration) to have the equation resemble Newton's second law of motion. Substituting Eq. (3.33) and converting the mass integral into a volume integral, Eq. (3.38) becomes

$$\vec{F}_b + \vec{F}_s - \int_V \vec{a}_r \rho dV = \frac{\partial}{\partial t} \int_V \vec{v}_{xyz} \rho dV + \int_{\text{area}} \vec{v}_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \quad (3.39)$$

To account for the acceleration of an inertial body, relative to the inertial reference frame, the conservation of linear momentum formulation requires one extra term (assuming that the fluid system is irrotational). When the system is not accelerating relative to the inertial frame, $\vec{a}_r$ is zero and Eq. (3.39) simplifies to Eq. (3.33). To apply Eq. (3.39) to a system, it is required that two coordinate systems are defined at the beginning of the solution attempt; one is the inertial coordinate system (XYZ), and the other coordinate system stays with the moving control volume (xyz). The reader should note that the control volume variables are represented on the right-hand side of the equation. This formula is valid for one instant in time, similar to Eq. (3.33). However, it is possible in particular situations that the mass (i.e., $\vec{F}_b, \rho$) and the acceleration are known functions of time and can thus be incorporated into the base equation relatively easily. Also, Eq. (3.39) is a vector equation, with all velocity components related to the noninertial reference frame (xyz). Written in component form, Eq. (3.39) becomes

$$\begin{aligned} \vec{F}_{bx} + \vec{F}_{sx} - \int_V \vec{a}_{rx} \rho dV &= \frac{\partial}{\partial t} \int_V u_{xyz} \rho dV + \int_{\text{area}} u_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \\ \vec{F}_{by} + \vec{F}_{sy} - \int_V \vec{a}_{ry} \rho dV &= \frac{\partial}{\partial t} \int_V v_{xyz} \rho dV + \int_{\text{area}} v_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \\ \vec{F}_{bz} + \vec{F}_{sz} - \int_V \vec{a}_{rz} \rho dV &= \frac{\partial}{\partial t} \int_V w_{xyz} \rho dV + \int_{\text{area}} w_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \end{aligned} \quad (3.40)$$

Example 3.7

One of the first implantable mechanical heart valves was designed as a ball within a cage that acted as a check valve. Using the conservation of momentum (with acceleration), we will model the acceleration of the ball after it is hit by a jet of blood being ejected from the heart (Fig. 3.15). The ball has a turning angle of 45 degrees and a mass of 25 g. Blood is ejected from the heart at a velocity of 150 cm/s, through an opening with a diameter of 27 mm. Determine the velocity of the ball at 0.5 s. Neglect any resistance to motion (except mass).

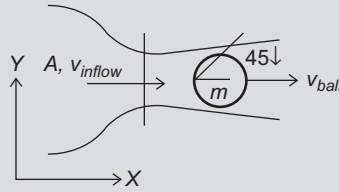
Example 3.7 (cont'd)

FIG. 3.15 Acceleration of a ball and cage mechanical heart valve for the in-text problem.

Solution

The inertial reference frame is chosen at the aortic valve; the noninertial reference frame is chosen to coincide with ball, and this reference frame moves with the ball at all times. We have made the choice that the volume of interest will coincide with the flow direction around the ball (Fig. 3.16) to represent the approximated flow conditions. We will analyze only half of the equation because the flow is assumed to be symmetrical around the uniform ball.

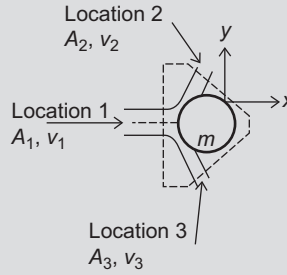


FIG. 3.16 Free body diagram for ball and cage mechanical heart valve Example 3.7.

$$\vec{F}_{bx} + \vec{F}_{sx} - \int_V \vec{a}_{rx} \rho dV = \frac{\partial}{\partial t} \int_V u_{xyz} \rho dV + \int_{\text{area}} u_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A}$$

If we make the assumption that the blood flow is steady and uniform, the equation reduces to

$$-\int_V \vec{a}_{rx} \rho dV = \int_{\text{area}} u_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A}$$

because there are no external forces (e.g., we were not given a pressure difference in the prompt) acting on the system. Substituting known values into this equation, we obtain

$$-\int_V \vec{a}_{rx} \rho dV = u_1 \left(-\frac{\rho v_1 A_1}{2} \right) + u_2 (\rho v_2 A_2)$$

We will make the assumption that as blood flows around the ball, there is no loss of velocity (and the area does not change) because of friction between the ball and blood. We will also assume that there is no change in velocity between the aortic valve location and the location about the ball. With these assumptions we can obtain the following quantities.

$$\frac{v_1}{2} = u_1 = u_2 = v_{\text{inlet}} - v_{\text{ball}}$$

Continued

Example 3.7 (*cont'd*)

which is also the relative velocity. Furthermore, the areas of interest can be defined as

$$\frac{A_1}{2} = A_2 = A_3 = A$$

Simplifying each term of the momentum equation and considering only the top half of the ball because the flow is symmetrical

$$\int_V \vec{a}_{rx} \rho dV = \vec{a}_{rx} \rho V = \vec{a}_{rx} m = \frac{dv_{\text{ball}}}{dt} m$$

Assuming that the relative acceleration and the density are not functions of the volume of interest

$$u_1(-\rho u_1 A) = (v_{\text{inlet}} - v_{\text{ball}})(-\rho(v_{\text{inlet}} - v_{\text{ball}})A) = -\rho A(v_{\text{inlet}} - v_{\text{ball}})^2$$

$$u_2(\rho u_2 A) = (v_{\text{inlet}} - v_{\text{ball}})\cos(45^\circ)(\rho(v_{\text{inlet}} - v_{\text{ball}})A) = \rho A(v_{\text{inlet}} - v_{\text{ball}})^2 \cos(45^\circ)$$

Substituting these values into the simplified conservation of momentum equation

$$-\frac{dv_{\text{ball}}}{dt} m = -\rho A(v_{\text{inlet}} - v_{\text{ball}})^2 + \rho A(v_{\text{inlet}} - v_{\text{ball}})^2 \cos(45^\circ) = (\cos(45^\circ) - 1)\rho A(v_{\text{inlet}} - v_{\text{ball}})^2$$

To solve this differential equation, we must separate the variables as follows.

$$\frac{dv_{\text{ball}}}{(v_{\text{inlet}} - v_{\text{ball}})^2} = \frac{(1 - \cos(45^\circ))\rho A}{m} dt$$

Integrate this equation as shown.

$$\begin{aligned} \int_0^{v_{\text{ball}}} \frac{dv_{\text{ball}}}{(v_{\text{inlet}} - v_{\text{ball}})^2} &= \int_0^t \frac{(1 - \cos(45^\circ))\rho A}{m} dt \\ \left. \frac{1}{(v_{\text{inlet}} - v_{\text{ball}})} \right|_0^{v_{\text{ball}}} &= \left. \frac{(1 - \cos(45^\circ))\rho A t}{m} \right|_0^t = \frac{(1 - \cos(45^\circ))\rho A t}{m} \\ \frac{1}{(v_{\text{inlet}} - v_{\text{ball}})} - \frac{1}{v_{\text{inlet}}} &= \frac{v_{\text{ball}}}{v_{\text{inlet}}(v_{\text{inlet}} - v_{\text{ball}})} = \frac{(1 - \cos(45^\circ))\rho A t}{m} \end{aligned}$$

Solving this equation for $v_{\text{ball-max}}$

$$\begin{aligned} \frac{v_{\text{ball}}}{v_{\text{inlet}}^2 - v_{\text{inlet}} v_{\text{ball}}} &= \frac{(1 - \cos(45^\circ))\rho A t}{m} \\ v_{\text{ball}} &= (v_{\text{inlet}}^2 - v_{\text{inlet}} v_{\text{ball}}) \left(\frac{(1 - \cos(45^\circ))\rho A t}{m} \right) \\ &= v_{\text{inlet}}^2 \left(\frac{(1 - \cos(45^\circ))\rho A t}{m} \right) - v_{\text{inlet}} v_{\text{ball}} \left(\frac{(1 - \cos(45^\circ))\rho A t}{m} \right) \end{aligned}$$

Example 3.7 (cont'd)

$$\begin{aligned}
v_{\text{ball}} + v_{\text{inlet}} v_{\text{ball}} \left(\frac{(1 - \cos(45^\circ)) \rho A t}{m} \right) &= v_{\text{ball}} \left(1 + v_{\text{inlet}} \left(\frac{(1 - \cos(45^\circ)) \rho A t}{m} \right) \right) \\
&= v_{\text{inlet}}^2 \left(\frac{(1 - \cos(45^\circ)) \rho A t}{m} \right) \\
v_{\text{ball}} &= v_{\text{inlet}}^2 \left(\frac{(1 - \cos(45^\circ)) \rho A t}{m \left(1 + v_{\text{inlet}} \left(\frac{(1 - \cos(45^\circ)) \rho A t}{m} \right) \right)} \right) = v_{\text{inlet}}^2 \left(\frac{(1 - \cos(45^\circ)) A t}{m + v_{\text{inlet}} ((1 - \cos(45^\circ)) \rho A t)} \right) \\
&= \left(150 \frac{\text{cm}}{\text{s}} \right)^2 \left(\frac{(1 - \cos(45^\circ)) \left(1050 \frac{\text{kg}}{\text{m}^3} \right) \frac{\pi}{2} \left(\frac{27 \text{ mm}}{2} \right)^2 t}{25 \text{ g} + \left(150 \frac{\text{cm}}{\text{s}} \right) \left((1 - \cos(45^\circ)) \left(1050 \frac{\text{kg}}{\text{m}^3} \right) \frac{\pi}{2} \left(\frac{27 \text{ mm}}{2} \right)^2 t \right)} \right) \\
&= \frac{198 \text{ g} * \text{m/s}^2 * t}{25 \text{ g} + 132 \text{ g/s} * t}
\end{aligned}$$

To account for the bottom half of the flow

$$v_{\text{ball}} = 2 \left(\frac{198 \text{ g} * \frac{\text{m}}{\text{s}^2} * t}{25 \text{ g} + \frac{132 \text{ g}}{\text{s}} * t} \right)$$

At $t = 0.5 \text{ s}$

$$v_{\text{ball}} = 2 \left(\frac{198 \text{ g} * \frac{\text{m}}{\text{s}^2} * 0.5 \text{ s}}{25 \text{ g} + \frac{132 \text{ g}}{\text{s}} * 0.5 \text{ s}} \right) = 218 \frac{\text{cm}}{\text{s}}$$

This is consistent with a rapid opening of the valve; however, the total length that the ball would traverse would only be approximately 4 cm (at most). Over time, the velocity of the ball would follow a logarithmic relationship (Fig. 3.17) if there was no mechanism to stop the ball from moving (i.e., the cage).

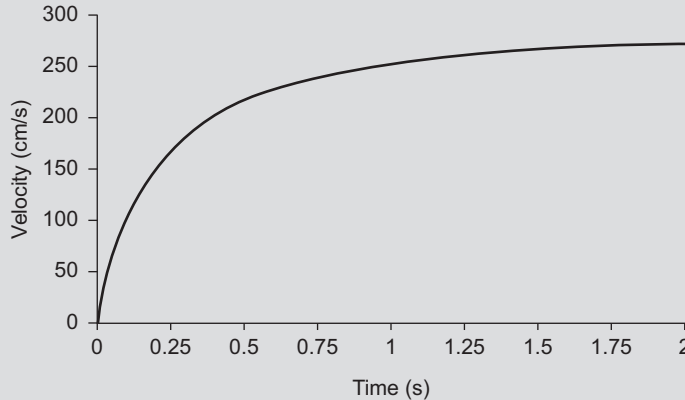


FIG. 3.17 Velocity of the ball with respect to time.

In the derivation of Eq. (3.40), we made the assumption that the flow was irrotational, and therefore the fluid experienced only pure translation. We will not show the derivation of the formula for rotational fluids here, but the most general formula for the conservation of momentum must include all possible velocity components under these highly complex flow conditions. This formula takes the form of

$$\begin{aligned} \vec{F}_b + \vec{F}_s - \int_V (\vec{a}_r + 2\vec{\omega} \times \vec{v}_{xyz} + \vec{\omega} \times (\vec{\omega} \times \vec{r}) + \vec{\omega} \times \vec{r}) \\ = \frac{\partial}{\partial t} \int_V \vec{v}_{xyz} \rho dV + \int_{\text{area}} \vec{v}_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \end{aligned} \quad (3.41)$$

where ω is the angular velocity (note that $\vec{\omega} \times \vec{v}_{xyz}$ is the Coriolis acceleration, $\vec{\omega} \times (\vec{\omega} \times \vec{r})$ is the centripetal acceleration, and $\vec{\omega} \times \vec{r}$ is the tangential acceleration resulting from angular velocity). This formula would be used if the fluid elements rotate, accelerate, and translate about each other or an arbitrary reference coordinate axis (XYZ). Note again that this is a vector equation and can be written in terms of its component equation.

3.6 The first and second laws of thermodynamics

The conservation of energy within a system is defined by the first law of thermodynamics, which is

$$\dot{Q} - \dot{W} = \frac{dE}{dt}$$

$\dot{Q}$ is the time rate of change of heat transfer and is positive when heat is added to the system. $\dot{W}$ is the time rate of change of work and is positive when work is done by the system. The energy of a system can be defined as

$$E = \int_V e \rho dV = \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV \quad (3.42)$$

where e is the energy per unit mass, u is the specific internal energy of the system, v is the speed of the system (not velocity), and z is the height of the system relative to a reference point. You may recall from a class in physics or engineering mechanics that the energy per unit mass is related to the total energy of the system and includes the gravitational potential energy (e.g., gz), kinetic energy (e.g., $\frac{v^2}{2}$), and any other internal energy (represented here as u). In developing Eq. (3.22), we stated that for energy conservation the system property was E and the inherent property was e . Substituting these values into Eq. (3.22), we have a statement for the conservation of energy

$$\frac{dE}{dt} = \frac{\partial}{\partial t} \int_V e \rho dV + \int_{\text{area}} e \rho \vec{v} \cdot d\vec{A} \quad (3.43)$$

If we define the system of interest to be the same as the volume of interest at the instant in time that is of interest to us, we can make the following statement

$$\dot{Q} - \dot{W}|_{\text{system}} = \dot{Q} - \dot{W}|_{\text{volume of interest}}$$

Substituting this into Eq. (3.43), we get

$$\begin{aligned} \frac{dE}{dt} = \dot{Q} - \dot{W} &= \frac{\partial}{\partial t} \int_V e \rho dV + \int_{\text{area}} e \rho \vec{v} \cdot |d\vec{A}| \\ &= \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz \right) \rho \vec{v} \cdot d\vec{A} \end{aligned} \quad (3.44)$$

In general, the rate of work is hard to quantify in fluid mechanics and is typically divided into four categories: work from normal stresses (W_n), work from shear stresses (W_{sh}), shaft work (W_s), and any other work (W_o)

From a physics course, you should remember that work is defined by force multiplied by the distance over which the force acts. When describing the work on a differential element,

$$dW = \vec{F} \cdot d\vec{x}$$

The normal force acting on a differential element would be defined as

$$d\vec{F}_n = \sigma_n d\vec{A}$$

To define the time rate of change of work associated with the normal force

$$\dot{W}_n = \lim_{\Delta t \rightarrow 0} \frac{\partial W}{\Delta t} = \lim_{\Delta t \rightarrow 0} \frac{d\vec{F}_n \cdot d\vec{x}}{\Delta t} = \sigma_n d\vec{A} \cdot \vec{v}$$

because $\frac{d\vec{x}}{dt} = \vec{v}$. Therefore, the total work done by normal forces is

$$\dot{W}_n = - \int_{\text{area}} \sigma_n \vec{v} \cdot d\vec{A} \quad (3.45)$$

where the negative sign is needed to quantify the work done on the control volume instead of by the control volume.

The work of a shear force is defined in a similar way. Remember that shear force is defined as

$$d\vec{F} = \vec{\tau} dA$$

In this formulation, the shear stress is the vector quantity (to provide directionality of the stress, which is different from the area vector's direction) and not the area normal vector. Using the same process as previously, the work of shear becomes

$$\dot{W}_{sh} = - \int_{\text{area}} \vec{\tau} \bullet \vec{v} dA \quad (3.46)$$

The work done by a shaft is not applicable to many biofluid mechanics problems, but would be defined as the negative of work input into the shaft to move the fluid. Similarly, other work would need to be defined by the type of work being done. For instance, if energy from an x-ray is being absorbed into the fluid, this can be considered work being absorbed by the system. Using these definitions, [Eq. \(3.44\)](#) becomes

$$\begin{aligned} \dot{Q} + \int_{\text{area}} \sigma_n \vec{v} \cdot d\vec{A} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} \\ = \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz \right) \rho \vec{v} \cdot d\vec{A} \end{aligned}$$

by replacing e with various forms of internal energy that the system may contain, as discussed. Rearranging, we can obtain

$$\begin{aligned} \dot{Q} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} = \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV \\ + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz \right) \rho \vec{v} \cdot d\vec{A} - \int_{\text{area}} \sigma_n \vec{v} \cdot d\vec{A} \end{aligned}$$

We make use of the definition of specific volume (ν)

$$\rho = \frac{1}{\nu}$$

and then we can combine like integrals to obtain

$$\begin{aligned} \dot{Q} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} \\ = \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz \right) \rho \vec{v} \cdot d\vec{A} - \int_{\text{area}} \sigma_n \nu \rho \vec{v} \cdot d\vec{A} \\ = \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz - \sigma_n \nu \right) \rho \vec{v} \cdot d\vec{A} \end{aligned}$$

From a previous discussion, we have defined that the normal stress is equal to the negative of the average hydrostatic pressure (in most cases without large viscous effects); therefore,

$$\begin{aligned} \dot{Q} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} &= \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV \\ &+ \int_{\text{area}} \left(u + \frac{v^2}{2} + gz + pv \right) \rho \vec{v} \cdot d\vec{A} \end{aligned} \quad (3.47)$$

In most cases for this textbook, the pressure is acting in one dimension and we do not consider the hydrostatic pressure in the remaining directions.

Example 3.8

One of the functions of the cardiovascular system is to act as a heat exchanger, to maintain body temperature (Fig. 3.18). Calculate the rate of heat transfer through a capillary bed, assuming that the blood velocity into the capillary is 100 mm/s and the flow velocity out of the capillary bed is 40 mm/s. The pressure on the arterial side is 20 mmHg, and the pressure on the venous side is 12 mmHg. Assume that the arteriole diameter is 75 μm and the venule diameter is 50 μm . The temperature on the arterial side is 35°C, and the temperature on the venous side is 33°C. Assume that the power put into the system throughout the muscular system is 15 μW .

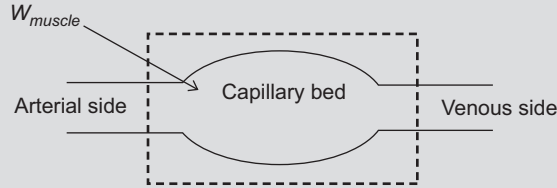


FIG. 3.18 Schematic of a capillary heat exchanger for Example 3.8.

Solution

To solve this problem, we will make the assumptions that the flow is steady and uniform, the height difference between the arterial side and venous side is zero, and there is negligible internal energy or work done by stresses in the capillary bed. Note that for this problem, the conservation of mass does not hold across the capillary bed, because fluid is lost into the interstitial space

$$\begin{aligned} \dot{Q} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} &= \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz + pv \right) \rho \vec{v} \cdot d\vec{A} \\ \dot{Q} &= -\dot{W}_{\text{muscle}} + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz + pv \right) \rho \vec{v} \cdot d\vec{A} \end{aligned}$$

Continued

Example 3.8 (*cont'd*)

$$\dot{Q} = -\dot{W}_{\text{muscle}} + \left(\frac{v_1^2}{2} + gz_1 + p_1 v_1 \right) (-\rho v_1 A_1) + \left(\frac{v_2^2}{2} + gz_2 + p_2 v_2 \right) (\rho v_2 A_2)$$

Substituting known values into this equation

$$\begin{aligned} \dot{Q} &= -15 \mu W + \left(\frac{\left(100 \frac{\text{mm}}{\text{s}}\right)^2}{2} + gz_1 + \frac{20 \text{ mmHg}}{1050 \frac{\text{kg}}{\text{m}^3}} \right) \left(- \left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(100 \frac{\text{mm}}{\text{s}}\right) \pi \left(\frac{75 \mu\text{m}}{2}\right)^2 \right) \\ &\quad + \left(\frac{\left(40 \frac{\text{mm}}{\text{s}}\right)^2}{2} + gz_2 + \frac{12 \text{ mmHg}}{1050 \frac{\text{kg}}{\text{m}^3}} \right) \left(\left(1050 \frac{\text{kg}}{\text{m}^3}\right) \left(40 \frac{\text{mm}}{\text{s}}\right) \pi \left(\frac{50 \mu\text{m}}{2}\right)^2 \right) \\ &= -15 \mu W + \left(-1 \mu W - \left(4.64_E - 4 \frac{\text{g}}{\text{s}}\right) gz_1 \right) + \left(0.126 \mu W + \left(8.25_E - 5 \frac{\text{g}}{\text{s}}\right) gz_2 \right) \\ &= -15.874 \mu W + g(0.825_E - 4(z_2) - 4.64_E - 4(z_1)) \frac{\text{g}}{\text{s}} \end{aligned}$$

We are making the assumption that there is no height difference between the arterial side and venous side ($z_2 = z_1$).

Therefore, the rate of heat transfer is $-15.874 \mu W$. For every millimeter difference in height, where z_2 is lower than z_1 , the rate of heat transfer would change by approximately -0.8 nW .

Example 3.9

Calculate the time rate of change of mass flow rate ($\rho v A$) of air entering the lungs. Assume that the lungs have a capacity of 6 L. The temperature of the lungs is 37°C . The air pressure inside of the lungs is 0.98 atm. At the instant that air enters the lungs, the temperature of the lungs raises by 0.0001°C/s . The height of the trachea is 20 cm. Assume that there is no work added to the system. Assume that air behaves as an ideal gas. Assume that the velocity is slow within the trachea.

Solution

$$\begin{aligned} \dot{Q} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} &= \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV \\ &\quad + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz + p v \right) \rho \vec{v} \cdot d\vec{A} \end{aligned}$$

From the assumptions made, the governing equation can be simplified to

Example 3.9 (cont'd)

$$0 = \frac{\partial}{\partial t} \int_V (u + gz) \rho dV + \int_{\text{area}} (u + gz + p\nu) \rho \vec{v} \cdot d\vec{A}$$

because there is no work/heat done by the system. We also assume that because the velocity is slow, the square of the velocity can be neglected. The velocity is included in the second area integral so we can calculate the mass flow rate. In addition, we will make the assumption that the internal potential energy of the system, height, gravity, density, and pressure are not functions of the volume of interest or the inflow area.

$$\begin{aligned} 0 &= \frac{\partial}{\partial t} \int_V (u + gz) \rho dV + (u + gz + p\nu)(-\rho v A) = \frac{\partial}{\partial t} [(u + gz)m] - (u + gz + p\nu)(\dot{m}) \\ &= \frac{\partial}{\partial t} (um + gzm) - (u + gz + p\nu)(\dot{m}) \\ &= \frac{\partial}{\partial t} (um) + \frac{\partial}{\partial t} (gzm) - u \frac{\partial m}{\partial t} - gz \frac{\partial m}{\partial t} - p\nu \frac{\partial m}{\partial t} \end{aligned}$$

This is found by taking the area/volume integrals (making the assumption that none of the variables are a function of area/volume) and replacing the $\rho v A$ term with $\dot{m}$. We also distribute the partial derivative across the summation and replace $\dot{m}$ with $\partial m / \partial t$. By making use of the product rule we can arrive at

$$\begin{aligned} 0 &= m \frac{\partial u}{\partial t} + u \frac{\partial m}{\partial t} + m \frac{\partial (gz)}{\partial t} + gz \frac{\partial m}{\partial t} - u \frac{\partial m}{\partial t} - gz \frac{\partial m}{\partial t} - p\nu \frac{\partial m}{\partial t} = m \frac{\partial u}{\partial t} - p\nu \frac{\partial m}{\partial t} \\ \dot{m} &= \frac{\partial m}{\partial t} = \frac{m}{p\nu} \frac{\partial u}{\partial t} \end{aligned}$$

if you make the assumption that the gravitational constant and height are not functions of time and rearrange the variables. Since we were told that the air behaves as an ideal gas, the following definitions apply.

$$\begin{aligned} m &= \rho V \\ p\nu &= \frac{p}{\rho} = RT \\ \frac{\partial u}{\partial t} &= C_v \frac{dT}{dt} \end{aligned}$$

to obtain

$$\begin{aligned} \dot{m} &= \frac{m}{p\nu} \frac{\partial u}{\partial t} = \frac{\rho V}{RT} C_v \frac{dT}{dt} = \frac{pV}{R^2 T^2} C_v \frac{dT}{dt} \\ \dot{m} &= \frac{0.98 \text{ atm} * 6L}{(287 \text{ Nm/kgK})^2 ((37 + 273) \text{ K})^2} \left(717 \frac{\text{Nm}}{\text{kgK}} \right) \left(\frac{0.0001 \text{ K}}{\text{s}} \right) = 3.24_E - 4 \text{ g/min} \end{aligned}$$

This is consistent with normal breathing.

The second law of thermodynamics is a statement about the disorder of a system. It states that the change of entropy of a system is greater than or equal to the amount of heat added to the system at a particular temperature.

$$dS \geq \frac{dQ}{T} \quad (3.48)$$

The time rate of change of entropy can therefore be defined as

$$\frac{dS}{dt} \geq \frac{\dot{Q}}{T} \quad (3.49)$$

for one specific volume of interest. When developing Eq. (3.22), we stated that for energy conservation the system property was S and the inherent property was s (entropy per unit mass). Substituting these values into Eq. (3.22), we have a statement for the conservation of energy related to the second law of thermodynamics.

$$\frac{dS}{dt} = \frac{\partial}{\partial t} \int_V s \rho dV + \int_{\text{area}} s \rho \vec{v} \cdot d\vec{A} \quad (3.50)$$

Substituting Eq. (3.49) into Eq. (3.50),

$$\frac{\partial}{\partial t} \int_V s \rho dV + \int_{\text{area}} s \rho \vec{v} \cdot d\vec{A} \geq \frac{\dot{Q}}{T} \quad (3.51)$$

Eq. (3.51) is a statement of the second law of thermodynamics, which can be directly applied to fluid mechanics problems. In some instances, it may be useful to know that

$$\left(\frac{\dot{Q}}{T} \right)_V = \int_{\text{area}} \frac{\dot{Q}}{AT} dA \quad (3.52)$$

$\dot{Q}/A$ is defined as the heat flux along one particular area. This is normally constant for one particular surface area of interest if the material properties of the bounding channel do not change.

3.7 The Navier–Stokes equations

In the previous sections, we have applied various physical laws to a fluid volume of interest. However, to obtain an equation that describes the motion of the fluid at any time or location within the flow field, it may be easier to apply Newton's second law of motion to a particle. For a system such as this, Newton's second law becomes

$$d\vec{F} = dm \frac{d\vec{v}}{dt} \quad (3.53)$$

The derivation for the acceleration of a fluid particle has already been shown in Chapter 2. Using that relationship for particle acceleration, Newton's law becomes

$$d\vec{F} = dm \left(\frac{\partial \vec{v}}{\partial t} + u \frac{\partial \vec{v}}{\partial x} + v \frac{\partial \vec{v}}{\partial y} + w \frac{\partial \vec{v}}{\partial z} \right) \quad (3.54)$$

As discussed before, the forces on a fluid particle can be body forces or surface forces. To define these forces, let us look at the forces that act on a differential element with mass dm and volume $dV = dxdydz$. As done previously to describe the pressure acting on a differential element, we will assume that the stresses acting at the cubes center (denoted as p on Fig. 3.19) are σ_{xx} , τ_{yx} , and (see Fig. 3.19). Note that only the stresses that act in the x -direction are shown on this figure and used for our derivation. However, the same discussion applies to the other Cartesian directions, and the forces that act in those directions will be used in the final form of the equation.

Summating the forces in the x -direction as a component of the total surface forces,

$$\begin{aligned} dF_{sx} &= \left(\sigma_{xx} + \frac{\partial \sigma_{xx}}{\partial x} \frac{dx}{2} \right) dydz - \left(\sigma_{xx} - \frac{\partial \sigma_{xx}}{\partial x} \frac{dx}{2} \right) dydz + \left(\tau_{yx} + \frac{\partial \tau_{yx}}{\partial y} \frac{dy}{2} \right) dxdz \\ &\quad - \left(\tau_{yx} - \frac{\partial \tau_{yx}}{\partial y} \frac{dy}{2} \right) dxdz + \left(\tau_{zx} + \frac{\partial \tau_{zx}}{\partial z} \frac{dz}{2} \right) dxdy - \left(\tau_{zx} - \frac{\partial \tau_{zx}}{\partial z} \frac{dz}{2} \right) dxdy \\ &= \left(\frac{\partial \sigma_{xx}}{\partial x} + \frac{\partial \tau_{yx}}{\partial y} + \frac{\partial \tau_{zx}}{\partial z} \right) dxdydz \end{aligned} \quad (3.55)$$

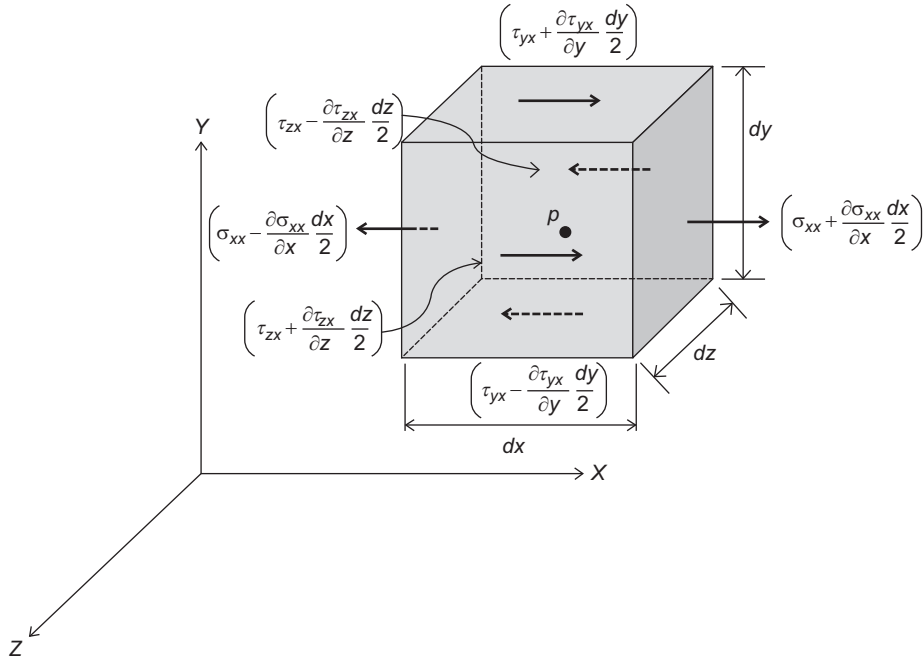


FIG. 3.19 The normal and shear stresses acting in the x -direction on a differential fluid element. The stresses that act in the other Cartesian directions can be derived in a similar manner. Recall that only six of these stress values are independent for momentum conservation.

Eq. (3.55) is derived from the known stresses that act at point P , plus or minus the spatial gradient of the stress multiplied by the distance from P to the surface of interest of the cube. To obtain a force, the stress that was quantified is then multiplied by the area over which it acts. Using a similar analysis for each of the remaining two directions and assuming that the gravitational force is the only body force, the summation of the force in each direction becomes

$$\begin{aligned} dF_x &= dF_{bx} + dF_{sx} = \left(\rho g_x + \frac{\partial \sigma_{xx}}{\partial x} + \frac{\partial \tau_{yx}}{\partial y} + \frac{\partial \tau_{zx}}{\partial z} \right) dx dy dz \\ dF_y &= dF_{by} + dF_{sy} = \left(\rho g_y + \frac{\partial \tau_{xy}}{\partial x} + \frac{\partial \sigma_{yy}}{\partial y} + \frac{\partial \tau_{zy}}{\partial z} \right) dx dy dz \\ dF_z &= dF_{bz} + dF_{sz} = \left(\rho g_z + \frac{\partial \tau_{xz}}{\partial x} + \frac{\partial \tau_{yz}}{\partial y} + \frac{\partial \sigma_{zz}}{\partial z} \right) dx dy dz \end{aligned} \quad (3.56)$$

For this formulation, we do not assume that gravity aligns with a particular Cartesian direction; however, if the gravitational force aligns with one direction, the equation set will simplify somewhat. Substituting Eq. (3.56) into Eq. (3.54) and writing the velocity in terms of its vector components gives us

$$\begin{aligned} \left(\rho g_x + \frac{\partial \sigma_{xx}}{\partial x} + \frac{\partial \tau_{yx}}{\partial y} + \frac{\partial \tau_{zx}}{\partial z} \right) dx dy dz &= dm \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) \\ \left(\rho g_y + \frac{\partial \tau_{xy}}{\partial x} + \frac{\partial \sigma_{yy}}{\partial y} + \frac{\partial \tau_{zy}}{\partial z} \right) dx dy dz &= dm \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) \\ \left(\rho g_z + \frac{\partial \tau_{xz}}{\partial x} + \frac{\partial \tau_{yz}}{\partial y} + \frac{\partial \sigma_{zz}}{\partial z} \right) dx dy dz &= dm \left(\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) \end{aligned}$$

Using the relationship that $dm = \rho dV = \rho dx dy dz$, the equations of motion become

$$\begin{aligned} \left(\rho g_x + \frac{\partial \sigma_{xx}}{\partial x} + \frac{\partial \tau_{yx}}{\partial y} + \frac{\partial \tau_{zx}}{\partial z} \right) &= \rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) = \rho \frac{Du}{Dt} \\ \left(\rho g_y + \frac{\partial \tau_{xy}}{\partial x} + \frac{\partial \sigma_{yy}}{\partial y} + \frac{\partial \tau_{zy}}{\partial z} \right) &= \rho \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) = \rho \frac{Dv}{Dt} \\ \left(\rho g_z + \frac{\partial \tau_{xz}}{\partial x} + \frac{\partial \tau_{yz}}{\partial y} + \frac{\partial \sigma_{zz}}{\partial z} \right) &= \rho \left(\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) = \rho \frac{Dw}{Dt} \end{aligned} \quad (3.57)$$

Eq. (3.57) is the differential equations of motion, which are valid for any fluid that is a continuum and for any fluid that has the force of gravity as the only body force. In Chapter 2, we defined the normal stress as a function of hydrostatic pressure and the shear stresses as a function of viscosity and shear rate (which is a function of velocity). The following definitions apply for incompressible Newtonian fluids (complete derivations of these formulas can be found in classical fluid mechanics textbooks).

$$\begin{aligned}
\sigma_{xx} &= -p - \frac{2}{3}\mu \nabla \cdot \vec{v} + 2\mu \frac{\partial u}{\partial x} \\
\sigma_{yy} &= -p - \frac{2}{3}\mu \nabla \cdot \vec{v} + 2\mu \frac{\partial v}{\partial y} \\
\sigma_{zz} &= -p - \frac{2}{3}\mu \nabla \cdot \vec{v} + 2\mu \frac{\partial w}{\partial z} \\
\tau_{xy} &= \tau_{yx} = \mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \\
\tau_{xz} &= \tau_{zx} = \mu \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \\
\tau_{yz} &= \tau_{zy} = \mu \left(\frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right)
\end{aligned} \tag{3.58}$$

where ∇ is the gradient operator and is defined as

$$\nabla f = \frac{\partial f}{\partial x} \vec{i} + \frac{\partial f}{\partial y} \vec{j} + \frac{\partial f}{\partial z} \vec{k}$$

for any function, f , in the Cartesian coordinate system (note that the gradient function can be calculated in any coordinate system for any function; we are just highlighting the Cartesian coordinate system for the derivation of the Navier–Stokes equations in a Cartesian system). Recall that the pressure is the mean of the principal stresses for a fluid with these criteria.

Substituting Eq. (3.58) into Eq. (3.57), the equations of motion become

$$\begin{aligned}
\rho \frac{Du}{Dt} &= \left(\rho g_x + \frac{\partial \left(-p - \frac{2}{3}\mu \nabla \cdot \vec{v} + 2\mu \frac{\partial u}{\partial x} \right)}{\partial x} + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \right)}{\partial y} + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \right)}{\partial z} \right) \\
&= \rho g_x - \frac{\partial p}{\partial x} + \frac{\partial \left[\mu \left(2 \frac{\partial u}{\partial x} - \frac{2}{3} \nabla \cdot \vec{v} \right) \right]}{\partial x} + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \right)}{\partial y} + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \right)}{\partial z} \\
\rho \frac{Dv}{Dt} &= \left(\rho g_y + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \right)}{\partial x} + \frac{\partial \left(-p - \frac{2}{3}\mu \nabla \cdot \vec{v} + 2\mu \frac{\partial v}{\partial y} \right)}{\partial y} + \frac{\partial \left(\mu \left(\frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right) \right)}{\partial z} \right) \\
&= \rho g_y - \frac{\partial p}{\partial y} + \frac{\partial \left[\mu \left(2 \frac{\partial v}{\partial y} - \frac{2}{3} \nabla \cdot \vec{v} \right) \right]}{\partial y} + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \right)}{\partial x} + \frac{\partial \left(\mu \left(\frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right) \right)}{\partial z}
\end{aligned} \tag{3.59}$$

$$\begin{aligned}
\rho \frac{Dw}{Dt} &= \left(\rho g_z + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \right)}{\partial x} + \frac{\partial \left(\mu \left(\frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right) \right)}{\partial y} + \frac{\partial \left(-p - \frac{2}{3} \mu \nabla \cdot \vec{v} + 2\mu \frac{\partial w}{\partial z} \right)}{\partial z} \right) \\
&= \rho g_z - \frac{\partial p}{\partial z} + \frac{\partial \left[\mu \left(2 \frac{\partial w}{\partial z} - \frac{2}{3} \nabla \cdot \vec{v} \right) \right]}{\partial z} + \frac{\partial \left(\mu \left(\frac{\partial u}{\partial z} + \frac{\partial w}{\partial x} \right) \right)}{\partial x} + \frac{\partial \left(\mu \left(\frac{\partial v}{\partial z} + \frac{\partial w}{\partial y} \right) \right)}{\partial y}
\end{aligned}$$

Eq. (3.59) is the full Navier–Stokes equations that are valid for any fluid. If we assume that the fluid is incompressible and the viscosity is uniform and constant, the equations simplify to

$$\begin{aligned}
\rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= \rho g_x - \frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\
\rho \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) &= \rho g_y - \frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\
\rho \left(\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) &= \rho g_z - \frac{\partial p}{\partial z} + \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right)
\end{aligned} \tag{3.60}$$

Eq. (3.60) is the form of the Navier–Stokes equations that will be used often in this textbook. In many biofluid mechanics examples, however, it is more useful to solve the Navier–Stokes equations in a cylindrical coordinate system, because the fluid is flowing through a vessel that may be approximated with a cylindrical cross-section. The Navier–Stokes equations in cylindrical coordinates are as follows for incompressible fluids with a constant viscosity.

$$\begin{aligned}
\rho \left(\frac{\partial v_r}{\partial t} + v_r \frac{\partial v_r}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_r}{\partial \theta} - \frac{v_\theta^2}{r} + v_z \frac{\partial v_r}{\partial z} \right) &= \rho g_r - \frac{\partial p}{\partial r} + \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r v_r) \right) + \frac{1}{r^2} \frac{\partial^2 v_r}{\partial \theta^2} - \frac{2}{r^2} \frac{\partial v_\theta}{\partial \theta} + \frac{\partial^2 v_r}{\partial z^2} \right] \\
\rho \left(\frac{\partial v_z}{\partial t} + v_r \frac{\partial v_z}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_z}{\partial \theta} + v_z \frac{\partial v_z}{\partial z} \right) &= \rho g_z - \frac{\partial p}{\partial z} + \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_z}{\partial \theta^2} + \frac{\partial^2 v_z}{\partial z^2} \right] \\
\rho \left(\frac{\partial v_\theta}{\partial t} + v_r \frac{\partial v_\theta}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_\theta}{\partial \theta} + \frac{v_r v_\theta}{r} + v_z \frac{\partial v_\theta}{\partial z} \right) &= \rho g_\theta - \frac{1}{r} \frac{\partial p}{\partial \theta} + \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r v_\theta) \right) + \frac{1}{r^2} \frac{\partial^2 v_\theta}{\partial \theta^2} + \frac{2}{r^2} \frac{\partial v_r}{\partial \theta} + \frac{\partial^2 v_\theta}{\partial z^2} \right]
\end{aligned} \tag{3.61}$$

Examples 3.10 and 3.11 illustrate how to use either the Cartesian form or the cylindrical form of the Navier–Stokes equations. Remember that the usefulness of these equations is that the fully developed velocity profile (e.g., the velocity as a function of space and time) of any flowing fluid can be determined. If the flow is 1D, this can be easily solved by hand; however, with flows in multiple dimensions, solutions to coupled differential equations may be needed. We will show through these two examples that the form of the Navier–Stokes equations do not matter significantly for the problem solution.

Example 3.10

Find an expression for the velocity profile and the shear stress (τ_{xy}) distribution for blood flowing in an arteriole with a diameter of 500 μm . Use the Navier–Stokes equations for Cartesian coordinates to solve this problem. The pressure driving this flow is given in Fig. 3.20. Assume that the flow is fully developed.

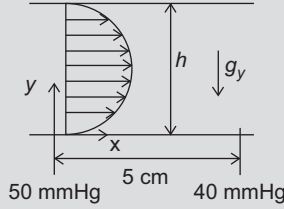


FIG. 3.20 Pressure-driven flow in an arteriole for Example 3.10.

Solution

To solve this problem, assume that $v_y = v_z = 0$ and v_x is a function of y only. Assume that the viscosity is constant and that the flow is incompressible and steady.

$$\begin{aligned}\rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= \rho g_x - \frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\ 0 &= -\frac{\partial p}{\partial x} + \mu \frac{\partial^2 u}{\partial y^2} = -\frac{\partial p}{\partial x} + \mu \frac{d^2 u}{dy^2} \\ \frac{d^2 u}{dy^2} &= \frac{1}{\mu} \frac{\partial p}{\partial x} \rightarrow d^2 u = \frac{1}{\mu} \frac{\partial p}{\partial x} dy^2 \\ \int d^2 u &= \int \frac{1}{\mu} \frac{\partial p}{\partial x} dy^2 \\ du &= \left(\frac{y}{\mu} \frac{\partial p}{\partial x} + c_1 \right) dy \\ \int du &= \int \left(\frac{y}{\mu} \frac{\partial p}{\partial x} + c_1 \right) dy \\ u(y) &= \frac{y^2}{2\mu} \frac{\partial p}{\partial x} + c_1 y + c_2\end{aligned}$$

To find the exact solution, we need boundary conditions that are associated with the particular flow scenario. Because of the no-slip boundary condition, we know that the velocity at both walls is zero and the shear stress at the channel centerline is zero. Therefore, our boundary conditions are

$$\begin{aligned}u(0) &= 0 \\ u(h) &= 0 \\ \frac{du(h/2)}{dy} &= 0\end{aligned}$$

Continued

Example 3.10 (*cont'd*)

Using two of these boundary conditions to solve for the integration constants,

$$u(0) = \frac{0^2}{2\mu} \frac{\partial p}{\partial x} + c_1 * 0 + c_2 = 0$$

$$c_2 = 0$$

$$\frac{du(h/2)}{dy} = \frac{h/2}{\mu} \frac{\partial p}{\partial x} + c_1 = 0$$

$$c_1 = -\frac{h}{2\mu} \frac{\partial p}{\partial x}$$

Substituting the values for these integration constants into the velocity equation,

$$u(y) = \frac{y^2}{2\mu} \frac{\partial p}{\partial x} - \frac{h}{2\mu} \frac{\partial p}{\partial x} y = \frac{1}{2\mu} \frac{\partial p}{\partial x} (y^2 - hy)$$

For this particular flow scenario

$$\mu = 3.5 \text{ cP}$$

$$\frac{\partial p}{\partial x} = \frac{40 \text{ mmHg} - 50 \text{ mmHg}}{5 \text{ cm} - 0 \text{ cm}} = -2 \text{ mmHg/cm}$$

$$h = 500 \text{ }\mu\text{m}$$

$$u(y) = \frac{1}{2 * 3.5 \text{ cP}} (-2 \text{ mmHg / cm}) (y^2 - (500 \text{ }\mu\text{m})y) = \frac{-3.81}{\mu\text{ms}} (y^2 - (500 \text{ }\mu\text{m})y)$$

The shear stress profile for this particular flow is equal to

$$\tau_{xy} = \mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) = \mu \frac{\partial u}{\partial y}$$

$$\tau_{xy} = \mu \left(\frac{y}{\mu} \frac{\partial p}{\partial x} - \frac{h}{2\mu} \frac{\partial p}{\partial x} \right) = \frac{\partial p}{\partial x} \left(y - \frac{h}{2} \right)$$

Substituting the appropriate known values for this particular scenario,

$$\tau_{xy} = \mu \left(\frac{y}{\mu} \frac{\partial p}{\partial x} - \frac{h}{2\mu} \frac{\partial p}{\partial x} \right) = \frac{\partial p}{\partial x} \left(y - \frac{h}{2} \right)$$

$$= -0.267 \text{ dyne/cm}^2 \text{ }\mu\text{m}(y - 250 \text{ }\mu\text{m})$$

Example 3.11

Find an expression for the velocity profile and the shear stress distribution for blood flowing in an arteriole with a diameter of 500 μm . Use the Navier–Stokes equations for cylindrical

Example 3.11 (cont'd)

coordinates to solve this problem. The pressure driving this flow is given in Fig. 3.21. Assume that the flow is fully developed

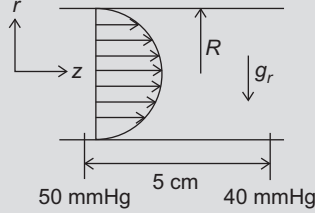


FIG. 3.21 Pressure-driven flow in an arteriole with cylindrical coordinates for Example 3.11. This is the same image as Fig. 3.20, but choosing a different coordinate system to illustrate the usage of Cartesian coordinates versus cylindrical coordinates.

Solution

To solve this problem, assume that $v_r = v_\theta = 0$ and v_z is a function of r only. Assume that the viscosity is constant and that the flow is incompressible and steady.

$$\begin{aligned} \rho \left(\frac{\partial v_z}{\partial t} + v_r \frac{\partial v_z}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_z}{\partial \theta} + v_z \frac{\partial v_z}{\partial z} \right) &= \rho g_z - \frac{\partial p}{\partial z} + \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_z}{\partial \theta^2} + \frac{\partial^2 v_z}{\partial z^2} \right] \\ 0 &= -\frac{\partial p}{\partial z} + \frac{\mu}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) \\ \frac{r}{\mu} \frac{\partial p}{\partial z} &= \frac{d}{dr} \left(r \frac{dv_z}{dr} \right) \\ \int \frac{r}{\mu} \frac{\partial p}{\partial z} dr &= \int d \left(r \frac{dv_z}{dr} \right) \\ \frac{r^2}{2\mu} \frac{\partial p}{\partial z} + c_1 &= r \frac{dv_z}{dr} \rightarrow \frac{r}{2\mu} \frac{\partial p}{\partial z} + \frac{c_1}{r} = \frac{dv_z}{dr} \\ \int \left(\frac{r}{2\mu} \frac{\partial p}{\partial z} + \frac{c_1}{r} \right) dr &= \int dv_z \\ v_z(r) &= \frac{r^2}{4\mu} \frac{\partial p}{\partial z} + c_1 \ln(r) + c_2 \end{aligned}$$

To find the exact solution, we need boundary conditions for the particular flow scenario. Because of the no-slip boundary condition, we know that the velocity at the wall is zero and that the shear stress at the centerline is zero. Therefore our boundary conditions are

$$\begin{aligned} v_z(R) &= 0 \\ \frac{dv_z(0)}{dr} &= 0 \end{aligned}$$

Note that we do not have a boundary condition of $v_z(-R) = 0$, because in cylindrical coordinates there is no negative radial direction. This location would be associated with 180

Continued

Example 3.11 (*cont'd*)

degrees in the theta direction and $+R$ in the radial direction. Using these conditions to solve for the integration constants,

$$\frac{dv_z(0)}{dr} = \frac{0}{2\mu} \frac{\partial p}{\partial z} + \frac{c_1}{0} = 0$$

Because of the discontinuity at $r = 0$, the only way for this equation to be valid is for $c_1 = 0$. Therefore, the discontinuity is removed from the equation set. Using the second boundary condition,

$$v_z(R) = \frac{R^2}{4\mu} \frac{\partial p}{\partial z} + c_2 = 0$$

$$c_2 = -\frac{R^2}{4\mu} \frac{\partial p}{\partial z}$$

Substituting the values for the integration constants into the velocity equation,

$$v_z(r) = \frac{r^2}{4\mu} \frac{\partial p}{\partial z} - \frac{R^2}{4\mu} \frac{\partial p}{\partial z} = \frac{R^2}{4\mu} \frac{\partial p}{\partial z} \left(\left(\frac{r}{R} \right)^2 - 1 \right)$$

For this particular flow scenario, we can use the same numerical values as illustrated in Example 3.10,

$$v_z(r) = \frac{R^2}{4\mu} \frac{\partial p}{\partial z} \left(\left(\frac{r}{R} \right)^2 - 1 \right) = -11.9 \text{ cm/s} \left(\frac{r^2}{62,500 \mu\text{m}^2} - 1 \right)$$

The shear stress distribution is

$$\tau_{zr} = \mu \left(\frac{\partial v_r}{\partial z} + \frac{\partial v_z}{\partial r} \right) = \mu \frac{\partial v_z}{\partial r}$$

$$\tau_{zr} = \mu \left(\frac{r}{2\mu} \frac{\partial p}{\partial z} \right) = \frac{r}{2} \frac{\partial p}{\partial z} = -0.1332 \text{ dyne/cm}^2 \mu\text{m}(r)$$

3.8 Bernoulli equation

The Bernoulli equation is a useful formula that relates the hydrostatic pressure, the fluid height, and the speed of a fluid element. However, there are a few important assumptions that are made during the derivation of this formula, which makes this powerful equation not necessarily the most useful in many biofluid mechanics applications, although as a back-of-the-envelope calculation, the Bernoulli equation can approximate real flow scenarios with reasonable accuracy. To derive this equation, the conservation of mass and conservation of momentum equations are simplified by making the assumptions that the flow is steady, incompressible, and inviscid (has no viscosity). We will reiterate the point that these assumptions may not be valid for the particular flow conditions.

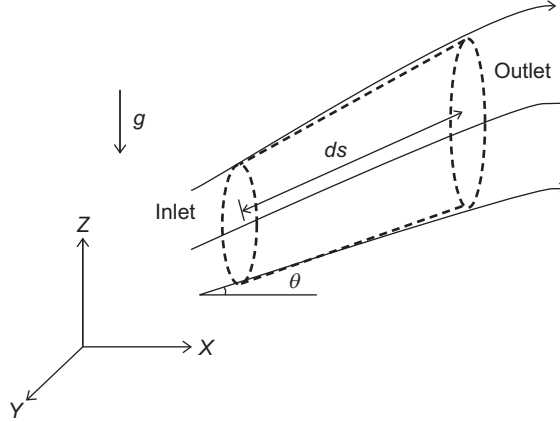


FIG. 3.22 A differential volume of fluid following expanding streamlines (streamlines are the *curved arrows* in the figure). The expansion causes an increase in area at the outlet compared with the inlet.

To derive the Bernoulli equation, let us follow a differential volume of fluid in an expanding streamline (Fig. 3.22). The applicable fluid properties at the inlet will be denoted as p_i, v_i, A_i , and ρ . The applicable fluid properties at the outlet will be denoted as $p_i + dp_i, v_i + dv_i, A_i + dA_i$, and ρ . This same analysis can be conducted for a reducing streamline, where the solution would include negative differential changes, as necessary.

Applying the conservation of mass to this condition, we find that

$$0 = \frac{\partial}{\partial t} \int_V \rho dV + \int_{\text{area}} \rho \vec{v} \cdot d\vec{A}$$

$$0 = \int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = -\rho v_i A_i + \rho(v_i + dv_i)(A_i + dA_i)$$

because we assumed that the flow is steady and incompressible, the time rate of change of mass within the control volume is equal to zero, and density is not a function of the flow conditions. Again, the inflow conditions have a negative term and the outflow conditions are positive because of the direction of the velocity/area normal vector. Simplifying the previous equation (by multiplying), we can obtain

$$\rho v_i A_i = \rho(v_i A_i + v_i dA_i + A_i dv_i + dv_i dA_i) = \rho v_i A_i + \rho v_i dA_i + \rho A_i dv_i + \rho dv_i dA_i \quad (3.62)$$

Remember that the product of two differentials ($dv_i dA_i$) is going to be negligible compared with the remaining terms, which allows us to simplify Eq. (3.62) to

$$0 = v_i dA_i + A_i dv_i \quad (3.63)$$

Under the assumed conditions, the conservation of mass can simplify to [Eq. \(3.63\)](#). Now we will simplify the conservation of momentum equation in the streamline direction (s). The conservation of momentum states that

$$F_{bs} + F_{ss} = \frac{\partial}{\partial t} \int_V v_s \rho dV + \int_{\text{area}} v_s \rho \vec{v} \cdot d\vec{A}$$

for the streamline direction (subscript s). Because we are assuming steady flow, this formula simplifies to

$$F_{bs} + F_{ss} = \int_{\text{area}} v_s \rho \vec{v} \cdot d\vec{A} \quad (3.64)$$

Since the fluid is inviscid, the only forces that arise are from the pressure acting on the two surfaces and the surrounding fluid and the body force because of gravity. These forces are

$$\begin{aligned} F_{ss} &= p_i A_i - (p_i + dp_i)(A_i + dA_i) + \left(p_i + \frac{dp_i}{2}\right) dA_i = -A_i dp_i \\ F_{bs} &= g_s \rho dV = (-g \sin \theta) \rho \left(A + \frac{dA_i}{2}\right) ds = -\rho g \left(A_i + \frac{dA_i}{2}\right) dz \end{aligned} \quad (3.65)$$

because $\sin \theta ds = dz$. The differential volume term (dV in the F_{bs} equation) is an approximation of the volume using the midpoint volume of the flow channel. The same analysis was used to approximate the pressure on the surrounding fluid; that is, use the midpoint pressure as the approximate pressure acting on the surfaces of the fluid. The flux term in [Eq. \(3.64\)](#) is equal to

$$\int_{\text{area}} v_s \rho \vec{v} \cdot d\vec{A} = v_i (-\rho v_i A_i) + (v_i + dv_i) (\rho (v_i + dv_i) (A_i + dA_i))$$

making use of the inflow/outflow conditions, as we have in the past. From the continuity equation (before simplifying the term)

$$v_i (-\rho v_i A_i) + (v_i + dv_i) (\rho (v_i + dv_i) (A_i + dA_i)) = v_i (-\rho v_i A_i) + (v_i + dv_i) (\rho v_i A_i) = \rho v_i A_i dv_i \quad (3.66)$$

Substituting [Eqs. \(3.65\)](#) and [\(3.66\)](#) into the momentum equation ([Eq. \(3.64\)](#))

$$-A_i dp - \rho g \left(A_i + \frac{dA_i}{2}\right) dz = -A_i dp_i - \rho g A_i dz = \rho v_i A_i dv_i$$

If we divide this equation by ρA_i , and simplify the velocity derivative (making use of a chain rule),

$$0 = v_i dv_i + \frac{dp_i}{\rho} + g dz = d\left(\frac{v_i^2}{2}\right) + \frac{dp_i}{\rho} + g dz$$

Integrating this equation and dropping the subscripts, we obtain the Bernoulli equation.

$$\frac{v^2}{2} + \frac{p}{\rho} + g z = \text{constant} \quad (3.67)$$

As we stated before, the Bernoulli equation is a powerful equation that relates the flow speed, the hydrostatic pressure, and the height differences at the inlet and outlet to a constant value for the particular flow conditions. It can be applied only to a situation in which the flow is steady, inviscid, and incompressible. In developing this relationship, we used a differential element, in which these three criteria were valid. In most cases, it will not be easy to justify the use of the Bernoulli equation instead of the Navier–Stokes equations, the conservation of mass, and the conservation of momentum formulations. However, as Example 3.12 will show, we can use the Bernoulli equation as an approximation for various flow situations. In this simplified form, the Bernoulli equation is a statement of the conservation of energy for an inviscid fluid.

Example 3.12

Blood flow from the left ventricle into the aorta can be modeled as a reducing nozzle (Fig. 3.23). Model both the left ventricle and the aorta as a tube with a diameter of 3.1 and 2.7 cm, respectively. The pressure in the left ventricle is 130 mmHg, and the pressure in the aorta is 123 mmHg. Blood is ejected from the left ventricle at a speed of 120 cm/s. Calculate the difference in height between these two locations.

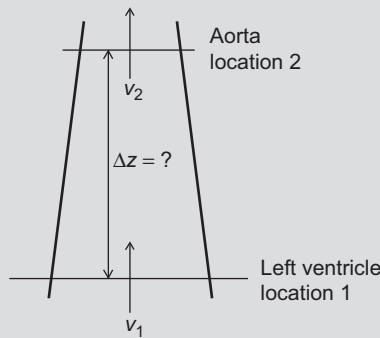


FIG. 3.23 Schematic of the aorta downstream to the left ventricle. The aorta would experience a slight contraction within this area.

Continued

Example 3.12 (cont'd)**Solution**

To solve this problem, we need to assume that the flow is steady, incompressible, and inviscid so that we can apply the Bernoulli principle. Apply the conservation of mass to determine the blood velocity within the aorta.

$$0 = \int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = -\rho v_1 A_1 + \rho v_2 A_2$$

$$v_2 = \frac{v_1 A_1}{A_2} = \frac{120 \frac{\text{cm}}{\text{s}} * \pi \left(\frac{3.1 \text{ cm}}{2} \right)^2}{\pi \left(\frac{2.7 \text{ cm}}{2} \right)^2} = 158 \frac{\text{cm}}{\text{s}}$$

Note, again, that we are seeing an acceleration of the fluid because of the decrease in area; this may not match the physiology well because blood vessels are not rigid. Regardless, we are illustrating a coupling of conservation of mass and the Bernoulli equation. Using the Bernoulli equation to solve for the difference in height

$$\begin{aligned} \frac{v_1^2}{2} + \frac{p_1}{\rho} + g z_1 &= \frac{v_2^2}{2} + \frac{p_2}{\rho} + g z_2 \\ g(z_2 - z_1) &= \frac{v_1^2}{2} + \frac{p_1}{\rho} - \frac{v_2^2}{2} - \frac{p_2}{\rho} \\ z_2 - z_1 &= \frac{\frac{v_1^2}{2} + \frac{p_1}{\rho} - \frac{v_2^2}{2} - \frac{p_2}{\rho}}{g} \\ &= \frac{\frac{(120 \text{ cm/s})^2}{2} + \frac{130 \text{ mmHg}}{1050 \text{ kg/m}^3} - \frac{(158 \text{ cm/s})^2}{2} - \frac{123 \text{ mmHg}}{1050 \text{ kg/m}^3}}{9.81 \text{ m/s}^2} = 3.68 \text{ cm} \end{aligned}$$

As you can imagine from Example 3.12, using the Bernoulli equation and the conservation of mass equations, we can estimate velocity, pressure, or height of a particular fluid. We want to emphasize that this is only an estimate in most real cases, because we need to make the assumption that the flow is inviscid to apply the Bernoulli equation. Use caution when applying this powerful relationship. In most situations, if the blood vessel is large enough (e.g., aorta or vena cava), the Bernoulli equation can be applied, but as the vessel diameter reduces, the viscous forces play a more critical role in the flow. Therefore, under these conditions, the Bernoulli equation cannot be used in these situations and the Navier–Stokes equations, the conservation of momentum, and the conservation of mass should be applied.

Summary

- 3.1. The body forces acting on a differential fluid element are $d\vec{F}_b = \vec{g}dm = \vec{g}\rho dxdydz$. The surface forces acting on a differential fluid element are $d\vec{F}_s = -\nabla\vec{p}dxdydz$. For static fluids, where all acceleration terms are zero, the pressure gradient is equal to the gravitational acceleration multiplied by the fluid density. In Cartesian components, this is

$$\begin{aligned}-\frac{\partial p}{\partial x} + \rho g_x &= 0 \\ -\frac{\partial p}{\partial y} + \rho g_y &= 0 \\ -\frac{\partial p}{\partial z} + \rho g_z &= 0\end{aligned}$$

Most pressures that are recorded in biofluids are gauge pressures, which can be defined as

$$p_{\text{gauge}} = p_{\text{absolute}} - p_{\text{atmospheric}}$$

- 3.2. Buoyancy is the net vertical force that acts on a floating or an immersed object. The buoyancy forces can be defined as

$$F_z = \int_V dF_z = \int_V \rho g dV = \rho g V$$

- 3.3. A generalized formulation for the time rate of change of a system property can be represented as

$$\frac{dW}{dt} = \frac{\partial}{\partial t} \int_V w \rho dV + \int_{\text{area}} w \rho \vec{v} \cdot d\vec{A}$$

Applying this formulation to the conservation of mass, we would get

$$\left. \frac{dm}{dt} \right|_{\text{system}} = \frac{\partial}{\partial t} \int_V \rho dV + \int_{\text{area}} \rho \vec{v} \cdot d\vec{A} = 0$$

Depending on the particular flow conditions, the conservation of mass formula can be simplified in various ways.

- 3.4. The conservation of momentum can be represented as

$$\frac{dP}{dt} = \vec{F} = \vec{F}_b + \vec{F}_s = \frac{\partial}{\partial t} \int_V \vec{v} \rho dV + \int_{\text{area}} \vec{v} \rho \vec{v} \cdot d\vec{A}$$

Again, this can be simplified depending on the particular flow conditions.

3.5. The conservation of momentum may also include acceleration components, in a more generalized form. In Cartesian component form this would be

$$\begin{aligned}\vec{F}_{bx} + \vec{F}_{sx} - \int_V \vec{a}_{rx} \rho dV &= \frac{\partial}{\partial t} \int_V u_{xyz} \rho dV + \int_{\text{area}} u_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \\ \vec{F}_{by} + \vec{F}_{sy} - \int_V \vec{a}_{ry} \rho dV &= \frac{\partial}{\partial t} \int_V v_{xyz} \rho dV + \int_{\text{area}} v_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A} \\ \vec{F}_{bz} + \vec{F}_{sz} - \int_V \vec{a}_{rz} \rho dV &= \frac{\partial}{\partial t} \int_V w_{xyz} \rho dV + \int_{\text{area}} w_{xyz} \rho \vec{v}_{xyz} \cdot d\vec{A}\end{aligned}$$

3.6. It is common for heat exchange to occur within biological flows. To account for the conservation of energy within a fluid, the formulation would become

$$\dot{Q} - \dot{W} = \frac{\partial}{\partial t} \int_V e \rho dV + \int_{\text{area}} e \rho \vec{v} \cdot d\vec{A} = \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz \right) \rho \vec{v} \cdot d\vec{A}$$

The rate of work in this equation would need to account for all of the various work terms that may be applied to the fluid. In a simplified form, this would be

$$\dot{Q} + \int_{\text{area}} \vec{\tau} \cdot \vec{v} dA - \dot{W}_{\text{shaft}} - \dot{W}_{\text{other}} = \frac{\partial}{\partial t} \int_V \left(u + \frac{v^2}{2} + gz \right) \rho dV + \int_{\text{area}} \left(u + \frac{v^2}{2} + gz + pv \right) \rho \vec{v} \cdot d\vec{A}$$

The second law of thermodynamics can be applied to biofluids. It is represented as

$$\frac{\partial}{\partial t} \int_V s \rho dV + \int_{\text{area}} s \rho \vec{v} \cdot d\vec{A} \geq \frac{\dot{Q}}{T}$$

3.7. The Navier–Stokes equations are the solutions of Newton’s second law of motion applied to fluid flow. For incompressible flows with a constant viscosity, these equations simplify to

$$\begin{aligned}\rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= \rho g_x - \frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\ \rho \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) &= \rho g_y - \frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\ \rho \left(\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) &= \rho g_z - \frac{\partial p}{\partial z} + \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right)\end{aligned}$$

in Cartesian coordinates and

$$\rho \left(\frac{\partial v_r}{\partial t} + v_r \frac{\partial v_r}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_r}{\partial \theta} - \frac{v_\theta^2}{r} + v_z \frac{\partial v_r}{\partial z} \right) = \rho g_r - \frac{\partial p}{\partial r} + \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r v_r) \right) + \frac{1}{r^2} \frac{\partial^2 v_r}{\partial \theta^2} - \frac{2}{r^2} \frac{\partial v_\theta}{\partial \theta} + \frac{\partial^2 v_r}{\partial z^2} \right]$$

$$\rho \left(\frac{\partial v_z}{\partial t} + v_r \frac{\partial v_z}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_z}{\partial \theta} + v_z \frac{\partial v_z}{\partial z} \right) = \rho g_z - \frac{\partial p}{\partial z} + \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_z}{\partial \theta^2} + \frac{\partial^2 v_z}{\partial z^2} \right]$$

$$\rho \left(\frac{\partial v_\theta}{\partial t} + v_r \frac{\partial v_\theta}{\partial r} + \frac{v_\theta}{r} \frac{\partial v_\theta}{\partial \theta} + \frac{v_r v_\theta}{r} + v_z \frac{\partial v_\theta}{\partial z} \right) = \rho g_\theta - \frac{1}{r} \frac{\partial p}{\partial \theta} + \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r v_\theta) \right) + \frac{1}{r^2} \frac{\partial^2 v_\theta}{\partial \theta^2} + \frac{2}{r^2} \frac{\partial v_r}{\partial \theta} + \frac{\partial^2 v_\theta}{\partial z^2} \right]$$

in cylindrical coordinates. From either of these sets of equations, the fully developed fluid velocity profile can be directly solved for as a function of location within the flow field.

- 3.8. The Bernoulli equation is a useful formula that relates the pressure variation in a fluid to the height and the speed of the fluid element. However, this formulation is valid only for steady, incompressible, and inviscid flows. The Bernoulli equation states that

$$\frac{v^2}{2} + \frac{p}{\rho} + gz = \text{constant}$$

Homework problems

- 3.1. A two-fluid manometer is used to measure the pressure difference for flowing blood in a laboratory experiment (Fig. 3.24). Calculate the pressure difference between points A and B in the fluid. Assume that the density of blood is 1050 kg/m^3 and the density of water is 1000 kg/m^3 .

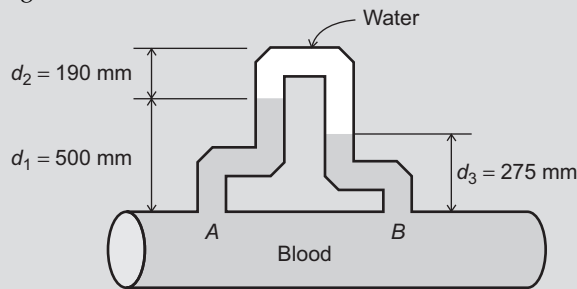


FIG. 3.24 Figure for Homework Problem 3.1.

- 3.2. NASA is planning a mission to a newly found planet and will monitor the density of the new planet's atmosphere. Assume that NASA knows that atmosphere behaves as an ideal gas and that the planet's gravitational force is a function of altitude

Continued

Homework problems (cont'd)

$\left(g(z) = \frac{18.7m}{s^2 \left(1 - \frac{z}{10,000m} \right)} \right)$, where z is in m). The temperature of the atmosphere is

constant at 250 K, and the gas constant is 340 Nm/kg K. Assume that the pressure at the planet's surface is 2 atm. Calculate the pressure and density at an altitude of 1, 5, and 9 km.

- 3.3. Calculate the hydrostatic pressure in the cranium and in the feet at the end of systole and the end of diastole for a hypertensive patient (end systolic pressure is equal to 185 mmHg and end diastolic pressure is equal to 145 mmHg). Assume that the blood density does not change significantly with height and that the cranium is 25 cm above the aortic valve and the feet are 140 cm below the aortic valve. Compare this with a normal patient (120 mmHg end systolic pressure and 80 mmHg end diastolic pressure).
- 3.4. A balloon catheter has been placed within a femoral artery of a patient to be passed to the coronary artery (use the same dimensions stated with Fig. 3.6). Assume that the catheter consists of two components: (1) a chamber to hold the balloon, which is 2 mm in diameter and 1 cm in length (a perfect cylinder) and (2) a tube 0.5 mm in diameter and the total length needed to transport the balloon to the opening locations. Calculate the buoyancy force on this catheter.
- 3.5. Consider the steady, incompressible blood flow through the vascular network as shown. Determine the magnitude and the direction of the volume flow rate through the daughter branch 2 (denoted as d_3 in Fig. 3.25). The velocity at location 1 is inflow and the velocity at location 2 is outflow.

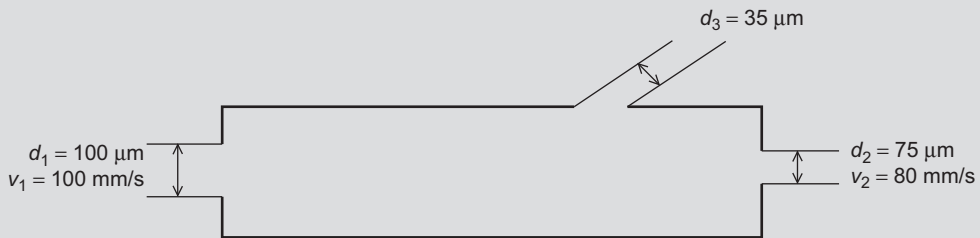


FIG. 3.25 Figure for Homework Problem 3.5.

- 3.6. The variation of air viscosity as a function of temperature can be represented by the following equation

$$\mu = \frac{\left(1.458 \times 10^{-6} \frac{\text{kg}}{\text{msK}^{\frac{1}{2}}} \right) T^{\frac{1}{2}}}{1 + \frac{110.4\text{K}}{T}}$$

Estimate changes in air viscosity as a function of altitude in Earth's atmosphere. Assume that the temperature is approximately -60°C , -40°C , and -80°C at an altitude of 10 km, 30 km, and 75 km, respectively.

Homework problems (cont'd)

- 3.7. A biofluid with a density of 1080 kg/m^3 flows through the converging network as shown in Fig. 3.26. Given that $d_1 = 15 \mu\text{m}$, $d_2 = 9 \mu\text{m}$, and $d_3 = 24 \mu\text{m}$, with $v_1 = 5 \text{ mm/s}$ $\vec{i}$ and $v_2 = 8 \text{ mm/s}$ $\vec{j}$, determine the velocity v_3 .

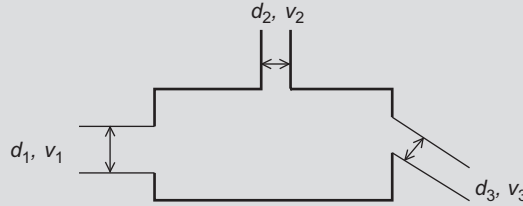


FIG. 3.26 Figure for Homework Problem 3.7.

- 3.8 Using the same details as described in Problem 3.7, calculate the change in time rate of change of volume if v_3 is equal to 10 mm/s (as outflow). Assume that the density is not a function of time.
- 3.9. Air enters the lungs through a circular channel with a diameter of 3 cm , velocity of 150 cm/s , and density of 1.25 kg/m^3 . Air leaves the lungs through the same opening at a velocity of 120 cm/s and a density equal to that of the air within the lungs, which has decreased its net density because of the lower density air entering the lungs. At the initial conditions the air within the lungs has a density of 1.4 kg/m^3 , with a total volume of 6 L . Find the aggregate rate of change of the density of air in the lung assuming that your time step includes one inhale and one exhale (takes 15 s) and that there is no change in the lung volume over this time.
- 3.10. During peak systole, the heart delivers to the aorta blood that has a velocity of 100 cm/s at a pressure of 120 mmHg . The aortic root has a mean diameter of 25 mm . Determine the force acting on the aortic arch if the conditions at the outlet are a pressure of 110 mmHg and a diameter of 21 mm (Fig. 3.27). The density of blood is 1050 kg/m^3 . Assume that the aorta is rigid and that blood is incompressible. Ignore the weight of the blood vessel and the weight of blood within the blood vessel.

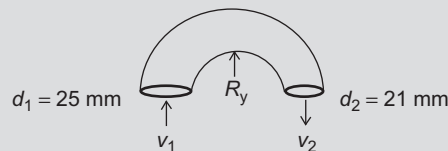


FIG. 3.27 Figure for Homework Problem 3.10.

- 3.11. A reducing blood vessel has a 30-degree bend in it. Evaluate the components of force that must be provided by the adjacent tissue to keep the blood vessel in place. All necessary information is provided in Fig. 3.28. Make sure to include the weight of blood within the blood vessel (the density of blood can be assumed to be 1050 kg/m^3).

Continued

Homework problems (cont'd)

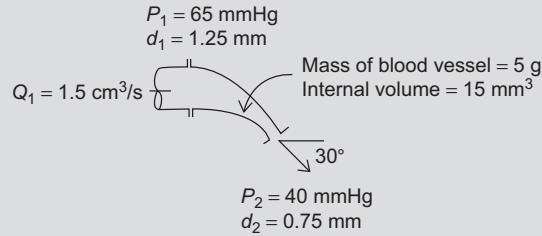


FIG. 3.28 Figure for Homework Problem 3.11.

- 3.12. The following segment of the carotid artery (Fig. 3.29) has an inlet velocity of 50 cm/s (diameter of 15 mm). The outlet has a diameter of 11 mm. The pressure at the inlet is 110 mmHg and at the outlet is 95 mmHg. Determine the reaction forces to keep this vessel in place. Assume that the blood density is 1050 kg/m^3 and ignore the mass of blood within the blood vessel and the mass of the blood vessel.

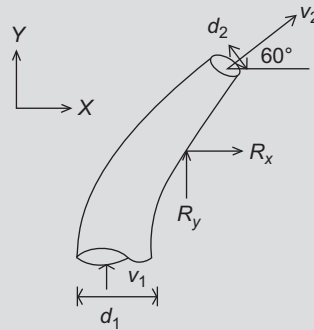


FIG. 3.29 Figure for Homework Problem 3.12.

- 3.13. One of the first implantable mechanical heart valves was designed as a ball within a cage that acted as a check valve. Using the conservation of momentum (with acceleration), model the acceleration of the ball after it is hit by a jet of blood, being ejected from the heart (see Fig. 3.15). The ball has a turning angle of 45 degrees and a mass of 20 g. Blood is ejected from the heart at a velocity of 110 cm/s through an opening with a diameter of 25 mm. Determine the velocity of the ball at 0.5 s. Neglect any resistance to motion (except mass) and assume that blood viscosity is 1050 kg/m^3 and there is no loss in area over this small distance.
- 3.14. During systole, blood is ejected from the left ventricle at a velocity of 125 cm/s. The diameter of the aortic valve is 24 mm, and there is no heat transfer or temperature change within the system. Assume that systole lasts for 0.25 s, that the height difference is 5 cm, and that there is no change in area within this distance. Determine the amount of work performed by the heart during systole and the power that the heart generates. The density of blood is 1050 kg/m^3 , and we will assume there are no internal energy changes associated with blood over this short time interval.

Homework problems (cont'd)

- 3.15.** Air at standard atmosphere conditions (1 atm and 25°C) enters the lungs at 50 cm/s and leaves at a pressure of 1.1 atm, 37°C, and a velocity of 60 cm/s (with a constant mass flow rate of 1.2 g/s, e.g., density changes). The body removes heat from the lungs at a rate of 15 J/g. Calculate the power required by the lungs (this would be energy put gained by the system). Assume that there is no internal energy associated with this system.
- 3.16.** The left common coronary artery has an axisymmetric constriction because of a plaque buildup (Fig. 3.30). Given the upstream conditions of a velocity of 20 cm/s (systole) and 12 cm/s (diastole), calculate the velocity at the stenosis throat and the pressure difference between the stenosis throat and the inlet during systole and diastole. Assume that the Bernoulli principle can be used and that the density of blood is 1050 kg/m³. Assume that there is no difference in height under these conditions.

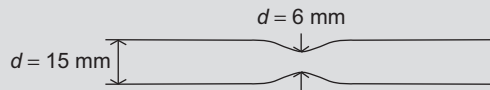


FIG. 3.30 Figure for Homework Problem 3.16.

- 3.17.** Blood flows through a 25% restricting (diameter reduces by 25%) blood vessel that experiences a 5-cm vertical drop (Fig. 3.31). The blood pressure at the inlet is 65 mmHg, and the blood velocity is 50 cm/s. Calculate the blood velocity and the pressure at the outlet. Assume that the density of blood is 1050 kg/m³.



FIG. 3.31 Figure for Homework Problem 3.17.

- 3.18.** The cross-sectional area of a diverging vein may be expressed as $A = A_1 e^{ax}$, where A_1 is the cross-sectional area of that inlet. Develop a relationship for the velocity profile within the vein (in terms of x , v_1). Also, develop a relationship for the pressure (if the inlet pressure is p_1) in terms of x . Assume that there is no variation in height and that the fluid properties remain constant within this channel.
- 3.19.** Blood flows through a vertical tube with a kinematic viscosity of $3 \times 10^{-4} \text{ m}^2/\text{s}$ by gravity only (Fig. 3.32). Solve the appropriate Navier–Stokes equations to find the velocity distribution $v_z(r)$ and compute the average velocity.

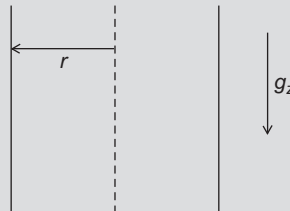


FIG. 3.32 Figure for Homework Problem 3.19.

Continued

Homework problems (cont'd)

- 3.20. Solve Problem 3.19 assuming that the blood is flowing within a vertical parallel plate (i.e., calculate with the Cartesian Navier–Stokes equations), where the coordinate system is aligned with the wall and channel width is h (Fig. 3.33).

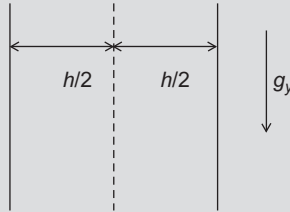


FIG. 3.33 Figure for Homework Problem 3.20.

- 3.21. Upon inserting a catheter into the aorta, the blood flow must pass around the catheter. Assume that the catheter is placed directly in the centerline of the flow field (and is not moving at this instance in time (Fig. 3.34). Derive an expression for the velocity profile assuming the flow is only pressure driven (dp/dz). The outer radius of the aorta is R and, the outer radius of the catheter is kR .

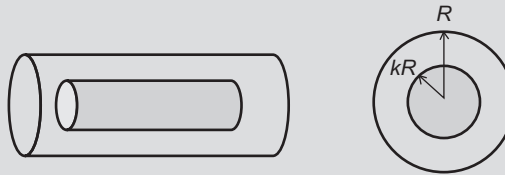


FIG. 3.34 Figure for Homework Problem 3.21.

- 3.22. A 1.5-m tall person is standing underwater. First, calculate the amount of force acting on the person, assuming that the pressure at the surface of the water is 1 atm and that the person's head is just below the water surface. Second, repeat the calculation but assume that the person's head is 2 m below the surface. Approximate the volume of the person as a rectangular prism with width of 50 cm and depth of 20 cm. The density of water is 1000 kg/m^3 .
- 3.23. Water leaves from a stationary hose and hits a moving vane with turning angle of $\theta = 40 \text{ degrees}$ (Fig. 3.35). The vane moves away from the hose with a constant speed of $u = 20 \text{ m/s}$ and receives a jet that leaves the hose with a velocity of 125 m/s . The hose has an exit area of 0.025 m^2 . Find the force that must be applied to maintain the speed of the vane. Assume that there is no loss/gain in area during the water motion, that the density of water is 1000 kg/m^3 and that the viscosity of water is 1 cP. Neglect the weight of water on the vane.

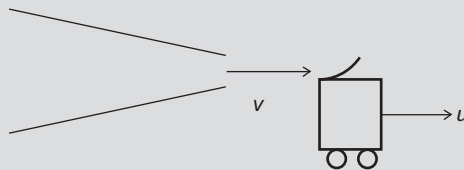


FIG. 3.35 Figure for Homework Problem 3.23.

Homework problems (cont'd)

- 3.24. The heart is supplied with 5 L/min of blood from the vena cava (assume one blood vessel with a diameter of 20 cm). The aorta discharges the heart and has a diameter of 26 cm. Determine the pressure drop across the heart if it generates $4 \mu W$ during the process into the system. Assume that there is no internal energy in the fluid and that there is a negligible elevation difference between the outflow of the vena cava and the inflow of the aorta. The density of blood is 1050 kg/m^3 .
- 3.25. The bladder acts as a pump that draws urine ($\rho = 1015 \text{ kg/m}^3$) from the ureters and forces it to the urethra. The ureter has a diameter of 15 cm, and the urethra has a diameter of 5 cm. The height distance between the ureter and the urethra is 20 cm, and the pressure on the urethra is 1 atm. The average speed in the urethra is 3 mm/s. If the bladder has an efficiency of 80%, determine the power required to perform this process.
- 3.26. A branching blood vessel can be considered as a splitting vane that divides the flow into two streams. Find the mass flow rate ratio $\dot{m}_2/\dot{m}_3$ required to produce zero force in the y -direction (Fig. 3.36). Determine the horizontal force under these conditions. Assume no energy loss because of branching and that velocity and diameters remain the same in each branch. There is no loss in area at the branch. The density of blood is 1050 kg/m^3 .

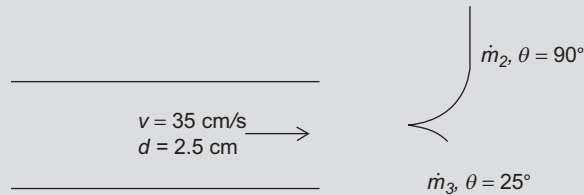


FIG. 3.36 Figure for Homework Problem 3.26.

Reference

See references of Chapter 2

Introduction to heat transfer

LEARNING OUTCOMES

- Describe the difference between heat transfer and thermodynamics
- Identify the different modes of heat transfer
- Describe the governing relationships for engineering heat transfer
- Explain how heat transfer is related to various biological processes, in particular the cardiovascular system
- Describe how energy can be balanced across various systems
- Develop the general heat transfer equation
- Derive the bioheat transfer equation and discuss its applications
- Solve heat transfer problems related to biological flows

4.1 Thermodynamics and engineering heat transfer

Thermodynamics and engineering heat transfer are two related fields of study that are often confused because similar concepts are discussed within each of the fields. It is important to distinguish the differences between the fields so that we can develop the fundamental relationships that are important during the study of heat transfer in biological systems. Concepts in thermodynamics are concerned with the amount of heat transfer that occurs when a system alternates from one equilibrium state to a second equilibrium state. However, there is no discussion related to the amount of time it takes for the system to convert between these two equilibrium states. Furthermore, the systems under thermodynamic analysis must be in two different equilibrium states. Although these concepts are important, many engineering fields are interested in the amount of time required to transfer the heat between various systems, commonly referred to as the *rate of heat transfer*. In most cases it is also atypical for these systems to be in equilibrium. Characterization and quantification of these rates of heat transfer and possibly characterizing the intermediate, nonequilibrium states is the concern of engineering heat transfer, and it typically elicits a more generalized solution methods than thermodynamics.

The reader may recall from an earlier engineering or physics course that there are many forms of energy that can be transferred between systems. Some of these forms of energy have been discussed in early sections of this textbook. For this chapter and some of the later sections of this textbook, we are primarily concerned with heat, which is the form of energy that can be transferred between systems that have a temperature difference between them. Importantly, this energy transfer is always from the higher temperature system to the lower temperature system. Furthermore, this energy transfer stops once the two systems achieve the same temperature; assuming there is no external energy source providing/absorbing energy in the form of heat.

Readers familiar with thermodynamics principles may be curious as to why we need heat transfer principles when undertaking a thermodynamic analysis can provide us with information about the amount of heat transferred between two systems. Simply, in most practical applications, engineers are not only concerned with the amount of heat transferred between the two systems but the amount of time required for this transfer. Furthermore, it is the amount of time that is typically the more important quantity to understand and optimize. As an example, insulated lunch boxes and thermoses are rated by the amount of time that they can keep the food or drink warm or cold. In this example, the user does not particularly care about how much heat is transferred between the food, the container, and the external environment, but instead the user cares about how long the food will stay at or near the desired temperature.

Heat transfer is also directly related to biological systems. In fact, the human body is constantly transferring heat to the external environment (in many environments the human body is the warmer medium and is actively losing heat, but in some conditions when the external temperature is greater than body temperature the human body can gain heat from the environment). Also, comfort (or thermal comfort) is an engineering area that is focused on developing and optimizing systems that humans interact with to maintain a comfortable environment. During the design of clothing, heating and air conditioning systems, chairs, and bedding, among many other everyday products heat transfer principles are considered. Clothing that is worn in warmer climates tend to exchange heat with the body and the environment more quickly than clothing worn in colder climates, which would tend to retain heat and thus exchange heat less efficiently. Athletic wear must exchange heat efficiently so that the body temperature of athletes can be maintained at a near uniform level during the sporting event/training. Similarly, in most businesses, office spaces, and classrooms, the exchange of heat through the space must be considered because doors or windows could be opened, altering the flow of energy (in the form of heat), and people move about the room, which can disturb the temperature differences. Engineers must also consider what environment would be most comfortable for people to complete typical tasks in that environment. To extend this example, the ability to exchange heat with and throughout the environment would probably need to be different in a classroom compared with a gym or a dance club, where the metabolic activity and thus heat generated by the body is likely different. I am confident that the readers of this text have experienced environments that are both acceptable to the activity level within that environment and environments that are not acceptable to the activity level (too hot or too cold). However, what may not be apparent to the reader is the amount of engineering design and prediction that is required to attempt to optimize heat transfer throughout various environments and maintain that environment in a thermally

comfortable climate with varying intrinsic and extrinsic factors (e.g., the number of people in the space and the external temperature).

It is also important to note that although thermodynamics deals with equilibrium states, it is typical that systems described with heat transfer principles are not in equilibrium states. Furthermore, many systems that we would interact with in daily life do not reach thermal equilibrium. For example, your body temperature (although it may be in equilibrium with itself) does not typically equilibrate with the surrounding environmental temperature. Thus the principles that we will develop in this chapter are extensions of thermodynamics principles and require the use of other additional governing relationships to fully describe them (e.g., more than just thermodynamics principles). To reiterate the thermodynamics principles, the first law of thermodynamics states that within a closed system no net energy can accumulate within or be used by that system. This is a conservation of energy statement; for a system to conduct work, energy must be supplied to the system. The second law of thermodynamics states that the total entropy of an isolated system cannot decrease and dictates that heat is transferred from a warmer system to a colder system.

Similar to many engineering phenomena, there must be a driving force for heat to transfer from one system to another. We have spoken about some of these driving forces in early chapters; pressure differences can instigate fluid flow, voltage differences can instigate electrical current flow, and, for the present case, temperature differences can instigate heat flow. The corollary to this is that if no net temperature differences exist between the two media, no net heat will be transferred between the medium (assuming there are no external heat sources). Furthermore, as the temperature difference between the two media increases, the rate of heat transfer between those two media will also increase, if all of the other parameters that alter heat transfer remain the same. This is analogous to the other driving forces that we have discussed in this text, whereby as the driving force increases and the other properties that affect the flow remain the same, the transfer of energy also increases (see Fig. 4.1). This is not to say that media with a greater temperature difference always transfer heat

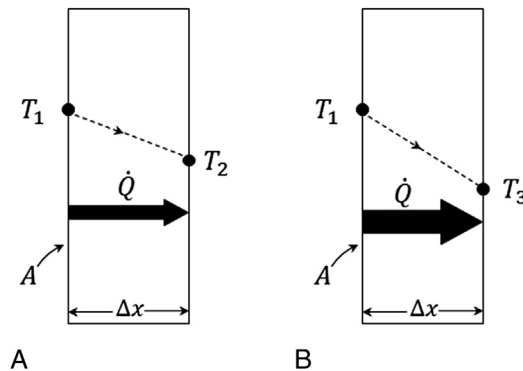


FIG. 4.1 Heat conduction through a solid material depends on a number of physical parameters. In the case of heat conduction, the heat transfer rate is greater when the temperature difference is larger, assuming that the other parameters that alter the heat transfer rate stay the same (e.g., area of interest, thickness of the medium, and the thermal properties of the material). This figure is illustrating that with a small temperature difference (*panel A*) the heat transfer rate ($\dot{Q}$) will be smaller compared with a case when the temperature difference is larger (*panel B*). Note that the magnitude of the heat transfer rate is illustrated by the thickness of the *full* arrow.

quicker than those with a smaller temperature difference; because many other physical properties (such as the conduction properties of the material) can alter how the heat flows from one system to another.

The history of heat as a substance and heat transfer as an engineering concept is quite interesting. The concept of heat, although it was not investigated in an engineering context, was known for hundreds and thousands of years as a mechanism to provide warmth. The earliest human ancestors built fires for many purposes, but one of these was to warm the environment. During the late 1700s the first theory of heat was proposed and termed the *caloric theory*. This theory postulated that heat was a fluid-like substance that can be “poured” (physically transferred) between two substances that reside at different temperatures. This pourable substance was termed *caloric* and was considered to be massless. As caloric entered a body, the temperature of that body would increase, and, conversely, if caloric was removed from a body, the temperature of that body would decrease. The caloric theory began to be discredited in the early 1800s when experiments were conducted showing that heat can be continually produced through various friction mechanisms, including rubbing ones hands together. The work of James Joule (who was honored by having the unit of energy named after him) in the mid-1800s finally put a rest to the caloric theory. Through a number of experiments that were elegant for the time, because of his work and understanding of the kinetic theory, Joule showed that heat was not a substance. The kinetic theory defines individual molecules as microscopic elements with a definite mass and size. These elements are in constant motion (if the temperature of the body is not at absolute zero) and therefore possessing of kinetic energy. Heat arises as a result of these random motions and the interactions of the molecules at the microscopic scale. Although our understanding of heat has advanced since this time, many of the principles of heat transfer can be traced back to these studies in the 1800s.

4.2 Heat and energy considerations

As discussed previously, energy comes in many forms. When discussing a system, it is typical to discuss or quantify the total energy of that system. Conceptually, the total energy, E , of the system is defined as the sum of all energies within that system. In some instances it is convenient to use a normalized version of the total energy; this is normally notated as e and is defined as the total energy per unit mass. However, the concept of energy and heat are slightly more complicated because molecular motion at the microscopic scale can generate heat that is substantially harder to quantify than traditional mechanical or electrical energies that partially make up the total energy. The sum of the microscopic energies are included within the internal energy of the system, defined as U (or u if normalized by unit mass). One easy way to conceptualize the difference between total energy and internal energy is that internal energy is intrinsic to a substance; moving that substance from a closed system to a second closed system at the same temperature should not change the internal energy significantly. However, the total energy of these two systems can be vastly different or can have the same nominal value but be composed of different forms of energy. This would suggest that the total energy is extrinsic to the substance under discussion.

A more strict definition of internal energy is that internal energy is the summation of both the potential and kinetic energies of each molecule that compose the body. The kinetic energy of molecules are directly proportional to temperature, because the average velocity and general degree of activity is affected by temperature. In general, as the temperature of the body increases, the molecular motion increases and thus the kinetic energy of the molecules increases. The energy associated with the internal molecular kinetic energy is given a special term, *sensible energy* (or sometimes sensible heat).

The potential energy of molecules composing the body undergoing a heat transfer problem have various forms. Two common potential energies that may need to be considered when analyzing the internal energy are the latent energy (or sometimes latent heat) and the body energy (or sometimes the chemical energy, which is different from the nuclear energy). The latent energy is the energy associated with the phase of the body and hence the intermolecular forces between the molecules of the system. These intermolecular forces tend to be the strongest in solids and weakest in gases. In a closed system, a gas is in a higher energy system, compared with a solid or liquid, because sufficient internal energy would need to be added and maintained within the system to prevent the molecules from forming and maintaining intermolecular bonds. Although this is an important concept to understand, many heat transfer problems, including most bioheat transfer problems, do not involve a phase change and thus there may be little variance in the latent energy of the system. However, please keep in mind that these may be important considerations for your particular problem.

To contrast the latent energy of a system, a body is also composed of bond energy. This is the internal energy of the system that is associated directly with the atomic bonds. The energy associated with these bonds varies based on many parameters, including the elements that are directly involved in the binding, neighboring elements that do not directly interact with the bond, and whether the bond is a single bond, double bond, or triple bond. The nuclear energy is the energy that is directly associated with the nucleus of the element. These energies can be released or absorbed during chemical or nuclear reactions. It is also uncommon for these energies to be directly considered during heat transfer problems because we will normally assume that other chemical reactions do not occur during the heat transfer process. However, as one can imagine, these processes may be important to your particular conditions and there are entire engineering disciplines that study these phenomena.

Before we move forward with our introduction to heat transfer, it is important to define some variables and quantities that will be common in our analyses. Units of energy have been standardized and are typically defined by the amount of energy required to raise a given mass of water by a given temperature from a starting temperature. For example, the calorie is defined as the energy required to raise the temperature of 1 g of water from 14.5°C to 15.5°C. Enthalpy, h , is a variable that is used to describe the internal and intrinsic energy of a flowing fluid. Enthalpy is defined as

$$h = u + Pv \quad (4.1)$$

where u is the internal energy by unit mass, P is the absolute pressure of the fluid, and v is the specific volume of the fluid. The quantity Pv is referred to as the flow energy and represents the amount of energy required to maintain a fluid flowing at particular conditions. In practice it is convenient to combine these energies into the one variable that represents the intrinsic

energy of the fluid and that energy to maintain flow (e.g., the definition of enthalpy). Some of these values are also important to ideal gas heat transfer problems, which may or may not be an assumption that is used during your heat transfer analysis. Recall that ideal gases are those gases that obey or can be approximated to obey the following

$$\begin{aligned} Pv &= RT \\ \text{or} \\ P &= \rho RT \end{aligned} \quad (4.2)$$

where P and v are as defined earlier for enthalpy, T is the absolute temperature, ρ is the fluid density, and R is the gas constant. Many gases in conventional heat transfer problems can be represented as ideal, but as the density and temperature of the gas increases, it is less likely for the gas to follow the ideal gas laws.

If the reader is familiar with thermodynamics, it is likely that they recall variables termed *specific heat*. The specific heat is the energy required to raise the temperature of a unit mass of a material by 1°C. In practice, the amount of energy required depends on the process by which the temperature is raised and thus may be hard to quantify. However, there are two common processes that are more easily quantified and tabulated for heat transfer applications. The first process is when the temperature is raised at a constant volume and the second process is when the temperature is raised under constant pressure conditions. The specific heat at constant volume (c_v) is always lower than the specific heat at constant pressure (c_p) because additional energy is required during expansion. Obviously, if the volume is held constant, there will be no expansion. Luckily, for ideal gases, these specific heats are related to each other by

$$c_p = c_v + R \quad (4.3)$$

There are a few other relationships associated with the specific heats that become important during heat transfer analyses. The differential change in internal energy and enthalpy for an ideal gas can be quantified as a function of a differential change in temperature and the tabulated specific heat values as

$$du = c_v dT \quad (4.4)$$

and

$$dh = c_p dT \quad (4.5)$$

It is typically more convenient to represent these differential values in terms of the specific heat values at the average temperature of the process, to provide an approximate change in internal energy or enthalpy as

$$\Delta u = c_{v,avg} \Delta T \quad \text{or} \quad \Delta U = mc_{v,avg} \Delta T \quad (4.6)$$

and

$$\Delta h = c_{p,avg} \Delta T \quad \text{or} \quad \Delta H = mc_{p,avg} \Delta T \quad (4.7)$$

We will extend these definitions to materials that have little variation in their volume or density during pressure and/or temperature changes. These materials are incompressible or can be modeled as incompressible. From our previous discussion we should remember that many solids and liquids are assumed to have negligible changes in their volume or density as a function of pressure and/or temperature (note that all materials are compressible to a certain extent; however, it may be convenient to use the following information in your analysis). For these materials and materials that can be approximated as incompressible, the manner in which the temperature is changed (e.g., constant volume conditions versus constant pressure conditions) does not matter and the values of specific heat are nearly identical. Thus, the specific heat subscripts are typically dropped and are represented as

$$c_p \cong c_v \cong c \quad (4.8)$$

Similarly, for these incompressible materials, we can define the change in internal energy as

$$\Delta u = c_{avg} \Delta T \quad \text{or} \quad \Delta U = mc_{avg} \Delta T \quad (4.9)$$

Note that Eqs. (4.6), (4.7), and (4.9) are particularly useful for determining the changes in internal energy for a system that remains in one phase during the heat transfer process.

4.3 Energy transfer and balances

In general, energy can be transferred to or from a system. The energy transfer is described through a heat transfer quantity, Q , if the driving force for the transfer is a temperature difference. All other transfer mechanisms are typically characterized as work, W . It is common to characterize the power of these transfer mechanisms, which is the work done per unit time, $\dot{W}$ (this is similar to the work definition from classical mechanics or other engineering applications with which the reader may be familiar). To help remind the reader about sign conventions, as a system completes net work, the energy of that system reduces, whereas if net work is done on the system, the energy of that system increases.

Many readers may be familiar with concepts related to power. These concepts can be extended to heat transfer, if one wants to quantify the amount of heat transferred per unit time across a particular medium. This is termed the *heat transfer rate* and is denoted as $\dot{Q}$. In practice, both the heat transfer rate and the amount of heat transferred are of interest and it is typical to make use of the following relationships to change between the two values.

$$Q = \int_0^{\Delta t} \dot{Q} dt \quad (4.10)$$

$$\dot{Q} = \frac{Q}{\Delta t} \quad (4.11)$$

Eq. (4.10) would require that one knows or can approximate the variation in the heat transfer rate as a function of time, whereas Eq. (4.11) would require that the heat transfer rate be constant or can be approximated as a constant over the time interval of interest. There is one more quantity that is commonly of interest in heat transfer applications. This value is termed the *heat flux* and represents the amount of heat transferred over an area of interest that is perpendicular to the direction of heat transfer. The average heat flux can be expressed as

$$\dot{q} = \frac{\dot{Q}}{A} \quad (4.12)$$

where A is the area at which the heat transfer occurs or is the area of interest. It is important to note that the heat flux can vary with time and location over a large surface, especially when one includes or ignores edge effects of heat transfer.

We would like to move to a discussion of a few special cases of heat transfer that help set the foundation for more complex analyses. As the reader is aware, energy can be neither created nor destroyed but it can be exchanged between different forms of energy. This is described by the first law of thermodynamics and is applicable in many problem types. In the context of heat transfer, we must include temperature changes when we account for all of the energy entering or leaving the system. This concept can be mathematically represented as

$$E_{\text{entering}} - E_{\text{leaving}} = \Delta E_{\text{system}} \quad (4.13)$$

The left side of Eq. (4.13) represents the net energy transferred into/from the system by heat, work, and any other form of energy. The right side of the equation represents the change in the internal energy of the system of interest. It is common to represent Eq. (4.13) in a rate form as follows

$$\dot{E}_{\text{entering}} - \dot{E}_{\text{leaving}} = \frac{dE_{\text{system}}}{dt} \quad (4.14)$$

The values within this relationship (Eq. (4.14)) now represent the rate of net energy transfer (left side) and the rate of change of internal energy of the system (right side). Under steady-state conditions the internal energy of the system or its rate, does not change as a function of time. Under these conditions, we can obtain the steady-state form of Eqs. (4.13) and (4.14) as

$$E_{\text{entering}} = E_{\text{leaving}} \quad (4.15)$$

$$\dot{E}_{\text{entering}} = \dot{E}_{\text{leaving}} \quad (4.16)$$

The energy balance equation (Eq. (4.13)) may be represented in a slightly different form in heat transfer applications, in which one is typically only concerned about the energy exchange resulting from temperature differences. In this case the heat balance form of the energy balance equation can be represented as

$$Q_{\text{entering}} - Q_{\text{leaving}} + E_{\text{generated}} = \Delta E_{\text{thermal}} \quad (4.17)$$

The first two terms on the left side of Eq. (4.17) represent the net heat transfer to and from the system of interest. The remaining term on the left side of Eq. (4.17) represents the conversion of energy from all other sources (e.g., mechanical work, chemical reactions, etc.) to heat as an energy generation term. All of these values equate to the change in the thermal energy of the system (right side of the equation).

A number of special cases for the energy balance equations have been derived. If one is attempting to represent the energy transfer within a closed system that has a fixed mass and for a system that does not translate with time, the energy balance becomes

$$E_{\text{entering}} - E_{\text{leaving}} = \Delta U = mc_v \Delta T \quad (4.18)$$

The importance of this formula is that most practical systems experience significant changes only within their internal energy. For example, a system that experiences a net change of height would also experience a net change in the gravitational potential energy, which may need to be considered (depending on the significance of this change compared with the other energy changes experienced). If the same system described to develop Eq. (4.18) experiences heat transfer as the only form of energy exchange, the energy balance equation simplifies further to

$$Q = mc_v \Delta T \quad (4.19)$$

If the system of interest includes the flow of material into or out of the volume of interest (using a control volume approach) with steady-state flow conditions, a simplified mass balance equation can be developed. These types of flow conditions are also relatively common in heat transfer applications and furthermore under these conditions, the total energy within the control volume remains constant throughout the process. This suggests that there is no change in the total energy of the system. Recall from our earlier discussions that the mass flow rate of fluid can be approximated with

$$\dot{m} = \rho v A$$

where v is the average velocity of the fluid and A is the cross-sectional area of the channel. Under steady-state flow conditions, the mass flow rate remains constant during the heat transfer application. Under conditions in which fluid is flowing through a single inlet/single outlet channel, there is no external work, and the changes in kinetic and potential energies are negligible, we can represent the heat transfer rate as

$$\dot{Q} = \dot{m} \Delta h = \dot{m} c_p \Delta T \quad (4.20)$$

This formula can be derived by remembering that the mass flow rate into the control volume must be equal to the mass flow rate out of the control volume for steady flow conditions. In addition, this formula (Eq. (4.20)) is developed from an expansion of Eq. (4.17), including and summarizing the important terms.

4.4 Mechanisms of heat transfer

Heat can be transferred using three different well-described methods. Each of these methods have their own defining characteristics and can be characterized by different solutions to the energy balance heat transfer equations that are applicable. It is important to note that we will describe these mechanisms as discrete, individual, exclusive methods of heat transfer, but it is possible and likely that two or more of these methods of heat transfer occur at the same time. However, in many practical applications, there is one dominant method of heat transfer and the other methods are considered or can be considered negligible. The three methods of heat transfer are conduction, convection, and radiation. This section will discuss these three modes of heat transfer and develop some of the governing equations for each of these methods. Importantly, we will also develop the bioheat transfer equation as a special case of steady-state conduction.

Conduction is the heat transfer modality in which the transfer of energy occurs directly from particles with a higher temperature (more energy) to those with a lower temperature (less energy) (see Fig. 4.2). For this mode of heat transfer to occur, the particles that are transferring heat must be in direct contact with each other. Interestingly, conduction can occur throughout solids, liquids, and gases, although there are subtle differences between the molecular interactions in the different phases. Furthermore, conduction can occur between materials that are in the different phases. For example, when one pours warm coffee into a mug, the mug warms as the coffee cools to some equilibrium temperature if enough time is allowed to pass. This can be described as heat conduction between a solid (mug) and a liquid (coffee). In parallel to this conduction mechanism, the coffee (and possibly the mug) is also providing heat to the air within the room (assuming that the room temperature is cooler than the coffee and the mug). This heat transfer can be described as conduction

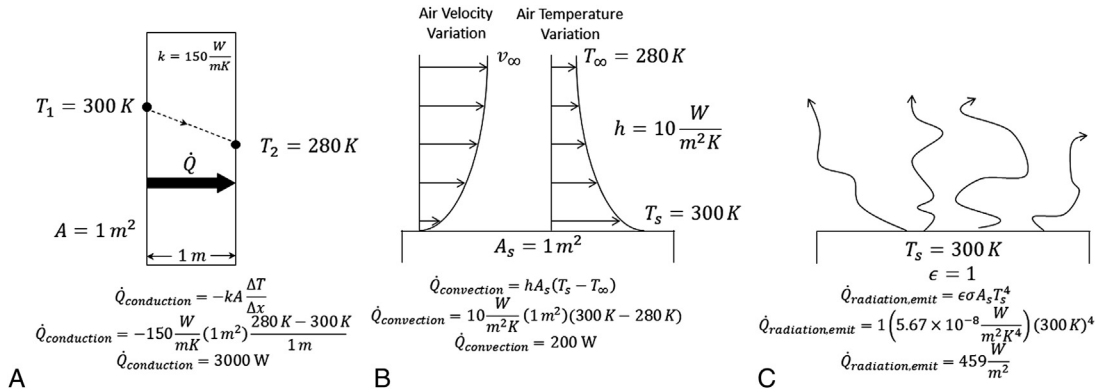


FIG. 4.2 Comparison of the three different modes of heat transfer. Heat can transfer by conduction (panel A), which is primarily a function of the temperature gradient and the physical properties of the material. When a fluid flows over a surface, heat can be transferred by conduction (panel B), which is primarily a function of the fluid properties and the temperature difference. Please note that for panel B we assumed that the free surface temperature was lower than the surface temperature. All materials not at absolute zero also emit radiation into the surrounding medium. This mode of heat transfer is termed *radiation* (panel C). Radiation is primarily a function of the emissivity of the material and the temperature of the surface.

between a liquid and a gas (coffee to room air) or solid to gas (mug to room air). At some point, the coffee, the mug, and the room would all be at the same temperature, if no external heat sources are provided to the system. As described, this example illustrates the transfer of heat between three different substances by a direct interaction of the materials. Conduction can also occur throughout one material; for instance heat can be provided to a room via a radiator system. The air near the radiator would be warmed because of the interaction with the heating system; but if one focuses only on the air by itself, heat would be transferred from the warm air regions (the air that is close to the radiator) to other cooler air locations (the air that is further away from the radiator). Note that warming a room is actually more complicated than described here because there may be air currents and natural convection effects that we are ignoring at this point to conceptualize the idea of conduction.

The mechanism of heat conduction between the different phases of matter are based on how the molecules themselves can interact. In solids, heat is principally conducted because of the transport of electrons between atoms and the vibrational energy of the atoms with the lattice structure. In contrast, heat transfer in liquids and gases primarily occurs from random collisions of molecules during the motion of those molecules. It is important to note that for pure convection purposes, there should be no external flow driving forces that affect the random motion of the particles (e.g., a pressure gradient).

Conduction heat transfer rates depend on the temperature difference, the surface area (or geometry) of the object, the material composition of the object, and the thickness of the material. For example, the heat transfer rate can be altered by adding or removing insulating materials to the material undergoing heat transfer (which changes the thickness and the material composition), which would either decrease or increase the heat transfer rate, respectively. Similarly, with a larger temperature difference over the materials of interest and a larger surface area over which heat transfer can occur, the heat transfer rate would increase (depicted in Fig. 4.1). Experimentally, a relationship for the heat transfer rate associated with conduction has been developed that correlates all of these variables as follows

$$\dot{Q}_{\text{conduction}} = -kA \frac{\Delta T}{L} \quad (4.21)$$

where A is the area normal to the heat transfer direction, ΔT is the temperature difference across the surface, L is the thickness of the surface, and k is a constant of proportionality termed the *thermal conductivity*. The thermal conductivity quantifies the particular material's ability to transfer heat; materials with a larger thermal conductivity will have a greater overall heat transfer rate than materials with lower thermal conductivities, assuming that the other parameters are the same. It is important to note that Eq. (4.21) is applicable to a plane homogeneous material and can be used only to approximate other materials.

The differential form of Eq. (4.21) is termed Fourier's Law of Heat Conduction and is represented as

$$\dot{Q}_{\text{conduction}} = -kA \frac{dT}{dx} \quad (4.22)$$

The advantage of this form of the conduction heat transfer equation is that it relieves some of the constraints on the homogeneity of the material. Using Eq. (4.21), we would have to assume that the thermal conductivity remains the same over the entire length L because, as we know, there are molecular inhomogeneities that would need to be considered and these inhomogeneities can alter the conduction of heat through the material. In heat transfer and most engineering courses, the value $\frac{dT}{dx}$ is termed the *temperature gradient* (as a function of spatial variables) and is used to describe these fluctuations over very small distances. It is important to illustrate that variations are possible in heat transfer properties for different common materials at room temperature (300 K). This should help illustrate to the reader why certain materials respond differently to thermal changes and why and how choices are made in the production of insulating materials. The thermal conductivity values for copper, concrete, and water are $401 \text{ W/m} \cdot \text{K}$, $1.4 \text{ W/m} \cdot \text{K}$, and $0.607 \text{ W/m} \cdot \text{K}$, respectively, at room temperature. This illustrates that copper is a very good conductor of heat, whereas the other two materials are poorer conductors of heat, at least with respect to copper at this particular temperature. Similarly let us compare the specific heat (c_p) of these same materials. At room temperature the specific heat at constant pressure for copper, concrete, and water have been estimated to be $385 \text{ J/kg} \cdot \text{K}$, $880 \text{ J/kg} \cdot \text{K}$, and $4180 \text{ J/kg} \cdot \text{K}$, respectively. These values illustrate that under these conditions for the three materials reported, water is the most effective material to store thermal heat, by approximately an order of magnitude. Thus at room temperature, water effectively stores significant quantities of heat but does not conduct heat (compared with copper and concrete). To make a few further comparisons, the thermal conductivity of skin, muscle, and fat at room temperature have been reported to be in the range of $0.37 \text{ W/m} \cdot \text{K}$, $0.41 \text{ W/m} \cdot \text{K}$, and $0.2 \text{ W/m} \cdot \text{K}$, respectively. However, it should be noted that individual variations in these values and variations based on the type of muscle (among other biological variations) should be expected. Note that these values for biological materials are in the range of the reported values for water.

For readers who are interested in some other engineering parameters related to conduction, we will introduce a few additional values that are commonly reported in this context. The heat capacity of a material is defined as the product of the specific heat and the density of the material (ρc_p) and quantifies the ability of a material to store energy in the form of heat as a value normalized by unit volume (note that the specific heat quantifies a similar value but normalizes the value by unit mass). The importance of the heat capacity is that it is used in a ratio termed the *thermal diffusivity* (α), which quantifies the speed with which heat transfers through a material. Thermal diffusivity has been defined as

$$\alpha = \frac{\text{heat conduction}}{\text{heat storage}} = \frac{k}{\rho c_p} \quad (4.23)$$

As the reader can see from this ratio, the numerator relates to the ability of a material to conduct heat and the denominator relates to how much energy the material can store. With larger values of thermal diffusivity, the conduction of heat through the material occurs at a faster rate than the amount of heat that can be stored within that same material. In the case, that the heat storage is much greater than the heat conduction suggests that the majority of the heat is absorbed/retained by the medium. To contrast various materials it is common for metals to have larger values of thermal diffusivity and insulating materials to have lower

values of thermal diffusivity. For example, the thermal diffusivity of copper is $\alpha_{copper} = 113 \times 10^{-6} \frac{m^2}{s}$, whereas the thermal diffusivity of water is $\alpha_{water} = 0.14 \times 10^{-6} \frac{m^2}{s}$; both of these reported values are at room temperature.

There has been significant work in bringing the classical engineering heat transfer equations into the biological realm. A commonly used formulation has been termed the *bioheat transfer equation*, which is a modified version of the steady-state conduction heat transfer equation. Before we develop the equation, it is important to realize the amount of heat transfer that is involved with biological systems. In the case of humans, multiple mechanisms can play a role in heat transfer, including conduction, convection, and radiation. However, additional processes, such as evaporation and metabolic heat generation also play an important role in the overall heat transfer associated with the human body. One of the first biological heat transfer formulations was proposed in the late 1940s by Harry Pennes. In this work, the temperature difference between the skin and the interior portions of the forearm were measured. Under resting conditions there was an approximate 3° to 4°C temperature difference between these two locations, and this difference was primarily attributed to blood flow through the arm and metabolic heat generation.

Using the steady-state convection heat transfer equation, Pennes developed the following formulation for the data he observed, assuming one-dimensional (1D) heat transfer (rectangular coordinates) and that material properties are constant.

$$\frac{d^2T}{dx^2} + \frac{\dot{e}_m + \dot{e}_p}{k} = 0 \quad (4.24)$$

The heat generation described by metabolic or perfusion changes are represented in Eq. (4.24) as $\dot{e}_m$ and $\dot{e}_p$, respectively (please note that the units for these values are W/m^3). Pennes was further able to develop a formulation to represent the perfusion heat source term. Through Pennes' work, he suggested that the perfusion heat source term was a function of the blood volumetric flow rate normalized by the volume of tissue ($\dot{p}$), the arterial blood temperature (T_a), the density of blood (ρ_b), and the specific heat of blood. The relationship for heat generation as attributed to perfusion changes can be described as

$$\dot{e}_p = \dot{p} \rho_b c_b (T_a - T) \quad (4.25)$$

Substituting Eq. (4.25) into Eq. (4.24), we can obtain a statement of the bioheat transfer equation as

$$\frac{d^2T}{dx^2} + \frac{\dot{e}_m + \dot{p} \rho_b c_b (T_a - T)}{k} = 0 \quad (4.26)$$

Eq. (4.26) has historically been written in a more simplified form to make the solution methods easier. This simplified form is

$$\frac{d^2\theta}{dx^2} - B^2\theta = 0$$

if we can assume that all of the properties in the perfusion heat source term and the metabolic heat source term are constant. θ is termed the temperature excess and is defined as

$$\theta = T - T_a - \frac{\dot{e}_m}{\dot{p}\rho_b c_b}$$

Similarly,

$$B^2 = \frac{\dot{p}\rho_b c_b}{k}$$

When a solid container experiences heat transfer to or from a flowing fluid (liquid or gas) that is within the solid container, the mode of heat transfer is described as convection (see Fig. 4.2). In the absence of significant fluid motion, the heat transfer between the fluid and the surrounding solid container is purely by conduction. In the presence of significant fluid motion, the heat transfer between the fluid and the solid is enhanced compared with the pure conduction case. However, the quantification of this transfer is significantly more complicated. As we have all experienced, the presence of a significant breeze, especially on a cold day, enhances the heat loss by the human body and is even quantified/reported as a wind chill factor. This enhancement occurs because as heat is transferred from the warm medium to the cooler medium the fluid that has experienced a change in its temperature translates to a different physical location and is replaced by fluid at the original temperature (or close to the original temperature). This would suggest that the original temperature gradient between the flowing fluid and the solid surface would not change and would stay at the original value (or would remain close to the original value). This concept of a steady-state maintained temperature gradient is in direct contrast with what occurs during conduction, in which eventually the temperature gradient disappears and the temperatures of all of the media equilibrate (in the absence of external elements that provide heat to the system undergoing conduction). Note that there are two main types of convection: forced convection, in which the fluid motion is maintained by an external source (e.g., a pump or the heart), and natural convection, in which changes in temperature within the fluid alter the density of the fluid, causing motion without an external source driving the fluid flow (e.g., in the absence of significant air currents caused by external sources, fluid motion can be observed around an open flame).

The complexity of convection analyses arise as a result of the combination of conduction and fluid movement. The same variables that we described as altering conduction rates (e.g., area, temperature difference, thickness, material composition, etc.) alter convection heat transfer rates. Additionally, the fluid velocity affects convection; with higher fluid velocities the rate of heat transfer increases. Sir Isaac Newton is credited with deriving a relationship for the convection heat transfer rate, which is known as Newton's Law of Cooling and is expressed as

$$\dot{Q}_{convection} = hA(T_s - T_\infty) \quad (4.27)$$

where h is the convection heat transfer coefficient, A is the surface area over which exchange occurs, T_s is the temperature of boundary surface between the solid and the fluid, and T_∞ is the temperature of the fluid sufficiently far from the boundary surface that it should not be

altered by the boundary surface. The distance of T_∞ from the boundary surface is not defined as an exact length because it would be a function of all of the heat transfer properties. Similar to the no-slip boundary condition for fluid velocity, we assume that the temperature of the fluid immediately along the surface of the container is equal to the temperature of the surface of the container.

One complication of convection is that the convection heat transfer coefficient is not a variable that is easily tabulated, because many parameters affect its numerical value. In practice, the convection heat transfer coefficient needs to be experimentally determined for the particular heat transfer problem; however, it has been shown that the fluid motion (laminar versus turbulent), fluid properties (e.g., viscosity, density), and fluid velocity and surface features (e.g., roughness, fouling, general material properties) all affect the convection heat transfer coefficient. Just to illustrate to the reader a range of values for convection heat transfer coefficients, coefficients have been reported to vary from values near unity (for the natural convection of gases) to values in the range of 100,000 under boiling/condensation conditions. For our purposes, we will have to supply the reader with the applicable value for the convection heat transfer coefficient or provide the reader with a direct means to calculate the value.

The final mechanism of heat transfer that we will discuss is radiation, which describes the mechanism when energy is emitted from a source in the form of electromagnetic waves (see Fig. 4.2). The electromagnetic waves, typically in the form of photons, are emitted as a result of changes in electron configurations. One of the major differentiating principles of radiation, compared with conduction or convection, is that the energy transfer does not require the presence of an intermediate or intervening medium. This suggests that radiation can occur through a vacuum. Furthermore, it is normal for heat transfer by radiation to occur faster, at a given temperature, compared with conduction or convection. The energy from the sun is transferred to the Earth by radiation and considering the distance over which this energy must travel (the average distance between the Earth and the sun is approximately 93 million miles or approximately 150 million km), one can see how quickly radiation can occur (it takes approximately 8.5 minutes for photons from the sun to reach the Earth).

For this discussion, we are principally interested in thermal radiation, that is, the form of radiation emitted by bodies because of their temperatures. In fact, all substances that have a temperature above absolute zero emit thermal radiation. It is also important to note that all bodies in all states of matter have the ability to emit thermal radiation (if the body's absolute temperature is not zero) and have the ability to absorb radiation. To simplify the analysis, heat transfer engineers typically consider the surface radiation properties, instead of the body's radiation properties, which would be a function of the volume (or mass) of the body. This is especially true for materials that are opaque to thermal radiation (or can be approximated as opaque), for instance, most solids. Liquids and gases are not normally opaque to thermal radiation but depending on the radiation properties, the thermal radiation from internal regions may be very marginal compared with the radiation from the surface (or near-surface) regions.

The Stefan-Boltzmann equation mathematically represents the maximum rate of energy that can be emitted from a surface. The equation has been experimentally found to be

$$\dot{Q}_{\text{emission,max}} = \sigma A_s T_s^4 \quad (4.28)$$

where σ is the Stefan-Boltzmann constant ($\sigma = 5.67 \times 10^{-8} \text{ W/m}^2 \cdot \text{K}^4$) and A_s is the relevant surface area that is emitting radiation at a given uniform temperature of T_s . In practice, Eq. (4.28) describes an idealized surface emitting radiation at the maximum rate. These bodies are described as undergoing blackbody radiation and the surfaces themselves are termed a blackbody. In practical applications, surfaces do not emit radiation at the maximum rate but instead emit radiation at some lower rate that depends on the material properties of the body itself and the temperature at which the body is emitting radiation. The modified Stefan-Boltzmann equation can be represented as

$$\dot{Q}_{\text{emission}} = \varepsilon \sigma A_s T_s^4 \quad (4.29)$$

where ε is the emissivity of the surface. A true blackbody would have an emissivity of 1, whereas most real materials have an emissivity between 0 and 1. At room temperature (300 K), the emissivity of human skin has been found to be 0.95. To contrast this value with common metals found at room temperature the emissivity of aluminum foil, gold, and stainless steel are 0.07, 0.03, and 0.17, respectively. Obviously, the numerical value of emissivity can drastically alter the radiation heat transfer from the surface of that material.

In addition to radiation heat transfer by emission, all surfaces can absorb incident radiation. This is characterized by the surface property, absorptivity (α). Absorptivity is defined as the fraction of the amount of incident radiation that is absorbed by the surface. Mathematically, this can be represented as

$$\alpha = \frac{\dot{Q}_{\text{absorbed}}}{\dot{Q}_{\text{incident}}} \quad (4.30)$$

where the two values on the right side of the equation represent the amount of radiation energy that is either absorbed by the surface or incident on the surface. A blackbody is defined to be a perfect absorber and thus has an absorptivity of 1. For a single surface, one can compare the amount of energy emitted by radiation to the amount of energy absorbed by radiation. This value is typically termed the *net radiation heat transfer*. If the amount of energy emitted by radiation is larger than that absorbed for a given surface, the surface is said to be losing energy by radiation. In opposition to this conclusion, when the amount of energy absorbed by a surface by radiation methods is greater than the amount emitted by radiation, the surface is said to be gaining energy by radiation.

In general, radiation heat transfer does not occur independent of either conduction or convection, because there is normally a medium between the two surfaces. Furthermore, in many cases of radiation, the intervening medium is in the gas phase. If there is bulk motion of the gas, radiation would occur in parallel with convection, whereas if there was no bulk motion of the gas, radiation would occur in parallel with conduction. In the case in which convection occurs in parallel to radiation, we can develop a formulation for the total (or combined) heat transfer, which becomes a function of a modified (or combined) heat transfer coefficient, as follows

$$\dot{Q}_{\text{total}} = \dot{Q}_{\text{convection}} + \dot{Q}_{\text{radiation}} = h_{\text{convection}} A_s (T_s - T_\infty) + \varepsilon \sigma A_s (T_s^4 - T_\infty^4) \quad (4.31)$$

$$\dot{Q}_{total} = h_{combined} A_s (T_s - T_\infty) \quad (4.32)$$

$$h_{combined} = h_{convection} + h_{radiation} = h_{convection} + \epsilon \sigma (T_s^2 + T_\infty^2) (T_s + T_\infty) \quad (4.33)$$

In essence the formulation of the total heat transfer is found from the summation of the heat transfer rates that are involved in the particular problem. (Eq. (4.31) illustrates this for a combined radiation and convection problem). Eq. (4.32) illustrates that we can mathematically represent the total heat transfer rate with a combined heat transfer coefficient, which is also found from the summation of the two heat transfer coefficients (note that we developed a radiation heat transfer coefficient to accomplish this mathematical feat.)

4.5 General heat transfer equations

For this section, we will develop some of the general heat transfer equations that will be applicable to analyses that can be conducted in many biological heat transfer cases. This is not intended to limit the reader to a certain small subset of cases or equations, but instead the authors intend for this to act as a springboard for further study into biological heat transfer. We would also like to point out that these equations have a similar form to the Navier–Stokes equations and that many of the mathematical techniques that were discussed to solve the Navier–Stokes equations can be applied to heat transfer examples.

As we did when developing the Navier–Stokes equations, we will first consider the heat transfer by conduction through a small volumetric element of lengths dx , dy , and dz . We will assume that this small differential element has a uniform density of ρ and write an energy balance across the element over a small time interval, dt . The energy balance would be represented by the difference in rate of heat conduction through the surfaces at x , y , and z and those surfaces at $x + dx$, $y + dy$ and $z + dz$, plus the rate of heat generation inside of the differential element. These values would equate to the rate of change of energy of the entire element. Mathematically, what was just described can be represented as

$$\dot{Q}_x + \dot{Q}_y + \dot{Q}_z - \dot{Q}_{x+dx} - \dot{Q}_{y+dy} - \dot{Q}_{z+dz} + \dot{E}_{generated} = \frac{dE_{element}}{dt} \quad (4.34)$$

The value for heat generated within the element as a function of time and the total change in energy of the element can be represented as a function of the volume of the element as

$$\begin{aligned} \dot{E}_{generated} &= \dot{e} dx dy dz \\ dE_{element} &= E_{t+dt} - E_t = mc(T_{t+dt} - T_t) = \rho c(T_{t+dt} - T_t) dx dy dz \end{aligned}$$

respectively. Substituting these values into Eq. (4.34) and dividing the equation by the differential volume ($dx dy dz$), we obtain

$$-\frac{1}{dydz} \frac{\dot{Q}_{x+dx} - \dot{Q}_x}{dx} - \frac{1}{dxdz} \frac{\dot{Q}_{y+dy} - \dot{Q}_y}{dy} - \frac{1}{dxdy} \frac{\dot{Q}_{z+dz} - \dot{Q}_z}{dz} + \dot{e}_{generated} = \rho c \frac{T_{t+dt} - T_t}{dt} \quad (4.35)$$

Further modifying Eq. (4.35), by making use of the definition of a derivative and Fourier's Law of Heat Conduction, we can obtain

$$\frac{\partial}{\partial x} \left(k \frac{\partial T}{\partial x} \right) + \frac{\partial}{\partial y} \left(k \frac{\partial T}{\partial y} \right) + \frac{\partial}{\partial z} \left(k \frac{\partial T}{\partial z} \right) + \dot{e}_{\text{generated}} = \rho c \frac{\partial T}{\partial t} \quad (4.36)$$

Eq. (4.36) is the general heat conduction equation in rectangular coordinates. The equation also can be represented in a more condensed form, known as the Fourier-Biot equation, if one introduces the thermal diffusivity as a constant heat transfer property $\left(\alpha = \frac{k}{\rho c} \right)$, as

$$\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} + \frac{\dot{e}_{\text{generation}}}{k} = \frac{1}{\alpha} \frac{\partial T}{\partial t} \quad (4.37)$$

There are a few special cases that have been developed from Eq. (4.37). Under steady-state conditions, the right side of Eq. (4.37) equates to zero. This has been termed the Poisson equation. Under steady-state conditions and when there is no heat generation ($\dot{e} = 0$), Eq. (4.37) simplifies to

$$\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} = 0 \quad (4.38)$$

which is termed the Laplace equation. As with the Navier–Stokes equation, an analogous general heat transfer equation can be derived for cylindrical coordinates and spherical coordinates. For cylindrical coordinates, we would use the following coordinate transformation on Eq. (4.37)

$$x = r \cos \phi \quad y = r \sin \phi \quad z = z$$

and for spherical coordinates, we would use the following coordinate transformation.

$$x = r \cos \phi \sin \theta \quad y = r \sin \phi \cos \theta \quad z = r \cos \theta$$

After using the substitutions listed and mathematically manipulating Eq. (4.37), we obtain the following heat transfer equations

$$\frac{1}{r} \frac{\partial}{\partial r} \left(kr \frac{\partial T}{\partial r} \right) + \frac{1}{r^2} \frac{\partial}{\partial \phi} \left(k \frac{\partial T}{\partial \phi} \right) + \frac{\partial}{\partial z} \left(k \frac{\partial T}{\partial z} \right) + \dot{e}_{\text{generation}} = \rho c \frac{\partial T}{\partial t} \quad (4.39)$$

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(kr^2 \frac{\partial T}{\partial r} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial}{\partial \phi} \left(k \frac{\partial T}{\partial \phi} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(k \sin \theta \frac{\partial T}{\partial \theta} \right) + \dot{e}_{\text{generation}} = \rho c \frac{\partial T}{\partial t} \quad (4.40)$$

for cylindrical (Eq. 4.39) and spherical coordinates (Eq. 4.40). As with our analytical solutions to the Navier–Stokes equations, we would need to know boundary conditions and initial conditions and probably limit ourselves to a discussion of a 1D heat transfer problem, to solve these equations by hand. With computational methods, one can obtain solutions to these equations in a more robust manner and describe more complex heat transfer scenarios.

Summary

- 4.1.** Thermodynamics and engineering heat transfer are two related fields of study that are often confused. Thermodynamics is concerned with the amount of heat transfer that occurs when a system alternates between equilibrium states. Heat transfer is concerned with the time required to transfer the heat between various systems. Heat transfer is primarily concerned with energy in the form of heat. This energy is measured in the form of temperature, and temperature differences between two systems is the driving force for heat transfer to occur.
- 4.2.** The total energy, E , of a system is defined as the sum of all energies within that system. The kinetic energy of molecules are directly proportional to temperature, because the average velocity and general degree of activity is effected by temperature. Enthalpy, h , is a variable that is used to describe the internal and intrinsic energy of a flowing fluid. Enthalpy is defined as $h = u + Pv$. If the heat transfer involves a gas that can be represented as an ideal gas, we can use the ideal gas law ($Pv = RT$) to help relate some of the variables of interest. The specific heat is the energy required to raise the temperature of a unit mass of a material by 1°C , and this typically depends on the process by which the heat was added to the system. Engineers typically can tabulate the specific heat at constant temperature and/or the specific heat at constant volume. The following formulas are applicable for these conditions: $c_p = c_v + R$, $du = c_v dT$, and $dh = c_p dT$.
- 4.3.** In general, energy can be transferred to or from a system. The energy transfer is described as heat transfer, Q , if the driving force for the transfer is a temperature difference. All other transfer mechanisms are typically characterized as work, W . The

rate of heat transfer can be characterized by $Q = \int_0^{\Delta t} \dot{Q} dt$. The average heat flux can

be expressed as $\dot{q} = \frac{\dot{Q}}{A}$. In many cases the heat balance form of the energy balance equation can be represented as $Q_{\text{entering}} - Q_{\text{leaving}} + E_{\text{generated}} = \Delta E_{\text{thermal}}$, which is a statement of the conservation of energy of a system.

- 4.4.** Heat can be transferred using three different well-described methods: conduction, convection, and radiation. Conduction is the heat transfer modality in which the transfer of energy occurs directly from particles with a higher temperature (more energy) to those with a lower temperature (less energy). The conduction heat transfer rate can be mathematically represented as $\dot{Q}_{\text{conduction}} = -kA \frac{\Delta T}{L}$ or $\dot{Q}_{\text{conduction}} = -kA \frac{dT}{dx}$. A biological heat transfer equation has been developed assuming steady-state conduction as $\frac{d^2 T}{dx^2} + \frac{\dot{e}_m + \dot{p} p_b c_b (T_a - T)}{k} = 0$. A second heat transfer modality is convection. This occurs when a solid container experiences heat transfer to or from a flowing fluid (liquid or gas) that is within the solid. Sir Isaac Newton is credited with deriving a relationship for the convection heat transfer rate, which is known as Newton's Law of Cooling and is expressed as $\dot{Q}_{\text{convection}} = hA(T_s - T_\infty)$. The final mechanism of heat transfer is radiation, which describes the mechanism when energy is emitted from a source in the form of electromagnetic waves. The Stefan-Boltzmann equation mathematically

represents the maximum rate of energy that can be emitted from a surface and is represented as $\dot{Q}_{\text{emission,max}} = \sigma A_s T_s^4$.

- 4.5. General heat transfer equations can be used for many heat transfer conditions and may be simplified based on the particular properties of the problem. The general heat conduction equation for rectangular, cylindrical, and spherical coordinates are

$$\frac{\partial}{\partial x} \left(k \frac{\partial T}{\partial x} \right) + \frac{\partial}{\partial y} \left(k \frac{\partial T}{\partial y} \right) + \frac{\partial}{\partial z} \left(k \frac{\partial T}{\partial z} \right) + \dot{e}_{\text{generated}} = \rho c \frac{\partial T}{\partial t}$$

$$\frac{1}{r} \frac{\partial}{\partial r} \left(kr \frac{\partial T}{\partial r} \right) + \frac{1}{r^2} \frac{\partial}{\partial \phi} \left(k \frac{\partial T}{\partial \phi} \right) + \frac{\partial}{\partial z} \left(k \frac{\partial T}{\partial z} \right) + \dot{e}_{\text{generation}} = \rho c \frac{\partial T}{\partial t}$$

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(kr^2 \frac{\partial T}{\partial r} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial}{\partial \phi} \left(k \frac{\partial T}{\partial \phi} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(k \sin \theta \frac{\partial T}{\partial \theta} \right) + \dot{e}_{\text{generation}} = \rho c \frac{\partial T}{\partial t}$$

Homework problems

- 4.1. In a biofluids laboratory, an excised blood vessel has been cannulated to measure the heat transfer properties of this biological tissue. Blood is flowed at a rate of 0.5 kg/s through the excised blood vessel with a diameter of 2.5 cm and 0.25 m in length. The excised vessel is maintained in a room with an external temperature of 25°C and the vessel itself has a surface temperature maintained at 37°C. If the temperature drop between the inlet and the outlet of the blood vessel is 5°C, determine the heat transfer coefficient as a result of convection between the blood vessel surface and the surrounding environment. Assume that the specific heat of blood is 3.8 kJ/kgK.
- 4.2. A person who has experienced hypothermia is heated steadily from an external source. The thermal conductivity of skin 0.4 W/m°C, and heat is being applied to the person over a flat circular surface of diameter 20 cm and thickness of 0.2 cm. Heat is transferred steadily to the person at a rate of 100 W. If the inner surface of the person is being warmed to 39°C, determine the temperature at the outer surface.
- 4.3. A skin sample has a heat flux meter attached to it in a laboratory. The meter indicates that a heat flux of 45 W/m² passes through a 4-cm-thick skin section. The temperature on the sides of the skin are 25°C and 35°C. Determine the average thermal conductivity of the skin section.
- 4.4. On a hot day, a fan is blowing warm air over a person. The air is at a temperature of 45°C and the person can be assumed to be represented as a flat plate with dimensions of 1 m × 0.2 m having a surface temperature of 28°C. If the convection heat transfer coefficient is found to be 100 W/m²K, determine the rate of heat transfer from the hot air to the person.
- 4.5. Consider an average person standing in the middle of a room. The various surfaces are found to be at a temperature of 15°C in the winter and 26°C in the summer. Calculate the rates of radiation heat transfer between this person and the surfaces in

Homework problems (cont'd)

- both the winter and summer. Assume that the average surface temperature of the person is 34°C . The surface area of the person is 1.5 m^2 , and the constant emissivity of the skin is 0.92.
- 4.6. A 0.5-m-long blood vessel, with outer diameter of 0.5 cm, is suspended in a laboratory that is maintained at a room temperature of 22°C . Heat is generated in the blood vessel as a result of the an external heating source and the outer surface of the vessel is found to be at a temperature of 50°C . The pressure drop across the blood vessel is 10 mmHg, and the flow rate through the vessel is found to be $1\text{ cm}^3/\text{s}$. Ignoring radiation heat transfer, calculate the heat transfer coefficient under these conditions.
- 4.7. A sunbather experiences a temperature difference on the side of the body that faces the sun versus the side of the body that is not exposed to the sun. Looking at the upper arm, as a 3-cm-thick body, it is observed that the surface temperature on one side of the arm is 40°C and the temperature on the surface of the arm facing away from the sun is 29°C . The surface of the arm that faces the sun exchanges heat with the surrounding atmosphere (at a temperature of 35°C) by radiation. Similarly, heat is transferred by convection to the atmosphere. The convection heat transfer coefficient for this transfer is $5\text{ W/m}^2\text{K}$. The solar radiation to heat the arm is observed to be 200 W/m^2 . If we assume that the emissivity and the absorptivity of the surface facing the sun can be approximated as 0.5 and 0.95, respectively, determine the effective thermal conductivity.
- 4.8. A branding iron is used to sear patterns into skin. We can estimate that the tip of the branding iron has a cylindrical geometry with a diameter of 2 cm and length of 10 mm, with a thermal emissivity of 0.75. What power is required to maintain the tip of the iron at 300°C , when the surrounding tissue is assumed to be 25°C . Further, the average convection heat transfer coefficient for this iron is calculated to be $40\text{ W/m}^2\text{K}$.
- 4.9. A sunbather who loses no heat through the surface pointing away from the sun is exposed to solar radiation at a rate of 750 W/m^2 . The absorptivity of the person can be estimated to be 0.55 with an air temperature of 27°C . Determine the surface temperature of the person if the convection heat loss is 0.9 of the solar energy absorbed by the person and assume that the convection heat transfer coefficient is $35\text{ W/m}^2\text{K}$. Disregard heat loss from radiation.
- 4.10. A heater is used to warm a room to an air temperature of 25°C . To maintain this air temperature, the heater uses 400 W of power and has a surface temperature of 100°C . Calculate the heater surface temperature when it uses 650 W of power, assuming negligible radiation and the surface area of the heater is 0.2 m^2 .

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- [3] H.H. Pennes, Analysis of tissue and arterial blood temperatures in the resting human forearm, J. Appl. Physiol. 1 (1948) 93.

The heart

LEARNING OUTCOMES

- Identify major structures that compose the heart
- Explain how blood flows through the heart
- Evaluate the action potential in the cardiac muscle compared with nerve cells
- Calculate the work that the heart undergoes to move blood through the cardiovascular system
- Describe the cardiac conduction system
- Relate the electrocardiogram waves to the contraction of heart muscle
- Explain the pressure–volume relationship within the cardiac cycle
- Model the motion of the heart in three dimensions
- Calculate the stress distribution throughout heart wall tissue
- Demonstrate the function of heart valves
- Examine how blood flows through heart valves
- Describe the tension–pressure relationship within heart valve leaflets
- Discuss the dynamics of heart valve motion and blood flow through the valves
- Compare salient disease conditions that are related to the heart and the heart valves

5.1 Cardiac physiology

The heart is a muscle that primarily acts to pump blood throughout the entire cardiovascular system (e.g., the systemic and pulmonary circuits). It is composed of two separate pumps that work in synergy to transport blood through the vascular system (Fig. 5.1). One of these pumps (the “left pump”) delivers oxygenated blood to all tissues that compose the body, and the other pump (the “right pump”) delivers deoxygenated blood to the

pulmonary circuit of the lungs to become oxygenated (note that the pulmonary circuit does not provide oxygenated blood to the lung tissue; the systemic circulation by the bronchial arteries provides oxygenated blood to the lung tissue). Each of these pumps is composed of two pumping chambers: the atrium (plural, atria) and the ventricle. The atria are more of a passive pumping system that facilitates blood movement into the ventricles. The atria, therefore, act as primer pumps for the ventricles. The ventricles are more of an active pumping system that provides sufficient force/energy for the blood to flow throughout the body or pulmonary circuit of the lungs. In the next few sections, we will discuss the physiological controls on heart motion and how blood flows through the heart. Blood flow through the vascular system will be discussed in subsequent chapters.

To understand the physiology of the heart and how the heart functions, we first need to understand what cardiac muscle is and how it functions. Cardiac muscle cells (or cardiac myocytes) have some similarities to skeletal muscle but have some important differences that make them specialized for the synchronous contraction of the heart. Cardiac muscle cells are long (longitudinal direction) and narrow (transverse direction). They are interconnected in a very special and unique way that allows the cells to function as one. This is dissimilar to skeletal muscle, which readers may be more familiar with

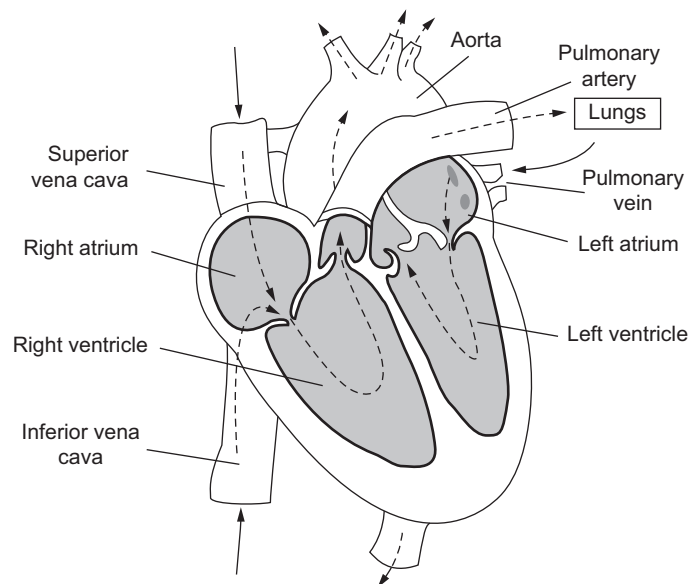


FIG. 5.1 Anatomy of the heart depicting the direction of blood flow through the four heart chambers. The right side of the heart collects deoxygenated blood from the systemic circulation and delivers it to the pulmonary circulation. The left side of the heart collects oxygenated blood from the pulmonary circulation and delivers it to the systemic circulation.

from previous physiology courses. Individual cardiac muscle fibers continually divide and merge, forming a highly interconnected meshlike structure (Fig. 5.2). The cell membranes of neighboring cardiac myocytes fuse at structures termed *intercalated discs*, which are typically present only along the longitudinal cell direction and not along the transverse direction (in Fig. 5.2 the intercalated discs are depicted as heavy black vertical lines penetrating the fibers). Many gap junctions are present at the intercalated discs, allowing for a rapid ion communication between neighboring cardiac muscle cells. These gap junctions effectively reduce the intercellular resistance to ion transfer, by at least 2 orders of magnitude, compared with nonmediated ion movement across a typical cell membrane. Thus, there is an enormous preference for communication molecules (e.g., ions) to move in the longitudinal direction to rapidly pass from one cardiac muscle cell to another cardiac muscle cell compared with movement in the transverse direction, which would be nonfacilitated across cell membranes (remember that the permeability of ions through cell membranes in the absence of specific channels is negligible). Additionally, desmosomes are present within the intercalated discs of cardiac myocytes. Desmosomes are specialized cell–cell adhesion molecules that allow the cardiac myocyte contraction to mechanically pass between each cell and prevent the cells from “pulling” each other apart during a contraction.

Although the physiology of cardiac muscle is quite different from that of skeletal muscle, cardiac muscle contracts in a manner very similar to that of skeletal muscle. Again, readers may be familiar with this from a previous physiology course. Cardiac muscle fibers are striated and composed of sarcomere structures similar to those of skeletal muscles. Actin and myosin cross-bridges (in the form of myofibril units) produce the necessary connections to allow for muscle contraction. The proteins in the cardiac muscle unit (e.g., actin and myosin)

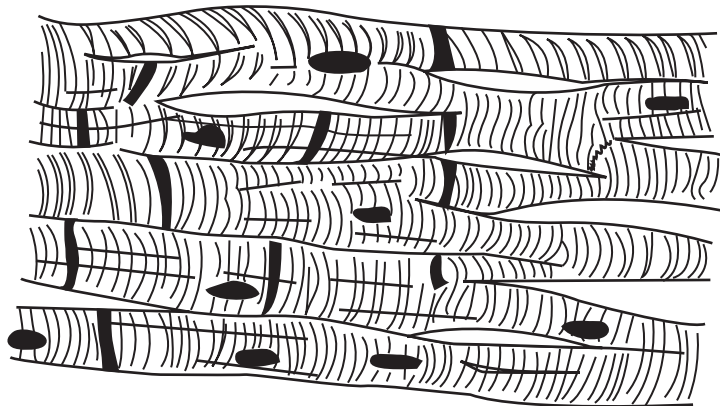


FIG. 5.2 Schematic of cardiac muscle cells depicting the highly interconnected fibers that form a syncytium, and the intercalated discs that divide individual muscle cells. There are many gap junctions present within the intercalated discs to facilitate the movement of ions between cells, thus allowing the action potential to continuously flow from one cell to the next. (Modified from Guyton and Hall, *Textbook of Medical Physiology*, 10th ed., W.B. Saunders, Philadelphia, 2000.)

are regulated with a system very similar to the troponin/tropomyosin system in skeletal muscles, which requires increased intracellular calcium to free actin binding sites. Again, similar to skeletal muscles, an action potential instigates contraction in cardiac muscle cells. Because of the presence of the intercalated discs (with many gap junctions), the action potential spreads from one cardiac myocyte to the neighboring myocytes with almost no impediment to the speed of the signal. This allows the formation of a muscle syncytium, which can work and produce a sustained contraction at the same time across large sections of the cardiac muscle mass.

The coupling between excitation of the cardiac myocytes and the contraction of the muscle fibers is dictated by changes in the cell's cytosolic calcium concentration. Calcium is released from the sarcoplasmic reticulum and then binds to troponin, which allows the actin–myosin cross-bridge formation to begin. Calcium release from the internal stores in the cardiac muscle cells occurs by a mechanism similar to skeletal muscle excitation–contraction coupling; however, there are some important differences to note. In cardiac muscle cells, the cell membrane (termed the sarcolemma) has many invaginations that surround the contractile elements (Fig. 5.3). These invaginations are termed the *transverse tubules*, or T-tubules, and they penetrate the muscle cell at or near the z-line of each sarcomere. Therefore, each sarcomere has effectively one T-tubule dedicated to its function and that tubule is located at an important anatomical structure. The purpose of the T-tubule system is to bring the extracellular space close to the critical calcium-containing intracellular space, termed the *sarcoplasmic reticulum*. The sarcoplasmic reticulum, which is analogous to the endoplasmic reticulum, is an organelle that surrounds the entire myofibrils (and thus each sarcomere unit). The sarcoplasmic reticulum makes contact with the T-tubules at a specialized location termed the *diad*.

At each diad unit, two very important calcium channels come into close proximity with each other. The dihydropyridine receptor (DHPR) can be found on the T-tubule membrane,

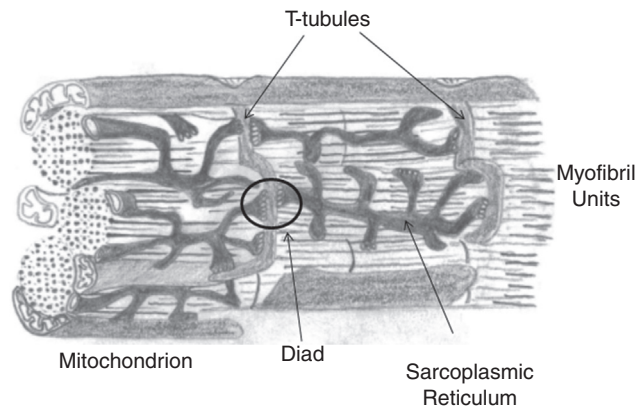


FIG. 5.3 Spatial organization of the cardiomyocyte T-tubule system and sarcoplasmic reticulum. Invaginations of the sarcolemma form the T-tubule system, which associates with the sarcoplasmic reticulum at specific locations termed the *diad*. (Modified from J. Feher, *Quantitative Human Physiology: An Introduction*. Elsevier, Waltham, MA, 2012).

and the ryanodine receptor (RyR) can be found on the sarcoplasmic reticulum membrane. Skeletal muscle and cardiac muscle contain DHPRs, but the protein subunits vary slightly, which is likely the cause of the different excitation–contraction coupling mechanisms between the two muscle types. In cardiac muscle cells, DHPR senses a depolarization of the T-tubule membrane and responds by activating the associated sarcolemma calcium channel. This small increase in intracellular calcium from external calcium sources is insufficient to elicit a contraction response. However, the importance of this influx of interstitial calcium is that it is localized to the region of the RyR on the sarcoplasmic reticulum. The RyRs are responsive to small increases in cytoplasmic calcium and open, allowing for a large increase in the intracellular calcium from the sarcoplasmic stores. This process is commonly referred to as *calcium-induced calcium release*. A similar process can be observed in skeletal muscle contraction.

Cytoplasmic calcium regulates the formation of actin–myosin cross-bridges within the sarcomere unit. Briefly, under conditions in which the cytoplasmic calcium concentration is low, tropomyosin blocks the myosin binding site on actin. When the intracellular calcium concentration rises, calcium binds to one of the troponin subunits (troponin C), causing a conformational change of troponin, in relation to the connections between troponin and actin and tropomyosin. This conformational change translocates tropomyosin from the myosin binding site of actin to a region sufficiently far away from the same binding site. This motion allows for cross-bridge formation to occur between the actin and myosin, assuming there is sufficient adenosine triphosphate (ATP) present to cause and maintain charging of the myosin heads. Cross-bridge cycling is normally divided into four steps. The first is when ATP binds to myosin, lowering the binding affinity of myosin for actin. The second step is when ATP is hydrolyzed into adenosine diphosphate (ADP) and an inorganic phosphate, changing the conformation of the myosin head. The conformation change of myosin allows for a high-affinity binding between myosin and actin. If the myosin binding site on actin is available (e.g., there is sufficient calcium present in the cardiac muscle cell cytosol), the charged myosin has the ability to bind to actin. The binding between actin and myosin is the third step in the contraction cycle. Finally, ADP and the inorganic phosphate are released from myosin, causing a second conformational change of the myosin head in which actin moves relative to myosin. This is termed the *power stroke* and is what elicits contraction and overall shortening of the sarcomere units. In the presence of an additional ATP molecule, which would bind to the myosin head, myosin releases from the actin binding site and the process would reset as described. The entire contraction cycle is illustrated in [Fig. 5.4](#).

This process of cross-bridge cycling will continue to occur as long as the calcium concentration in the cytosol remains high and ATP is present. The RyR is typically open for a very short period, causing a burst of calcium release into the cytosol. This calcium is pumped either back into the sarcoplasmic reticulum (reuptake of calcium) or out of the cell across the sarcoplasmic reticulum (extrusion of calcium). The sarcoplasmic reticulum contains smooth endoplasmic reticulum calcium ATPase pumps (SERCA pumps), which couple the movement of two calcium ions from the cytosol into the sarcoplasmic reticulum to the hydrolysis of ATP. This pump functions only if a regulatory protein, phospholamban, is colocalized with the SERCA pump and is phosphorylated. The sarcoplasmic reticulum can maintain a very high calcium concentration because of the presence of calsequestrin, which actively contains and “binds” free calcium ions. Additionally, the sarcolemma contains a number of

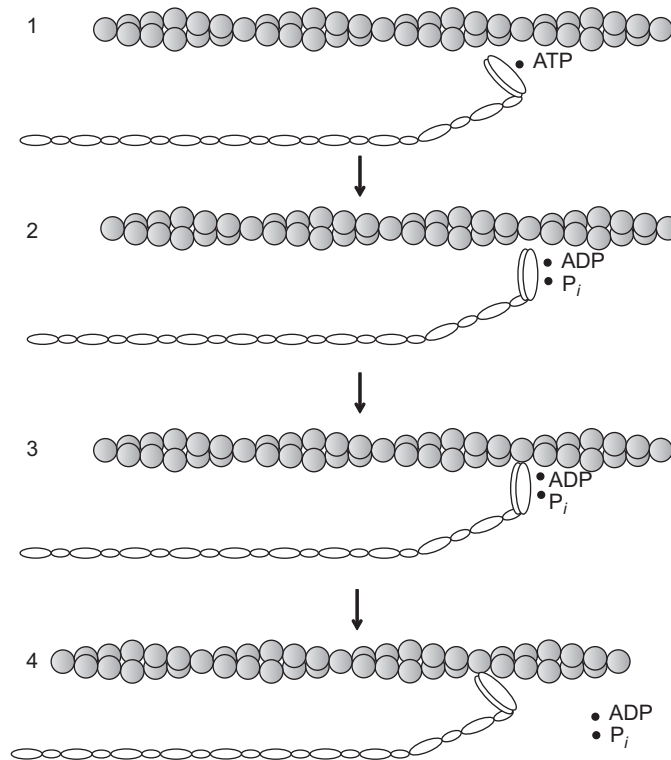


FIG. 5.4 Schematic of the actin–myosin cross-bridge cycle. Note that troponin and tropomyosin are not depicted on this figure. (1) Adenosine triphosphate (ATP) binds to myosin, lowering the binding affinity between myosin and actin. (2) ATP is hydrolyzed into adenosine diphosphate (ADP) and inorganic phosphate. The myosin head alters its conformation and stays in a “ready” state. In the absence of calcium the cycle will stop here. (3) In the presence of calcium, tropomyosin does not block the myosin binding site of actin and thus an actin–myosin cross-bridge is formed. (4) ADP and inorganic phosphate are released from the myosin head, inducing a conformation change of myosin. This conformation change forces actin to move relative to myosin in a process termed the *power stroke*. In the absence of ATP, the cycle will end at this stage (this is termed *rigor*).

pumps and exchangers to return the ion concentration to its normal levels. For example, a sodium–calcium exchanger and a plasma membrane calcium ATPase (PMCA) pump, along with the typical sodium–potassium ATPase all exist on the cardiac muscle cell membrane. The exchanger transports three sodium ions down its concentration gradient (e.g., into the cell) in exchange for one calcium ion transported out of the cell. PMCA pumps one calcium ion out of the cell for every ATP that is hydrolyzed. Finally, the sodium–potassium ATPase returns the sodium to the external environment, in exchange for potassium influx and ATP hydrolysis. To a lesser extent, cardiac myocyte mitochondria can uptake some calcium, through a sodium–calcium exchanger and a facilitated diffusion calcium channel. The entire pathway for calcium within a cardiac muscle cell, as discussed earlier, is shown in [Fig. 5.5](#).

Now that we understand contractile mechanisms of the myocytes, we can begin to discuss how the heart regulates contraction at the organ level. The atrial and ventricular myocytes

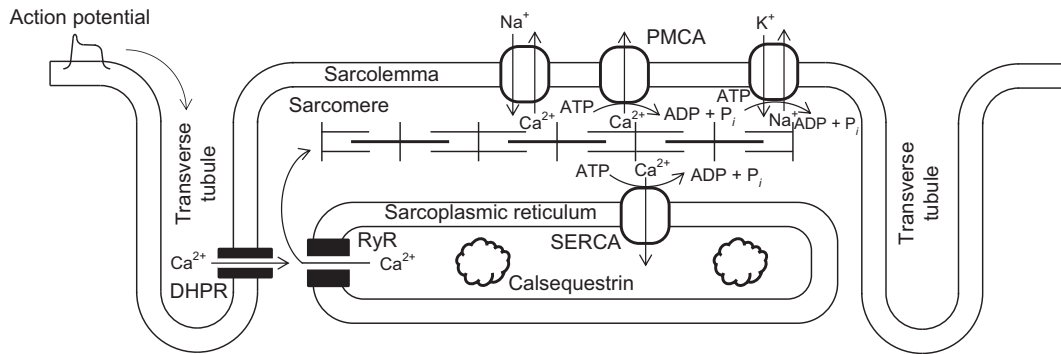


FIG. 5.5 Overview of calcium-induced calcium release within cardiac muscle cells. First an action potential passes along the sarcolemma into the transverse tubule system. The action potential induces the opening of the dihydropyridine receptor (DHPR), which allows a small amount of calcium into the muscle cell. This calcium induces the opening of the ryanodine receptor (RyR) found on the sarcoplasmic reticulum membrane, significantly increasing the cytosolic calcium concentration. This calcium is used to regulate cross-bridge formation (depicted in Fig. 5.4). Calcium is then taken up by the smooth endoplasmic reticulum calcium ATPase (SERCA) pumps to be stored in the sarcoplasmic reticulum and by the sodium calcium exchanger and plasma membrane calcium ATPase (PMCA) on the sarcolemma. ADP, Adenosine diphosphate; ATP, adenosine triphosphate.

compose two separate syncytiums in the heart. When the atrial syncytium contracts as a whole, blood is ejected from the left and right atria into the left and right ventricles, respectively. Remember, though, that atrial contraction is priming the ventricles and the majority of ventricular filling is not accomplished by this mechanism. When the ventricular syncytium contracts as a whole, blood is ejected from the two ventricles into the systemic or pulmonary circulatory system. These two syncytiums are separated by a fibrous tissue, which has a very high electrical resistance associated with it. The high-resistance tissue prevents the action potential signal from passing between the atria and the ventricles. Therefore, this prevents the ventricles from contracting at the same time as the atria and allows atrial contraction to fully fill the ventricles with blood. To couple atrial contraction with ventricular contractions, there is a specialized conduction pathway between these two chambers. This conduction pathway slows the action potential so that the atria can completely contract and eject sufficient blood to fill and prime the ventricles before the ventricles begin to contract. In addition, the conduction pathway brings the action potential to the apex of the heart, so that ventricular contraction proceeds from the bottom of the heart toward the top of the heart. This forces blood toward the aorta and the pulmonary arteries to exit the heart (see Section 5.2 for a detailed discussion on the cardiac conduction system).

Another difference between cardiac muscle cells and skeletal muscle cells is that the cardiac action potential differs from skeletal muscle action potential, allowing for the cardiac myocytes to contract in a sustained manner as an entire system, instead of as independent fibers (Fig. 5.6). As with normal nerve tissue and skeletal muscle action potentials, there is a rapid depolarization of the cells caused by an influx of sodium ions through rapid sodium channels. This depolarization increases the membrane potential from approximately -85 mV to approximately 15 to 20 mV. In a nerve cell and skeletal muscle cells, this rapid

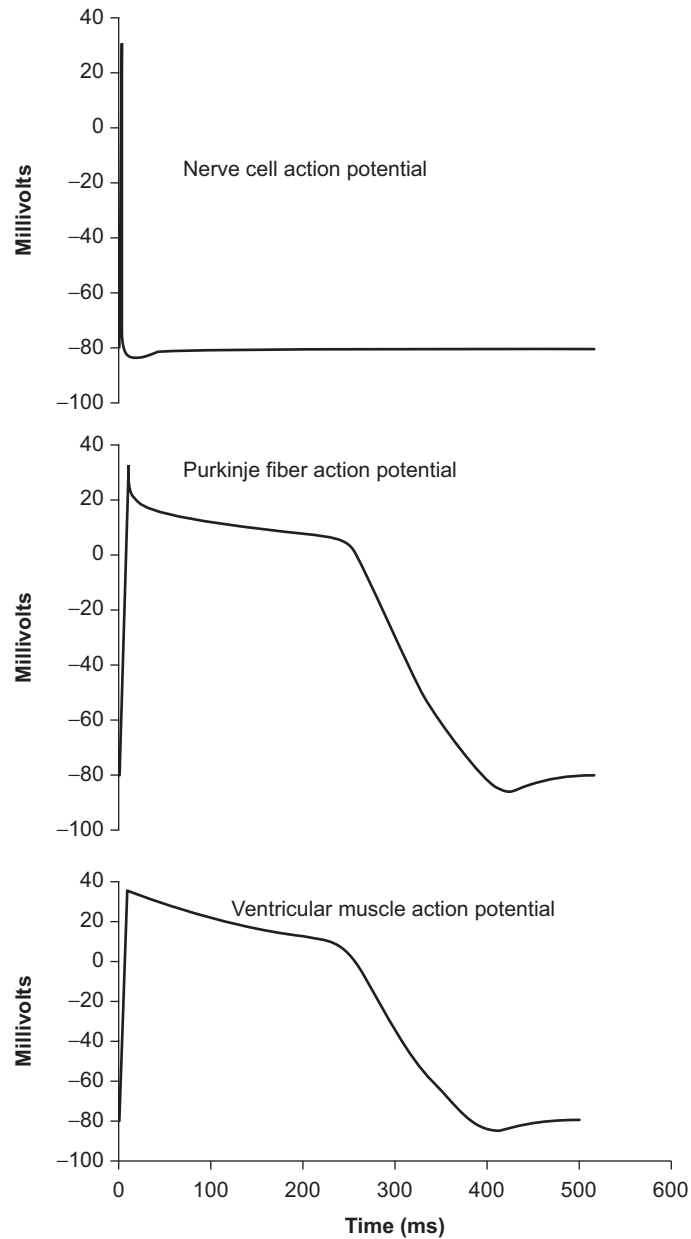


FIG. 5.6 Comparison of the action potentials in nervous tissue and cardiac tissue. There is a significant elongation of the depolarization phase in cardiac tissues compared with other excitable tissue. Note that the cardiac action potential varies slightly based on in which cardiac chamber the myocytes reside and that the myocytes of the SA node have a somewhat significantly different action potential waveform.

depolarization is followed by a rapid repolarization (the duration of the action potential is less than 0.1 second). Cardiac action potentials, however, exhibit an elongated plateau phase in which the cells remain depolarized for approximately 0.25 second. This elongated plateau region is caused by a constant influx of calcium ions through slow calcium channels. During the plateau phase, the permeability of potassium ions decreases, significantly slowing the efflux of potassium ions out of the muscle. This slowing balances the influx of calcium, and this is observed as a plateau in the membrane potential (e.g., there is no net change in the membrane potential of the cell during the plateau phase). This altered potassium permeability is also not observed in skeletal muscle action potentials, in which potassium efflux causes the rapid repolarization that was discussed previously. After the slow calcium channels close, the cell membrane permeability toward potassium ions is increased, allowing for the rapid repolarization of the cell. Repolarization occurs because there is nothing to balance the net loss of positive charges from the cytosolic side of the membrane. After the cell has repolarized, there is a latent period of about 0.25 second, in which it is difficult to excite the cardiac myocytes again. After this latent period, the myocytes are able to contract again as normal. Except for the slow movement of calcium ions into the cardiac muscle cell, the ion movement during the cardiac and skeletal action potentials is similar.

This entire discussion has brought us to a point at which it should be understood how the cardiac muscle contracts to effectively move blood throughout the cardiovascular system and the heart (see [Fig. 5.1](#)). To begin its path through the heart, deoxygenated blood enters from the superior vena cava or the inferior vena cava into the right atrium. The superior vena cava collects blood from the head, neck, and arms, and the inferior vena cava collects blood from the trunk and legs. Once the atrium contracts, blood passes through the right atrioventricular (AV) valve, also known as the *tricuspid valve*, into the right ventricle (as we will see later, blood actually passes through this valve during the majority of the cardiac cycle, and only a little remaining volume of blood passes from the atria to ventricles on atrial contraction). This valve acts to prevent the backflow of blood into the right atrium, when the right ventricle contracts. Once the right ventricle contracts, blood is ejected through the right semilunar valve (also known as the *pulmonary valve*) into the respiratory circulation to become oxygenated. Blood is transported to the pulmonary circulation by the pulmonary arteries. Oxygenated blood returns from the pulmonary circulation into the left atrium via the pulmonary veins. As the atria contract, blood passes through the left AV valve, also known as the *mitral valve*, into the left ventricle (note again that the majority of blood does not pass from the atria to the ventricles during atrial contraction). This valve also acts to prevent the backflow of blood during ventricular contraction, and blood passes through it during a majority of the cardiac cycle. Upon left ventricle contraction, oxygenated blood is ejected into the systemic circulation, through the left semilunar valve (also known as the *aortic valve*). Note that all of the valves in the heart open and close passively, in response to pressure changes; there are no muscles that contract and cause the opening of the heart valves. During atrial contraction, the fluid pressure within each atrium remains greater than the fluid pressure within the ventricles. This pressure gradient helps drive the remaining atrial blood to pass into the respective ventricles. As the atria relax and the ventricles contract, the pressure gradient reverses so that there is a higher pressure in the ventricles and a lower pressure in the atria. This exerts a force on the AV valves, causing them to close and thus prevent blood movement from the high-pressure ventricles

into the low-pressure atria. As for the semilunar valves, when the ventricle pressure exceeds the aortic or pulmonary artery pressure, these valves open. When the ventricles relax, the pressure gradient reverses and the semilunar valves close to prevent the backflow of blood into the heart from the pulmonary or systemic circuits. As soon as the ventricular pressure reduces to a level below the atrial pressure, the AV valves open and allow blood to pass directly from the venous circulation into the ventricles, bypassing the need for the atria to contract. In the anatomy of the heart valves, there are muscles attached to the AV valves (the papillary muscles). These muscles do not aid in valve opening but rather function to maintain the valves in a tightly closed position. During ventricle contraction, the papillary muscles contract to prevent the AV valves from opening in the reverse direction, into the atria. Without this preventive mechanism, blood would have a preference to flow back into the atria instead of into the aorta or pulmonary arteries, because the pressure in the respective atrial and venous circulation is far lower than either of these vessels. For a complete discussion on the motion of the heart and the heart valve function, see [Sections 5.4, 5.5, and 5.6](#).

The work required for the heart to function is directly related to the pressure–volume relationship of the two ventricles. A very small component of energy is needed to accelerate blood, but this is much less than the total work of the heart and is typically ignored when calculating the mechanical work associated with heart motion. In the pressure–volume relationship for the left ventricle, there are typically four phases that are discussed ([Fig. 5.7](#); this is shown for the left ventricle). The first phase (filling phase) is when the left atrium is contracting, filling the left ventricle with blood. During this phase, the blood volume in the left ventricle increases from approximately 45 mL (end-systolic volume) to approximately 115 mL (end-diastolic volume) (please note that the pressures and volumes discussed in this section are related to the adult human heart). The pressure in the left

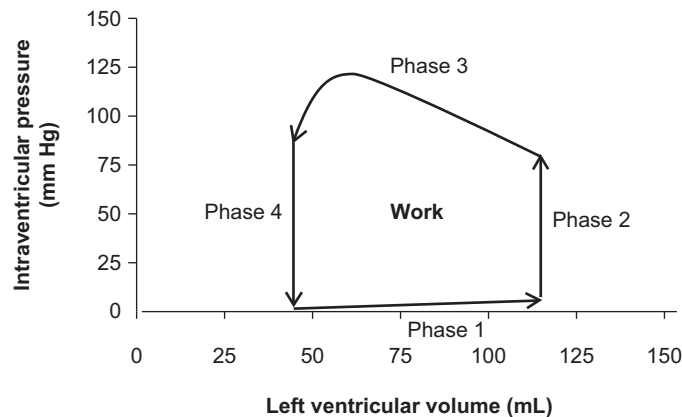


FIG. 5.7 The pressure–volume relationship for the left ventricle, which describes the work that the left ventricle conducts. The work is the area within the pressure–volume curve. The work the heart conducts can drastically change under disease conditions. Note that work associated with the acceleration of blood is ignored in this figure and typically within the analysis of work conducted by the heart.

ventricle increases from approximately 1 mmHg to approximately 5 mmHg during this period. The second phase (isovolumic contraction) is a period during which the volume of the left ventricle does not change but the pressure increases rapidly. There is no change in left ventricular volume because both the mitral and aortic valves are closed. However, the left ventricular myocytes are contracting, which effectively increases the pressure to approximately 80 mmHg. This is the pressure in the aorta before valve opening (it is assumed that blood is incompressible, and therefore there is no or negligible volume change). During the third phase (ejection phase), the pressure of the ventricle increases to approximately 120 mmHg, because of further contraction of the left ventricle myocytes, and then reduces back to approximately 80 mmHg. The volume of the left ventricle also reduces because blood is being ejected into the aorta (the aortic valve is open). The last phase (isovolumic relaxation) is also classified by no change in left ventricular volume. During this phase, the mitral and aortic valves are closed and the pressure in the left ventricle reduces from approximately 80 mmHg to 1 mmHg. The reduction in pressure occurs because the left ventricle myocytes are relaxing. The pressure–volume loop forms a closed cycle, in which the work can be quantified by the area enclosed within the cycle. The right ventricular pressure–volume relationship is very similar to the left ventricle pressure–volume curve, except that the pressure is approximately five to six times lower than the left ventricle (the right ventricle curve is not shown). The reader is cautioned that the pressure–volume relationship changes drastically under different pathological conditions, in which the systolic/diastolic pressure is not the “normal” 120/80 mmHg. Therefore, under a disease condition, the heart may work more than normal, potentially leading to other pathological conditions.

5.2 Cardiac conduction system and electrocardiogram

The cardiac conduction system is composed of a specialized structure that generates impulses to excite the heart and a specialized conduction system to induce all ventricular myocytes to contract within a very short time interval and, second, to have the ventricular myocytes contract only after atrial contraction completes (Fig. 5.8). The sinoatrial (SA) node is the specialized structure that generates impulses within the heart. It is located within the right atrium wall immediately below the opening of the superior vena cava. The SA node is a group of specialized muscle cells that have little to no contractility associated with them, but they are directly connected at many locations to the neighboring cardiac myocytes within the atrial syncytium.

The muscle cells that compose the SA node are surrounded by extracellular fluid with an abnormally high sodium concentration. Unlike other cardiac myocytes, the cells that compose the SA node have some cell membrane sodium channels that are always open in addition to the normal fast sodium channels. Remember that the normal fast sodium channels are the channels that open in response to an increased membrane potential in the range of -40 to -50 mV and are responsible for the rapid depolarization phase of the action potential. The additional sodium channels of the SA node remain open and facilitate the movement of sodium ions across the cell membrane at all times. Because of the presence of these continually open sodium channels (sometimes termed *leak channels*) and the continuous leak of

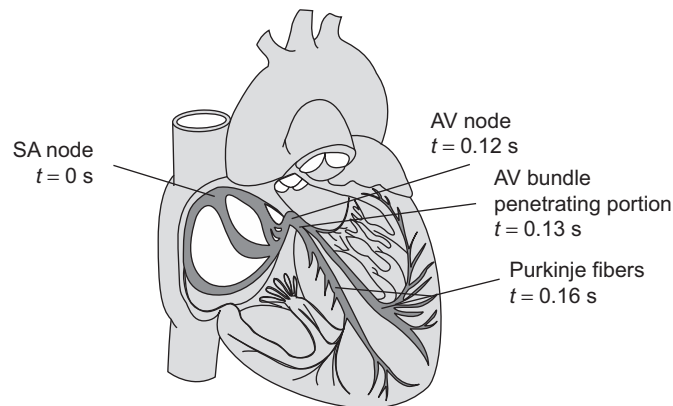


FIG. 5.8 The sinoatrial (SA) node and the Purkinje fiber system of the heart, showing the approximate times when the action potential signal reaches various locations within the conducting system. This conducting system allows for a rapid transmission of the cardiac action potential to each cardiac myocyte. For ease of viewing the interatrial band has been removed. This pathway conducts the action potential from the SA node to the left atrium rapidly. AV, Atrioventricular.

sodium ions into the SA node cells, there is a slow increase in the SA node cell membrane potential from approximately -60 mV to approximately -40 mV. It is important to note that the resting membrane potential of the SA node cells is slightly more positive compared with normal cardiac myocytes; this is caused by the higher than normal permeability of the SA node cell membrane to sodium ions (because of the presence of sodium leak channels). Once the membrane potential reaches approximately -40 mV (the SA node action potential threshold, which is also more positive than the normal action potential threshold for cardiac myocytes), the slow calcium channels and the fast sodium channels activate and open. As we saw earlier, this allows both calcium and sodium ions to pass rapidly into the myocytes that compose the SA node. Once the rapid influx of sodium and calcium begins, there is a rapid depolarization of the SA node cells, which leads to the action potential impulse throughout the atrial syncytium. Again, the cells that compose the SA node are directly connected with the neighboring atrial myocytes through extensive gap junction connections. Therefore, once the SA node has become depolarized, the action potential signal passes to neighboring myocytes through gap junctions with little impedance, allowing for and causing atria contraction. The action potential conduction speed through the atria proceeds at approximately 0.3 m/s. The SA node cells also contain potassium channels, allowing for the efflux of potassium out of the cells. Upon significant potassium efflux, the membrane potential repolarizes back to approximately negative 60 mV. The constant sodium leak is counterbalanced by the presence of these potassium channels and the inactivity of the calcium and fast sodium channels (after the channels close), allowing for the membrane potential to approach the potassium equilibrium potential (again note that the potassium equilibrium potential is more positive than in normal cardiac myocytes because of the presence of sodium leak channels and the higher than normal concentration of extracellular sodium). Part of the purpose of the potassium and calcium channel activity is to prevent the SA node cells from continually experiencing a positive resting potential (near the sodium equilibrium

potential) as a result of the continuous influx of sodium ions through these leak channels. The entire process of sodium leak into the SA node, depolarization of the SA node, and repolarization of the SA node occurs approximately once every second during normal resting conditions. It is also important to note that the changes in the membrane potential of the SA node cells are somewhat more complicated than a typical cardiac myocyte because of the presence of the sodium leak channels. In the absence of these channels the resting membrane potential of the SA node cells would be similar to that of the other cardiac myocytes.

The SA node is also directly coupled to an interatrial band and three internodal pathways. The interatrial band connects the left and right atria, so that the two atria can contract at approximately the same time. Remember that the result of atrial contraction is more passive on ventricular filling and that the atria act as primer pumps for the ventricles. The interatrial band passes through the right atrium wall into the left atrium and is composed of specialized conducting cells that pass the depolarization signal to the left atrium at a rate of at least 1 m/s. The three internodal bands initiate at the SA node, follow along the right atrium wall (along the anterior, middle, and posterior sides), and terminate at the AV node. These fibers rapidly conduct the action potential signal (less than 0.04 second after they become activated by the original action potential) to the AV node, which is responsible for instigating ventricle contraction.

The AV node is located in the wall of the right atrium and is primarily responsible for delaying the action potential signal from entering the ventricles. This allows both of the atria to fully prime the ventricles before ventricular contraction. The signal is delayed in the AV node for approximately 0.09 second before the action potential signal is allowed to pass through the penetrating portion of the AV node (total of approximately 0.13 second after SA node depolarization). The penetrating portion of the AV node passes directly through the highly resistant fibrous tissue that separates the atria and the ventricles. After passing through the fibrous tissue, there is another delay of approximately 0.03 second, in which time the action potential signal passes into the Purkinje fiber system to allow for rapid and synchronized depolarization of the ventricular muscle cells from the apex of the heart upward toward the outflows. The cause of this slowed transmission in the AV node system is a decreased number of gap junctions between the cells that constitute the various sections of the conducting system. This effectively increases the resistance to action potential transmission compared with the normal cardiac myocytes.

The Purkinje fibers act as a direct coupling between the AV node system and the ventricles. These fibers are very large and function to transmit the action potential signal very rapidly at speeds of up to 4 m/s. Recall that with an increase in fiber diameter there is a decrease in fiber resistance if other conditions remain the same; thus, part of the reason for an increased conduction speed is based on increased fiber diameter. However, an increased concentration of gap junctions is present in these cell types, to further enhance the conduction speed. Immediately distal to the AV bundle, the Purkinje fibers split into the right and left branches of the Purkinje fibers. These branches follow the ventricular septum (the wall that separates the right and left ventricles) all the way to the apex of the heart. At the heart apex, these fibers branch into smaller fibers that penetrate the entire ventricular cardiac muscle mass. Therefore, this acts to pass the action potential signal directly to every muscle cell within the ventricular wall. The first cells that contract are those near the heart apex, and the wave of contraction passes upward and outward to the remaining cardiac muscle cells. As the reader

may guess, the reason for the rapid conduction through the Purkinje fibers/ventricular mass is the presence of many gap junctions connecting the cells and the cardiac muscle mass. This high conductivity allows all of the ventricular muscle cells to contract within 0.05 second of the cells at the apex. The same fibrous mass that blocks the atrial action potential signal from entering the ventricles blocks the ventricle action potential signal from entering the atria.

One of the most common ways to monitor the electrical system of the heart is through an electrocardiogram (ECG). To measure an ECG, electrical leads are placed at particular locations on the skin to measure the heart leak current that enters surrounding tissues. The normal ECG is composed of three waves termed the *P wave*, the QRS complex (sometimes this can be considered as three independent waves), and the T wave (Fig. 5.9). Each of these waves represents a particular portion of the cardiac action potential. The P wave is associated with atrial depolarization and occurs immediately before atrial contraction. The P wave typically lasts for approximately 0.05 second under normal conditions. The QRS complex is associated with ventricular depolarization and occurs immediately before ventricular contraction. The QRS complex typically starts 0.15 second after the P wave starts and lasts for approximately 0.09 second. The T wave is associated with ventricular repolarization, and it occurs once the ventricular muscle cells recover from depolarization. This wave lasts for approximately 0.05 second, occurring approximately 0.25 second after the QRS complex ends. The atrial repolarization wave does not show up on the normal ECG because it occurs approximately 0.15 second after atrial depolarization. The atrial depolarization wave is a small wave, and it is hidden by the much larger QRS complex that occurs at the same time.

The normal ECG is characterized by the length of time of each wave, the time between each wave (typically called the *interval*, e.g., the P-Q interval or the Q-T interval), and the voltage associated with each wave. Many pathological heart conditions can be diagnosed

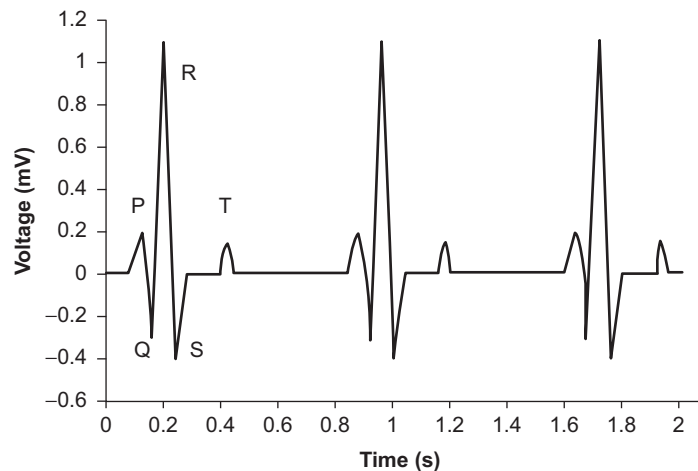


FIG. 5.9 Schematic of a normal electrocardiogram trace, depicting the various waveforms used to determine whether the heart is functioning properly. The P wave is associated with atrial contraction, the QRS complex is associated with ventricular contraction, and the T wave is associated with ventricular repolarization. Atrial repolarization is masked by the much larger QRS complex.

by changes in the ECG signal. For instance, an increased voltage associated with the QRS complex can be attributed to increased muscle mass. Decreased QRS voltage is typically associated with a decrease in muscle mass potentially because of infarctions present within the muscle mass. If the conduction system is blocked or damaged, it is typical to see a change in the onset time or the length associated with the QRS complex. Under these pathological conditions, the QRS complex can elongate to approximately 0.15 second or more. It is also typical to see an inverted T wave when the QRS complex is significantly elongated.

5.3 The cardiac cycle

The cardiac cycle describes all of the events that occur during one heartbeat and during the latent time until the next heartbeat. It makes the most sense to describe these events starting from the initiation of an action potential within the SA node (see [Section 5.2](#)). The cardiac cycle consists of two phases: diastole and systole. Cardiac myocytes do not contract during diastole, and this is when the majority of blood fills the heart chambers. During systole, the myocytes contract and eject blood from the particular chamber either into other heart chambers or into the vascular system. This textbook and many other resources use the terms *systole* and *diastole* interchangeably with ventricular systole and ventricular diastole. The contraction cycle of the atria can be described by their own systolic and diastolic pattern, however, the ventricular cycle is much more significant for the functionality of the heart and is typically the one referenced during normal discussion.

To depict the cardiac cycle, the aortic pressure, the left ventricular pressure, the left atrial pressure, the left ventricular volume, and the ECG are overlaid onto one figure that is plotted against time ([Fig. 5.10](#); a similar figure can be drawn for the right side of the heart, with pressure values that are approximately one-sixth of the value compared with the left side of the heart). Recall that the ECG P wave is associated with atrial depolarization. During this time, the mitral valve is open and the left atrium forces the remaining blood into the left ventricle, effectively priming the left ventricles for contraction. This priming action occurs because during much of left ventricular diastole (and left atrial diastole), the left atrial pressure is higher than the left ventricular pressure, which suggests that the mitral valve is open. Any blood that enters the left atria from the venous pulmonary circulation passes directly into the left ventricles. Hence, one can observe a steady rise in ventricular volume during the diastolic portion of the cardiac cycle. During atrial systole, 10 to 20 mL of blood is forced into the ventricles, which acts to expand the ventricular muscle mass. This expansion causes an initial elastic recoil response, in addition to the ventricle muscle contraction, to aid in moving blood through the cardiovascular system. Note again that although we are discussing the left side of the heart, the same pattern is observed on the right side of heart (e.g., during ventricular diastole, blood passes from the right atria directly into the right ventricles).

Upon the onset of the QRS complex, there is a rapid increase in ventricular pressure because of ventricle contraction. This is associated with the closing of the mitral valve and isovolumic contraction of the ventricle. The left ventricle contracts for a short amount of time without losing volume because both the mitral valve and the aortic valve are closed

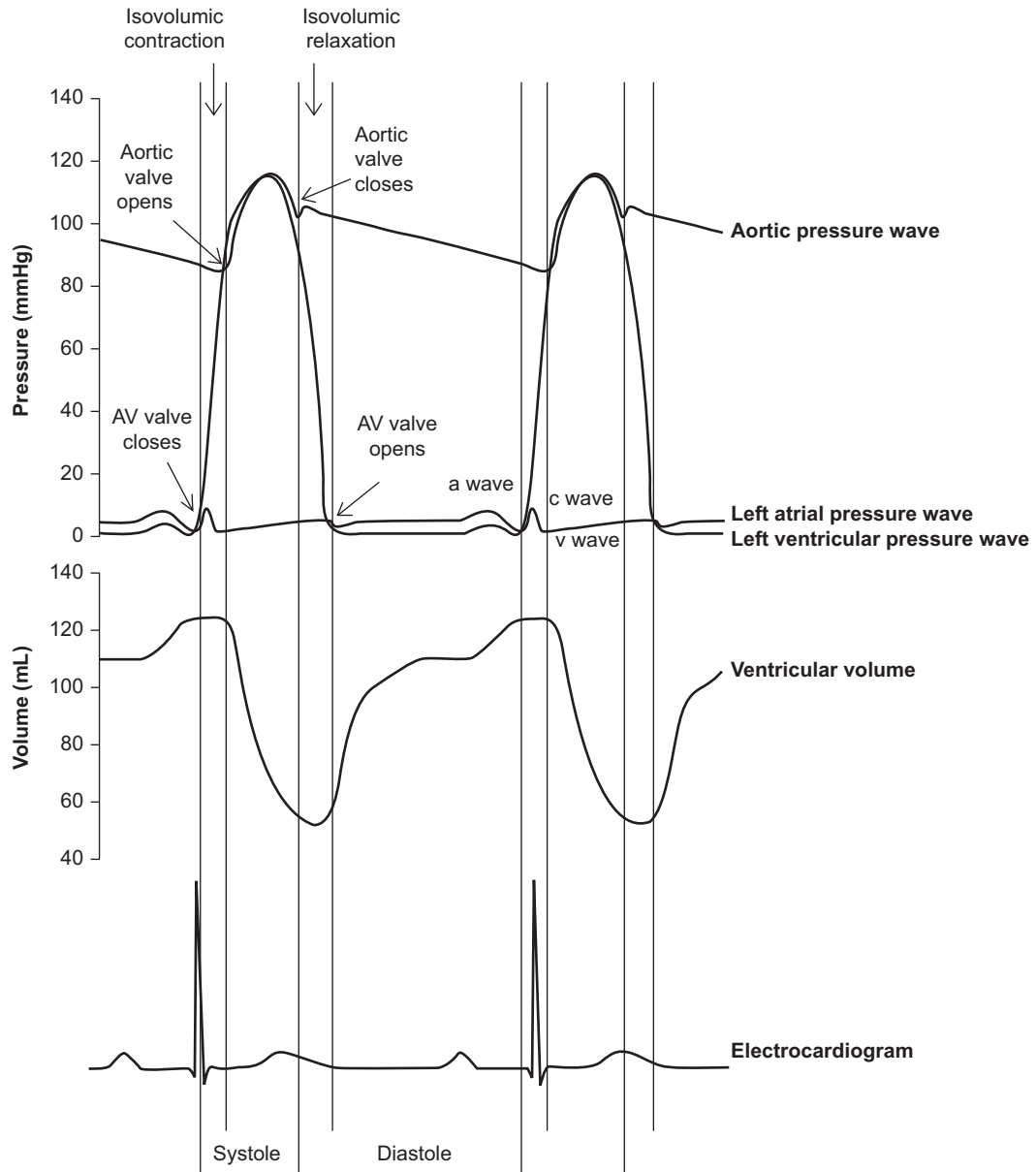


FIG. 5.10 Pressure and volume waves associated with the left side of the heart. This figure depicts the relationship between the electrocardiogram and the contraction and filling of the cardiac tissue. Various important points are noted such as valve opening and ventricular systole versus ventricular diastole. The named waves that are observed during the atrial pressure waveform are also shown in this figure. AV, Atrioventricular.

and we assume that the compressibility of blood is negligible. As the QRS complex ends, the aortic valve opens (as a result of the left ventricle pressure surpassing the aortic pressure) and the left ventricle ejects blood into the systemic circulation. The duration of ventricle contraction is termed *systole*. The volume of blood in the ventricles reduces from approximately 120 mL to approximately 45 mL, which is termed the *residual ventricular volume* or *end-systolic volume*. The difference between the end-diastolic volume and the end-systolic volume is referred to as the *stroke volume*. During systole, the T wave is recorded, and this is when the ventricles begin to relax. At this time, the vascular pressure (e.g., aortic) is still lower than the ventricular pressure, so that blood continues to be ejected out of the heart for a few milliseconds. Toward the end of the T wave, the aortic valve closes (because the left ventricular pressure drops below the aortic pressure) and the ventricle enters the isovolumic relaxation phase, which marks the beginning of ventricular diastole. After a few milliseconds, the pressure in the ventricles returns to approximately 1 mmHg and the mitral valve opens again. At this point, diastole continues until the ventricles begin to contract and the mitral valve closes once again. As mentioned earlier, during the entire period of diastole, even though the left atrium is not contracting, the left ventricle is filling with blood. In fact, approximately 75% of the blood that enters the atrium passes directly into the ventricle without the aid of atrial contraction. During atrial contraction, the remaining blood volume enters the ventricles. Note that the discussion was for the left side of the heart, which is shown in [Fig. 5.10](#). A similar discussion for the right side of the heart could be conducted, but the pressure would be reduced compared with the left side of the heart and the volumes are subtly different, although the stroke volume is largely the same.

The pressure in the atria remains fairly constant (and low) during the entire cardiac cycle. However, three major changes occur within the atrial pressure waveform, and they are denoted as the a (atrial contraction), c (ventricular contraction), and v (venous filling) waves. The a wave is associated with atrial contraction and occurs immediately after the P wave of the ECG. During the a wave, both atria experience an increase in pressure of about 6 to 7 mmHg, with the left atrium experiencing a slightly higher pressure increase than the right atrium. The c wave corresponds to the beginning of ventricular contraction and occurs immediately after the QRS complex of the ECG. This is caused primarily by the increased ventricular pressure acting on the AV valves. In addition, at the beginning of systole, there is a small amount of blood backflow into the atria because the valves have not yet fully closed. Combined, these two changes induce an increase in atrial pressure. The v wave represents a steady increase in atrial pressure that occurs during ventricular contraction, which is caused by venous blood from the systemic or pulmonary circuits entering the atria. When the AV valves reopen, this increased pressure aids in blood movement directly into the ventricles without atrial contraction.

[Fig. 5.10](#) depicts the cardiac cycle for the left ventricle, left atrium, and aorta. The aortic pressure curve is what is estimated when a patient has his or her blood pressure taken, or more accurately, the maximum aortic pressure and the pressure at which the aortic valve opens. At the point that the aortic valve opens, the pressure in the aorta increases because of blood being forced into the vascular system from the left ventricle. At peak systole, the blood pressure in the aorta reaches approximately 120 mmHg under normal healthy human adult conditions. At the point that the aortic valve closes, the pressure in the aorta is approximately 100 mmHg. At the time of valve closure, the pressure increases by approximately 5

to 10 mmHg as a result of aortic elastic recoil and blood passing from the apex of the aortic arch back toward to the aortic valve. The backflow of blood occurs because the left ventricular pressure has dropped below the aortic pressure, and then the pressure gradient favors blood moving down the aortic arch toward both the abdominal aorta and the aortic valve (e.g., the different sides of the arch). The slight rise in the aortic pressure is termed the *dicrotic notch*. The following rise in aortic pressure is referred to as the *dicrotic wave*. Then, as a result of the viscoelastic recoil of the aorta, there is a slow, but continual, decrease in aortic pressure during diastole. At the end of diastole and the isovolumic contraction phase, the aortic pressure is approximately 80 mmHg. Once the left ventricular pressure surpasses this, the aortic valve opens and the pressure increases again to approximately 120 mmHg.

An additional interesting point is the sound that the heart makes during the cardiac cycle. A physician can listen to these sounds with a stethoscope. These sounds are caused by first the closure of the AV valves and then the closure of the semilunar valves. The sounds are generated by the valve vibrations during the closing process. As mentioned previously, the AV valves can bulge into the atrium and the semilunar valves can bulge into the ventricles immediately after closure. This is caused by an increase and a reversal in the pressure gradient across the leaflets. With respect to the AV valves, the papillary muscles and the tendons that attach to the valves (the chordate tendineae) experience recoil, inducing valve leaflet vibration. The semilunar valves are highly elastic and experience recoil because of the pressure difference. This elastic recoil generates an audible sound.

As we know, the heart beats approximately 72 beats per minute for an average human. Comparing between other animals, one can see that heart rate is inversely proportional to body mass (Fig. 5.11). Many models can be used to describe this relationship, some of which account for if the animal is warm-blooded or cold-blooded, what the daytime activity of the animal is, and how the animal developed from an evolutionary standpoint. For this textbook, it is important to keep in mind that, in general, animals with a lower mass will have a higher heart rate compared with animals with a larger mass.

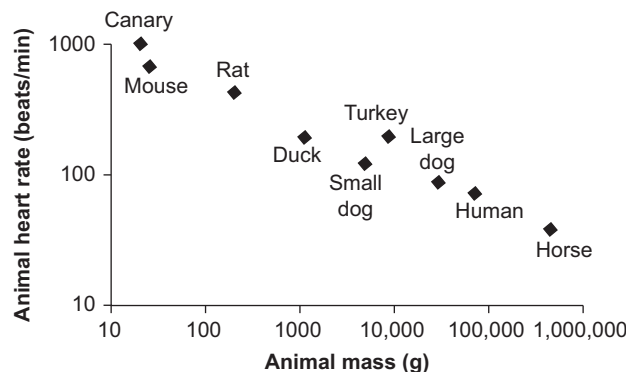


FIG. 5.11 The relationship between animal mass and heart rate. As the mass of the animal increases, there is a general decrease in heart rate. The relationship between these two measurements can be correlated to many different properties of the animal, as described in the text.

5.4 Heart motion

During cardiac myocyte contraction, the heart as a whole moves in three-dimensional (3D) space. This movement affects the blood flow within the heart and also the blood flow within the coronary blood vessels. Before discussing the motion of the heart, one must first understand how to model muscle contraction. In 1939, A.V. Hill modeled the active contraction of heart muscle using a three-component model (Fig. 5.12). The three components of this model are a parallel element, a contractile element, and a viscoelastic series element. The parallel element models the connective tissue that composes the heart and the resistance that this tissue provides toward motion. This component is typically modeled as a purely elastic material, and the empirical values that describe its responses to a load can be calculated from standard length–tension curves of explanted muscle. The empirical constants for this element will be variable based on the activity of the muscle, the age of the person, the type of muscle fibers, etc., and thus it is difficult to provide one value for these constants. The contractile element models the actin–myosin mechanism that actively causes muscle contraction. Note that the physiology of these mechanisms is discussed in Section 5.1 and that one must understand the kinetics of motion to use the Hill model. This contractile component of the system is modeled as a temporally active element that can generate tension and/or displacements. Known values for cross-bridge formation, including force generation and displacements, can depict this element. Again, it is somewhat difficult to provide empirical values for these constants because it depends on many different factors within the system. The series element models the viscoelasticity of the actin–myosin cross-bridges and the viscoelasticity of the system as a whole. The empirical values that describe this component of the system also can be quantified by stimulating muscle to contract and monitoring the relaxation of the system.

Since 1939, many experiments have been conducted to determine the empirical constants that can be used within this model. A full description of these experiments and the mathematical derivation of the ensuing formulas can be found in Y.C. Fung's biomechanics texts (see Further Readings for citation information). To summarize the salient results, the total force acting within the muscle (F) can be formulated as a summation of the parallel element force (P) and the contractile/series element force (S).

$$F = P + S \quad (5.1)$$

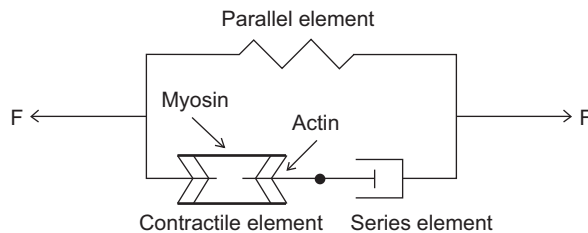


FIG. 5.12 A.V. Hill's model for heart muscle contraction, which couples the active contraction component (actin–myosin cross-bridge formation), a viscoelastic relaxation, and a parallel elastic resistance to motion. This is perhaps the most often used model of cardiac muscle contraction and has many forms of quantification.

P is a function of the length of the muscle fiber. It is proportional to the number of sarcomeres present and can be formulated as the length of one myosin fiber plus the length of two actin molecules minus the overlap of the myosin and actin proteins. Assuming that all sarcomeres have the same physical structure, the parallel element force (P) can then be multiplied by the fiber length (or number of sarcomeres). If the sarcomere is under a stressed state, there is an added constant to account for the viscoelastic extension (η); again, note that each of these variables may be a function of other physiological states such as age and overall health of the individual. S has been shown to be an exponential function that depends on the initial tension in the fiber and the extension of the fibers. The Hill model neglects the kinetics of the biochemical reactions that need to take place for actin and myosin to form cross-bridges between each other; however, as mentioned previously, these can be critical parameters that alter the force generated in muscle tissue. These (and other) necessary components of the heart model have been incorporated into theoretical models by others that represent the tension and length curves reasonably well. However, the Hill model provides a fairly good prediction of how cardiac tissue responds to forces.

A second form of the Hill equation relates the tension generated within a muscle under maximum tetanic contraction to the velocity of contraction and thermodynamic properties of the tissue. This equation has been shown to take the form of

$$F = \frac{\beta(F_0 + q)}{v + \beta} - q \quad (5.2)$$

where F is the force (as tension) generated within the muscle, F_0 is the maximum tetanic load generated within the muscle, v is the velocity of the contraction, q is the thermodynamic coefficient that relates to the heat lost during contraction, and β is defined as $\frac{qv_0}{F_0}$, where v_0 is the maximum velocity of contraction that occurs when F is equal to zero. One can observe that this equation would predict a rapid contraction velocity when the muscle is under low loads, whereas the velocity of contraction would be slower under higher load. This loss in velocity appears to be the result of both biochemical interactions during the contraction period (e.g., reduced tension generation when the sarcomere is shorter and an increase in the amount of intracellular fluid that must be moved to generate these motions).

Combining all of the observations from the Hill model, we can state that the force generated in the parallel element plus the force generated in the contractile element is equal to the total force generated in the muscle (e.g., Eq. (5.1)). Additionally, the force generated in the contractile element is equal to the force generated in the series element. As for the length of the muscle, the total muscle length is equal to the length of the parallel element, which is also equal to the length of the contractile element plus the series element. Clearly, more detailed and physiologically accurate mathematical representations of each of these components are needed to accurately model this relationship, but as stated earlier, the modeling of these elements depends on many factors that are not always constant with time and between people.

To understand heart motion, we will briefly discuss the solid mechanics associated with the heart. As learned in previous solid biomechanics courses, biological tissue is inhomogeneous, is viscoelastic, is subjected to a very complex loading condition, and has a complex 3D geometry. This makes its mechanical analysis relatively difficult. However, to first understand the loading conditions and how the elasticity can affect blood flow, let us first

consider the simplest case. If the left ventricle can be modeled as a homogenous isotropic spherical shell, the radial stress can be defined as

$$\sigma_r(r) = \frac{p_o b^3 (r^3 - a^3)}{r^3 (a^3 - b^3)} + \frac{p_i a^3 (b^3 - r^3)}{r^3 (a^3 - b^3)} \quad (5.3)$$

Recall that the radial stress acts “through” the muscle wall from some center point in the heart outward. The circumferential stress, which is greatest along the inner surface of the sphere, can be defined as

$$\sigma_\theta(r) = \frac{p_o b^3 (2r^3 + a^3)}{2r^3 (a^3 - b^3)} - \frac{p_i a^3 (2r^3 + b^3)}{2r^3 (a^3 - b^3)} \quad (5.4)$$

Recall that the circumferential stress acts along the circumference of the heart muscle wall at every location through the wall. Although we did not derive Eqs. (5.3) and (5.4), these come from standard mechanics of materials courses and are developed from a force balance across the particular direction of interest. The variables in Eqs. (5.3) and (5.4) are the inner radius of the sphere (a), the outer radius of the sphere (b), internal pressure (p_i), and external pressure (p_o) (In Fig. 5.13, circumferential stress is depicted to act into or out of the textbook page, but its direction will vary with position along the cylindrical shell). As the reader can see, Eq. (5.4) is maximized when r is equal to a (remember that b must be greater than a). Looking at these two formulas, one can imagine that these wall stresses would induce a stress on the fluid next to the ventricle wall. In fact, the internal pressure, acting on the inner heart wall, can be equal to the left ventricular hydrostatic pressure (which is also a function of time, see Section 5.3), but this is not necessarily accurate because of residual stresses within the cardiac muscle fibers. However, it is not as simple as equating only the hydrostatic and normal pressures. In fact, the systolic pressure is determined by the circumferential stress in the ventricular wall, which is caused by muscle contraction. As the sarcomere length increases, the maximal circumferential stress also increases, because with a longer sarcomere

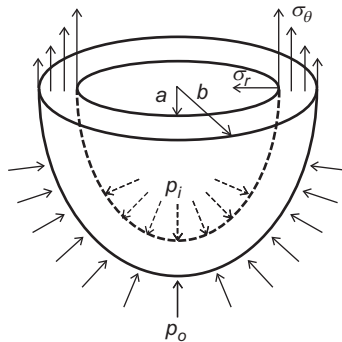


FIG. 5.13 Schematic of the radial and circumferential stress in the left ventricle. This assumes that the cardiac tissue is homogeneous in size (and a perfect cylindrical shell) and homogeneous in mechanical properties and that the pressure loading conditions are uniform. These formulations also neglect the blood flow through the ventricles. Note that we have tried to depict that the circumferential stresses act into and out of the paper, whereas the radial stresses act toward (or away from) the center of the sphere.

length, the sarcomere can perform more work (at least to a certain extent, which is limited by the finite size of the sarcomere). A higher circumferential stress must be balanced by the internal fluid pressure, so that an increase in sarcomere length also increases the left ventricular pressure waveform (the most critical component is the peak systolic pressure, i.e., 120 mmHg). Some have shown that the number of sarcomeres in the heart remain fairly constant with time independent of physiological conditions. Therefore, with an increase in the internal radius of the heart, the muscle tension and the blood pressure increase. This is seen in pathological conditions in which the heart enlarges but there is little increase in the number of cardiac myocytes, and thus contractile strength must balance the changes with little to no additional cells to distribute any additional work/force needed. As a reference note, the external pressure is equal to the pleural pressure, which is slightly lower than atmospheric pressure (−4 to −2 mmHg).

Example 5.1

Calculate the circumferential stress distribution in the left ventricle during peak systole (assuming that the ventricle is a homogenous spherical shell). The inner radius and outer radius of the sphere that represents the cardiac tissue are 3.5 and 4 cm, respectively. The external pressure is −3 mmHg.

Solution

$$\sigma_{\theta} = \frac{p_o b^3 (2r^3 + a^3)}{2r^3 (a^3 - b^3)} - \frac{p_i a^3 (2r^3 + b^3)}{2r^3 (a^3 - b^3)}$$

$$\sigma_{\theta} = \frac{(-3 \text{ mmHg})(4 \text{ cm})^3 (2r^3 + (3.5 \text{ cm})^3)}{2r^3 ((3.5 \text{ cm})^3 - (4 \text{ cm})^3)} - \frac{(120 \text{ mmHg})(3.5 \text{ cm})^3 (2r^3 + (4 \text{ cm})^3)}{2r^3 ((3.5 \text{ cm})^3 - (4 \text{ cm})^3)}$$

$$\sigma_{\theta} = 252.64 \text{ mmHg} + \frac{1.065 \text{ J}}{r^3}$$

When $r = a$

$$\sigma_{\theta} = 252.64 \text{ mmHg} + \frac{1.065 \text{ J}}{(3.5 \text{ cm})^3}$$

$$= 438.9 \text{ mmHg}$$

When $r = b$

$$\sigma_{\theta} = 252.64 \text{ mmHg} + \frac{1.065 \text{ J}}{(4 \text{ cm})^3} = 377.5 \text{ mmHg}$$

Under these conditions the stress distribution within the ventricular wall is described by

$$\sigma_{\theta} = 252.64 \text{ mmHg} + \frac{1.065 \text{ J}}{r^3}$$

with the limit that $3.5 \text{ cm} \leq r \leq 4 \text{ cm}$.

As Example 5.1 illustrates, this formulation predicts a differential workload carried out by the muscle cells that line the inner wall versus those that line the outer wall of the heart. In fact, it indicates that the cells along the endocardium (inner wall) would need to produce more work than the cells along the epicardium (outer wall), to meet the demands of increased loading. To satisfy this criterion, there should be an increased concentration of ATP, calcium, and blood supply to the inner wall, which has never been measured in a laboratory setting, although many have investigated this apparent contradiction. To account for this contradiction, it has been suggested that there is a residual stress and strain within cardiac muscles, even under an unloaded condition. These residual stresses and strains balance the uneven workload requirement that has been previously summarized and, therefore, the need for increased ATP, calcium, and blood. As this discussion and Example 5.1 show, these formulas are fairly limited in their accuracy because of the simplifying assumptions made about the homogeneous isotropic mechanical properties and the geometrical properties of the left ventricle.

To couple the solid mechanics of heart motion and the fluid mechanics of blood flow within the heart, the use of computation fluid dynamics would be required (see Chapter 15). Fluid structure interaction and multiscale modeling should be incorporated within these models to make the prediction as accurate as possible. There have been attempts to compute an analytic solution to heart motion and blood flow in the heart conditions, but they are generally overly simplified. For instance, most will use an idealized geometry for the heart (similar to the spherical shell described previously) combined with homogenous mechanical properties and incompressible inviscid fluid flow. Without going into much detail about these models here, the pressure and the fluid velocity in the ventricle can be solved by using the Bernoulli equation. From [Section 3.8](#), we learned that the Bernoulli equation can be applied only to very specialized flow situations and that the actual physiological scenario does not usually satisfy the assumptions necessary to apply the Bernoulli equation. Finally, these solutions typically show that the fluid is nonturbulent, which may not be the most accurate depiction for blood flowing into/out of the left ventricle, where short-duration turbulent-like properties may develop (recall that true turbulence will not be found in the cardiovascular system but one can approach turbulent-like flows). From fluid dynamics courses, recall that many accelerating viscous flows through a constriction will become turbulent at particular locations within the flow regime, but this developed turbulence is typically not self-sustaining and will rapidly dissipate. These locations are typically characterized by flow separation and recirculation zones. A more thorough analysis of these types of turbulent flows can be found in other classical fluid mechanics textbooks and textbooks that are focused on turbulent flow properties.

The goal of this discussion is to illustrate how solid mechanics and fluid mechanics can be coupled to determine the pressure forces that act on blood within the heart and that can even drive fluid flow through the heart and the cardiac vasculature. For a course at this level, to calculate a solution, many assumptions need to be made concerning the geometry, the mechanical properties, and the fluid properties. With these assumptions, a meaningful solution may still be reached (see the discussion of the Bernoulli equation, [Section 3.8](#)), but it is typically more accurate to minimize the assumptions made. As stated before, solutions that use this complex approach will be discussed in Chapter 15.

5.5 Heart valve function

As discussed in previous sections, the primary function of the heart valves is to prevent the backflow of blood during cardiac muscle contraction. The mechanism by which the valves accomplish this is fairly interesting, and this section will briefly discuss valve function and some of the mechanisms by which the valves accomplish these functions. We will discuss the mitral valve and the aortic valve, because this is where most of the research has been conducted. The function of the tricuspid valve mimics the mitral valve (except that it has a tri-leaflet structure versus the bileaflet structure of the mitral valve) and the function of the pulmonary valve mimics very closely the function of the aortic valve. In addition, recall that a major difference between the left side and the right side of the heart is that the pressure gradients across the valves are much greater on the left side of the heart than the right side of the heart. The anatomy of the mitral valve and the aortic valve is shown in [Fig. 5.14](#) and is discussed later.

Recall that the mitral valve regulates the blood flow between the left atrium and the left ventricle. The mitral valve consists of two thin membranes that are connected by tendons (the chordate tendineae) to the papillary muscles. The papillary muscles in turn are connected directly to the left ventricular muscle mass. The mitral valve remains open, allowing blood to

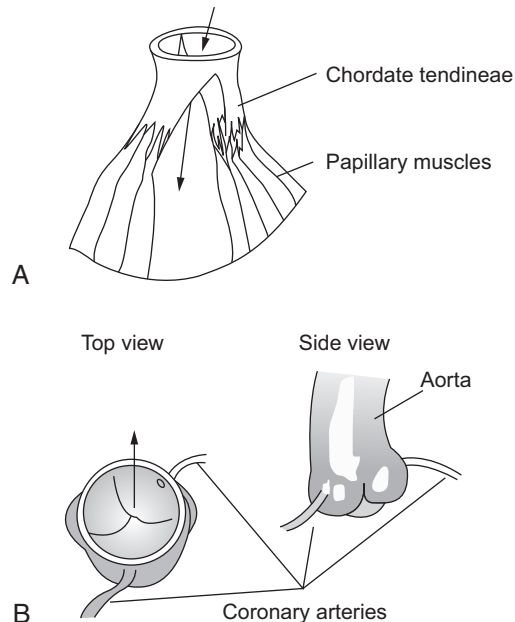


FIG. 5.14 The mitral valve (A) and the aortic valve (B) determine the blood flow characteristics and blood flow direction through the left side of the heart. The chordate tendineae and the papillary muscles do not open or close the mitral valve, but instead prevent the leaflets from bulging into the atria during ventricular contraction and prevent the leaflets from opening in the reverse direction. The coronary arteries branch from the aortic valve sinuses and feed the cardiac tissue with blood. As described in [Section 5.7](#), the flow through the coronary circulation opposes normal systemic blood flow (e.g., the majority of flow occurs during ventricular diastole).

flow directly into the left ventricle from the pulmonary circuit, for approximately 75% of the cardiac cycle (this is during ventricular diastole, Fig. 5.15). Because the valve has no active components, the observation that it remains open during the majority of the cardiac cycle suggests that the pressure is higher in the left atrium than the left ventricle during this portion of the cardiac cycle. Fig. 5.10 illustrates that in fact this observation is correct; the atrial pressure is greater than the ventricle pressure. For approximately two-thirds of this open time, blood flows passively through the mitral valve with a fairly steady and nonturbulent flow profile. This steady flow is due to a pressure gradient of positive 2 to 4 mmHg from the pulmonary venous circulation through the left atrium into the left ventricle (thus, the

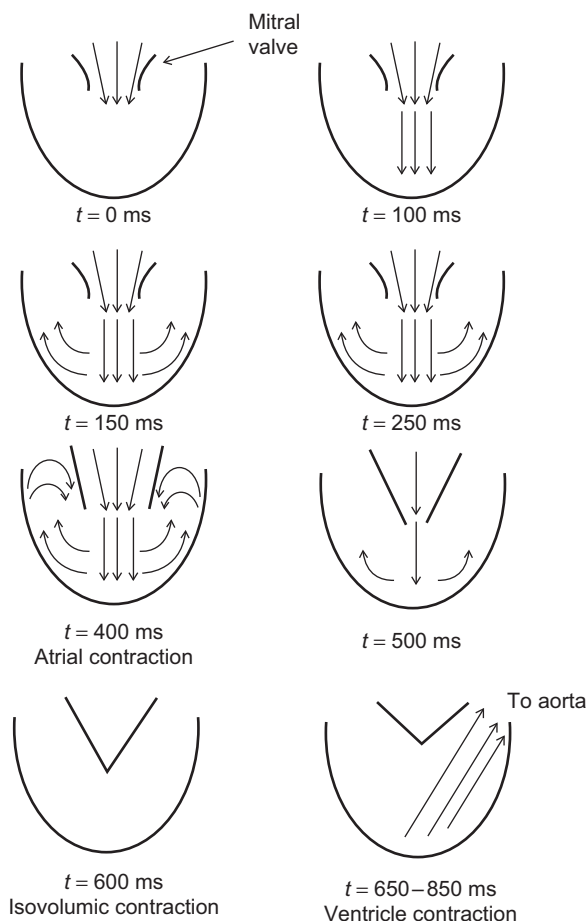


FIG. 5.15 Schematic of blood flow through the mitral valve during the cardiac cycle (the papillary muscles and chordate tendineae are not shown, so that we can illustrate blood motion). The times listed beneath each panel are approximate during the cardiac cycle but rather depict the relative change in blood flow characteristics with time. Note that the blood flow through the mitral valve is largely laminar, even though there is some mixing that may occur behind the valve leaflets.

pressure within the left ventricle is 2 to 4 mmHg below that of the pulmonary veins). Also, note that in Fig. 5.10 the majority of blood volume enters the left ventricle during this period, further illustrating that the valve remains open during this portion of the cardiac waveform. Once the atrium begins to contract (atrial systole), the flow through the valve becomes more jetlike and recirculation zones form behind the mitral valve leaflets within the left ventricle. Because of the cardiac muscle mass contraction we can observe a subtle change in the geometry and orientation of the mitral valve leaflets, causing more of a jetlike flow through a nozzle-like orifice. As the valves begin to close, the jet flow increases (there is a decrease in the valve opening cross-sectional area) and the turbulent flow zones that formed behind the valve leaflets deteriorate quickly because of the increased area behind the valve. The valves begin to close before ventricular contraction because of an increased blood volume in the ventricles themselves. This increase in fluid volume physically applies pressure on the mitral valve leaflets. Furthermore, this increased fluid pressure begins to reverse the pressure gradient across the mitral valve leaflets and induces an increased force on the valve area itself to promote closing of the valves. Note that all of these changes that occur during the end of atrial systole are predominately caused by the priming action of atrial muscle contraction, an overall increase in size of the left ventricle (further distention of the muscle mass), and a decrease in the driving force for fluid flow into the ventricle (reversal of pressure gradient). In addition, during valve closure a majority of the fluid flow becomes stagnant in the upper portion of the valve (atrial side), although there still is a small jet of blood entering the ventricle. Upon valve closure (approximately 50 ms before true left ventricular contraction), there is no flow observed between the atrium and the ventricle because the valves are sealed in the closed position.

As hinted at earlier, the pressure gradient across the valve is the driving force for mitral valve opening and closing. During ventricular diastole, the intraventricular pressure reduces to a value below the intraatrial pressure, which causes blood within the atrium to push against the mitral valve leaflets, inducing valve opening. The imbalance in the forces across the valve area leads to valve opening and closing. Additionally, blood entering from the venous circulation aids in increasing the local pressure of the atria. Once blood begins to enter the ventricle, the intraventricular pressure slowly rises, eventually surpassing the pressure within the atrium. This adverse pressure gradient slows the blood flow into the ventricles and helps close the mitral valve leaflets. An interesting occurrence during mitral valve function is that when the ventricles are in a relaxed state, the valve orifice is larger than when the ventricles are actively contracting. This aids in blood flow through the valve and aids the valve achieving a secure closed position.

The papillary muscles and the chordate tendineae do not function to open or close the valve; instead they prevent the reversing of the valve leaflet direction during ventricular systole (i.e., preventing the mitral valve from opening into the left atrium, when the left ventricular pressure far exceeds the left atrial pressure). The papillary muscles compose approximately 10% of the total cardiac mass, which suggests that they play an important role in heart functions. In fact, these muscles are also a structural extension of the valve leaflets and can assume some of the stresses and strains that the leaflets experience during the cardiac cycle. When both the mitral valve and the aortic valve are closed (isovolumic contraction and isovolumic relaxation), which is coupled to the initial stages of ventricular

contraction or relaxation, the papillary muscles have a small but regulatory role on intraventricular pressure. Recall that during this time, the majority of the intraventricular pressure is generated from the contraction of the cardiac muscle mass (during isovolumic contraction) or is relieved by the relaxation of the muscle cells (during isovolumic relaxation). However, the tension generated by the papillary muscles can change the radius of curvature of the mitral valve leaflets, which may change the surface area of the ventricular wall. These changes and tensions are directly related to the pressures that are exerted on the internal and external surfaces of the leaflet (the internal surfaces are those that face into the ventricles, whereas the external surfaces are those that face into the atrium). Therefore, by changing the tension in the papillary muscles, the pressure within the ventricle and the atrium must be changed to balance the forces. The relationship that governs the pressure–tension relationship of the mitral valve leaflets is

$$(p_i - p_e) = \frac{T_1}{r_1^2} + \frac{T_2}{r_2^2} \quad (5.5)$$

where p is the pressure experienced on the leaflet surface acting on the internal surface (i) or the external surface (e) of the valve leaflet, T is the principal membrane stress, and r is the radius of curvature, acting in the principal directions (1 and 2), assuming uniform mechanical and geometrical properties of the tissue and that the leaflets are relatively thin. Eq. (5.5) is derived from the Law of Laplace, which relates the pressure gradient across a thin-walled chamber, suggesting that as the radius of the chamber increases, more tension is required in the wall to maintain the original shape of the vessel and can be represented as

$$p = T \left(\frac{1}{r_1} + \frac{1}{r_2} \right)$$

where p is the transmural pressure acting on the surface, T is the surface tension acting on the surface, and r_1 and r_2 are the principal radii of curvature, assuming that the surface tension is constant in all directions. However, in the case that the membrane tension is not the same in all directions, Eq. (5.5) is used, assuming that the principal membrane stress directions coincide with the principal radii of curvature. For this example, the membrane must be thin, so that bending stresses can be ignored and it assumes that there is one uniform internal pressure (p_i) and one uniform external pressure (p_e). Note that these equations are not valid for thick-walled surfaces, in which the stress distribution through the wall can vary significantly and alter the pressure in the chambers. The papillary muscles contract at the same time as the ventricular muscle mass, because they are contiguous with the muscle mass. The action potential signal passes directly to the papillary muscle from the same Purkinje fiber system that induces ventricular muscle mass contraction.

Example 5.2

Calculate the principal stress needed in direction 1 of the mitral valve leaflet to maintain the valve in the closed state immediately after valve closure. Assume that at valve closure there is a pressure difference of 1.5 mm Hg between the ventricle and the atrium. The atrial pressure is 3 mmHg, and the principal radii of curvature for the two directions of the leaflet surface are 1 cm and 1.2 cm, respectively. Assume that the mitral valve leaflet is one-third of a spherical shell with a uniform width and thickness of 2 mm. Use Eq. (5.5) to estimate the tension on the leaflets, but note that as the thickness of the tissue increases, it may be more appropriate to use Eq. (5.4).

Solution

To calculate the unknown principal tension on the leaflet we first need to calculate the exposed area of the leaflet. With the assumption that the leaflet is a spherical shell, the area of interest is

$$L = 2\pi * 1.2 \text{ cm} * \left(\frac{120^\circ}{360^\circ}\right) = 2.51 \text{ cm}$$

$$A = 2.51 \text{ cm} * 2 \text{ mm} = 50.2 \text{ mm}^2$$

where L is the arc length of the exterior portion of the leaflet. From our previous discussion, we will make the assumption that the pressure in the atrium will be equal on all surfaces, including the leaflet. Therefore, the tension that the leaflet must have to maintain its shape is

$$T_2 = 3 \text{ mmHg} * 50.2 \text{ mm}^2 = 20 \text{ mN}$$

The tension in the unknown direction can be calculated from

$$p_i - p_e = \frac{T_1}{r_1^2} + \frac{T_2}{r_2^2}$$

$$T_1 = r_1^2 \left(p_i - p_e - \frac{T_2}{r_2^2} \right) = (1 \text{ cm})^2 \left(1.5 \text{ mmHg} - \frac{20 \text{ mN}}{(1.2 \text{ cm})^2} \right) = 6 \text{ mN}$$

The aortic valve consists of three thin leaflets, each in a crescent shape. Immediately distal to the three leaflets is an enlargement of the aorta (which is normally around 27 mm in diameter in an adult human immediately downstream of the aortic valve) termed the *sinuses of Valsalva*. The aortic sinus plays an important role in valve closure, which will be discussed later. The aortic valve remains closed until the pressure within the left ventricle exceeds the pressure in the aorta (under normal conditions this is approximately 80 mmHg). Upon valve opening, the blood flow is split into two separate streams (Fig. 5.16). The first stream comprises the majority of the blood and directly enters the ascending aorta as a pseudo jet to enter the systemic circulation. The second portion of the blood flow is directed into the valve sinus behind the valve leaflets. This second portion of blood flows in a slow vortex behind the valve leaflets and eventually rejoins the majority of blood in the ascending aorta. This happens only upon valve closure. Immediately after peak systole, the ventricular

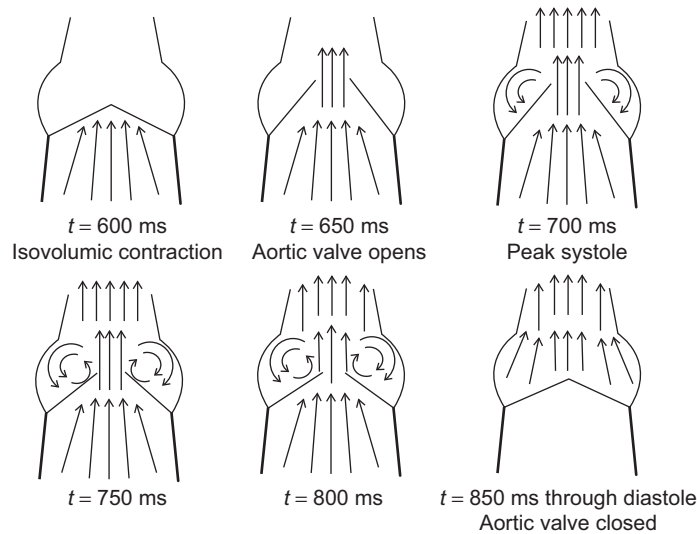


FIG. 5.16 Schematic of blood flow through the aortic valve during the cardiac cycle (the times overlap and continue from Fig. 5.15). Again, the times are relative, but give a general idea of blood flow through the aortic valve. Again, the flow may approach turbulence through the aortic valve, but this turbulent flow is not self-sustaining and would dissipate instantaneously.

muscles begin to relax and the intraventricular pressure begins to reduce from a maximum value of approximately 115 mmHg (in healthy adults). However, because of the viscoelastic mechanical properties of the aorta, the pressure in the aorta does not fall as rapidly but continues to increase for a few milliseconds (reaching approximately 120 mmHg under normal conditions for adults). This causes a backward flow pressure gradient; the pressure is higher at the tip of the aortic valve leaflet and is lower at the valve orifice. During the backward pressure gradient, the aortic valve would tend to want to open more fully. However, the blood that was already in the valve sinus prevents the tips of the aortic valve leaflets from opening more fully in response to the reverse pressure gradient. The reverse pressure gradient also causes more blood to flow into the aortic valve sinus, which further aids in forcing the valve leaflets into the secure closed position. During the closing period, blood passes into the sinus at a higher rate than into the ventricle, because the effective open area of the sinus is greater than the orifice. Furthermore, as more blood enters the sinus, the open area of the valve orifice further decreases until the valve is fully closed. Once the valve is completely closed, the blood in the sinus enters the aortic mainstream flow and is delivered to the body because of the elastic recoil properties discussed. The aortic valve is open for approximately 25% of the cardiac cycle.

The Gorlin equation provides us with an approximation to the aortic valve opening area, as a function of the cardiac output, the heart rate, the hydrostatic pressure, and the ejection period. The cardiac output, the heart rate, and the ejection period will approximate the flow across the valve leaflet during ejection, whereas the pressure gradient provides a measure of the driving force for flow across the valve. This formulation takes the form of

$$\text{Valve area} = \frac{\text{Cardiac output}}{44.3(\text{Heart rate})(\text{Systolic ejection Period})(\sqrt{\text{Mean pressure gradient}})} \quad (5.6)$$

If the cardiac output is measured in milliliters per minute, the heart rate is measured in beats per minute, the ejection period is measured in seconds, and the mean pressure gradient is measured in mmHg, the valve area will be in units of square centimeters. The constant of 44.3 holds only if the discussed units for the other variables are used; note that this constant of proportionality was empirically derived. Typically, the ejection period is in the range of 0.33 second, and the mean pressure gradient is 50 mmHg, but both of these values can change drastically in pathological conditions.

We would like to remind the reader that the function of the valves on the right side of the heart are nearly identical to those in the discussion of the valves on the left side of the heart. There are subtle differences, but because valve diseases tend to form preferentially on the left side of the heart (compared with the valves on the right side), more research and a stronger understanding of the motion of the left side valves is currently held by the scientific community. The pressure gradient across the right side valves is very similar to that of the left side valves; however, the numerical values of pressure on the right side are considerably lower than those on the left side of the heart.

5.6 Heart valve dynamics*

We have previously discussed the basic anatomy and physiology of the four cardiac valves. It is important to remember that although each of these valves operates passively, the motion of the heart valves, the forces/stresses throughout the heart valve leaflets, and the fluid flow through the valves are highly dynamic. As a simple example, the reader can imagine the difference in the motion of the valves during strenuous activities compared with normal resting activities. Descriptions and numerical values for these differences are still under investigation, but there is some information pertinent to our discussion that will be highlighted later.

Anatomically, the AV valves are very thin compared with the much heavier and thicker semilunar valves. Because of these anatomical differences, the AV valves have little inertia compared with the semilunar valves. The significant inertial differences can be observed during valve opening and closing. The AV valves require very small changes in the trans-valvular pressure gradient to open or close; this is more pertinent during closing, in which very little blood back-flowing into the atria initiate the closing of the AV valves. In contrast, the semilunar valves require much more significant and rapid blood backflow to generate enough force to cause closing. Again, this would be measured as a change in the pressure gradient. In practice, this occurs during a relatively short time frame (approximately 3 to 5 ms) because of the rapid decline in intraventricular pressure and relatively constant pressure in the blood vessels.

*This section is considered advanced and can be skipped without a loss of continuity.

These changes can also be observed in the rate of closure of the valves. The AV valves have a much slower and softer closing, whereas the semilunar valves snap shut quickly and can be heard through the use of a stethoscope. Similar changes are observed during opening and are directly related to the pressure waveform changes and the changing direction of the trans-valvular pressure gradients. Recall that the difference in pressure between the atria and ventricle during valve opening and closing (e.g., during ventricular filling) tend to be relatively small (on the order of a few millimeters of mercury) and the nominal values in pressure are relatively low. In contrast, the rapid increase in ventricular pressure during ventricle ejection, the relatively large pressure difference between the blood vessels and the ventricle and the overall larger nominal value in pressure would all suggest a rapid opening and closing of the semilunar valves.

In the open valve configuration, the area available for ejection is much smaller in the semilunar valves compared with the AV valves. As we know from the continuity equations, this will help increase the ejection velocity if the remaining fluid parameters stay constant; however, this does not describe the physiological case in which the pressure difference also increases in parallel with a significant drop in open area. One major pathological condition associated with these changes is that the edges of the semilunar valves are much more susceptible to mechanical abrasion than the edges of the AV valves. The constant exposure to rapidly changing and significant magnitude pressure gradients have been observed to cause more significant damage to the leaflet structure more quickly than the slower changes and smaller magnitude experienced by the AV valve leaflets.

One of the mechanisms that heart valves use to allow for repeated opening and closing (approximately 40 million times per year) and to withstand the dynamic forces (fluid shear forces and solid stretching forces) is to have a functional and structurally organized extracellular matrix. All four valves have similarly structured extracellular matrices, so at this point we will discuss important common features that are generally shared among the valves and not differentiate among the different types of valves. The surface on the upstream side of the valve (e.g., the surface that faces the ventricles for the semilunar valves and the surface that faces the atria for the AV valves) is rich in elastin. The opposing surface on the downstream side of the valve is composed primarily of a dense collagenous layer. These two opposing surfaces sandwich a core composed of loose connective tissue. The strength of the valve comes primarily from the dense collagenous layer, whereas the flexibility comes primarily from the elastin layer. We would like to point out some of our initial discussion on quantifying valve properties assuming that the tissue was homogeneous in mechanical properties. It should be apparent from this brief discussion of extracellular matrix composition that the valves are not uniformly homogenous across their thickness and in some instances may require the use of thick-walled assumptions.

As the major stress-bearing component, collagen fiber orientation is critical to valve opening and closing dynamics. There has been significant work illustrating the changes in collagen orientation during these translational events in which the majority of the collagen is reorganized when exposed to lower reverse-pressure gradients. In fact, in the closed position, the pattern of collagen organization allows for some shifting of the stresses into the heart wall. The complexity of these patterns are that in the radial direction, the valves experience more significant stretching and compliance compared with the circumferential direction (note that the elastin tends to align radially and the collagen circumferentially). In addition

to this, there are significant differences in composition based on the position within the valve. The region of the valves closest to the heart wall (cuspal belly region) is stiffer than the commissural region (where the valves abut each other). These compositional differences are required for normal valve function, and in fact the cellular matter within the valve is affected by the compositional changes and partially dictate those changes.

Furthermore, these compositional differences lead to important mechanical changes that relate to the dynamics of the semilunar valve motion. The valve leaflets have been found to be anisotropic and inhomogeneous because of the anatomical differences described. Additionally, the leaflets are viscoelastic and thus have time-dependent responses associated with their mechanical properties. There has been some work on the loading behavior, and although there is an anisotropic force distribution throughout the leaflets, it has been shown that the responses are independent of the loading rate. Thus, the motion and mechanical force distribution throughout the valve leaflets are quite complex to observe, quantify, and model.

The opening and closing dynamics of the aortic valves is conventionally described in three phases; the rapid opening phase, the slow closing phase, and the rapid closing phase. During the rapid opening phase the valve leaflets move with an average velocity of at least 20 cm/s over a period of approximately 60 ms. Immediately after the opening phase, the valve leaflets enter the slow closing phase, which is the phase that is associated with the bulk ejection of blood from the left ventricle. This phase lasts for 300 to 350 ms, and the valve leaflets move on the order of 10 mm. The valve leaflets fluctuate with motion of the blood through the valve opening but have an overall net closing motion as a result of blood entering the sinuses. These events are followed by the rapid closing phase, in which the valve leaflets move with an average velocity of 25 cm/s over a time interval of approximately 30 to 40 ms. These motions also have been shown to be coupled to a significant amount of mechanical stretch, although the valves are naturally stretched, even during diastole. It has been estimated that the valves are stretched by about 20% in the circumferential direction and about 50% in the radial direction during diastole. During systole the valve leaflets stretch even further in the radial direction and experience a small decrease in stretch in the circumferential direction (because of the Poisson ratio for deformable materials).

The mitral and tricuspid valves experience similar dynamic changes during their opening and closing. These changes have also been linked to the compositional changes within the valve leaflets that lead to anisotropic behavior during the motion and through the response to differential mechanical loading conditions. The AV valves experience different stress-strain relationships in the circumferential and radial directions, which has all been shown to be somewhat independent of the loading rate. The mechanical properties of the AV valves have been shown to be more complicated than the semilunar valves because of the presence of the chordate tendineae and papillary muscles, which can act to localize additional and/or concentration stresses throughout the valve leaflet area. The mechanical stress within the chordate tendineae are proportional to the ventricular pressure waveforms for the majority of the cardiac cycle but are a function of the cross-sectional area of the chordate tendineae.

Most work on AV valve dynamics have focused on the closing of these valves, because for a majority of the cardiac cycle, the valves remain in the open configuration. As a reminder, this is to allow for ventricular filling; although some of the characteristic filling fluid vortices are required for normal valve closing (as discussed in the previous section). Since the AV valves are located in close proximity to the ventricular muscle mass, contraction of the

ventricles causes a significant change in the valve area. This may help with a tighter closing in the valve; however, all of these motions are coupled to the papillary muscle contraction and activity. In fact, a significant balance among ventricular contraction, AV valve geometry and composition, and papillary muscle activity is required for normal valve function. An upset of this balance can and does lead to various valvular diseases.

5.7 Disease conditions

In most of the following chapters, the authors have chosen to include a section for disease conditions that are associated with some of the topics that we have discussed in that particular chapter. We want to preface this particular disease condition section by stating that most of the diseases of the cardiovascular system are related to each other and in some instances new links between particular diseases are still emerging. With that said, the authors had to make a decision on which chapter should include the discussion. This was not an easy decision because of the overlap between many of the cardiovascular conditions, which have wide-ranging effects at multiple locations throughout the cardiovascular system. As an example, one of the major causes of coronary artery disease is atherosclerosis, but atherosclerosis is a disease that can affect the entire vascular system. One of the major downstream effects of coronary artery disease is myocardial infarction. Altered platelet activity and inflammatory responses are observed during coronary artery disease. Because of these overlapping effects, it was not easy to choose where to include the particular discussion for these three highlighted diseases. In this instance our choice was to include coronary artery disease and myocardial infarction in this disease condition section and we leave the extensive discussion of the more general atherosclerosis for Chapter 6. Again, we hope that this does not suggest that particular diseases are restricted to particular components of the vascular system but that they can and do interact with multiple sections.

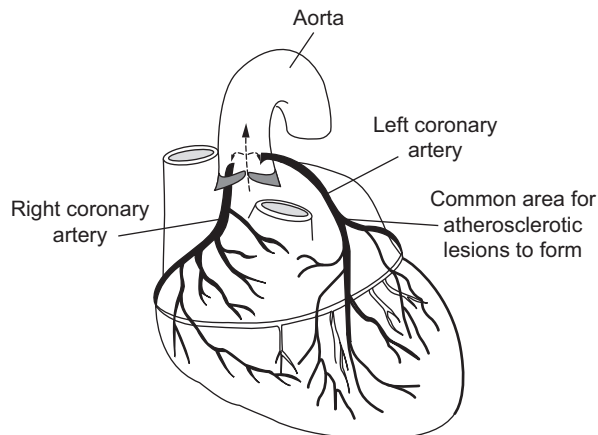


FIG. 5.17 The coronary arteries that supply the entire cardiac muscle with blood. These vessels are principal locations for atherosclerotic lesions and other cardiac diseases. Depending on the severity of the damage to these vessels, blood flow to the cardiac muscle cells can be severely impaired.

5.7.1 Coronary artery disease

The coronary arteries supply the cardiac muscle mass with blood ([Fig. 5.17](#)). The left main coronary artery and the right main coronary artery branch off from the ascending aorta approximately 0.5 to 1 cm downstream of the aortic valve. The left coronary artery is responsible for providing the left ventricular muscle mass with blood (along with sections of the right ventricle and the left atrium). In total, the left coronary artery delivers blood to approximately 75% of the cardiac tissue. The remaining portions of the cardiac muscle are supplied with blood from the right coronary artery. The coronary blood vessels branch into smaller vessels that penetrate the muscle mass to supply blood to the entire heart. Because the heart does not stop contracting, it requires about 5% of the total cardiac output, which amounts to approximately 250 mL/min, to maintain its function. The majority of the venous coronary blood flow is returned directly to the right side of the heart by the coronary sinus. In addition, a small portion of deoxygenated blood is returned to all chambers of the heart by the thebesian veins. The thebesian veins are similar to open-ended blood vessels that penetrate the cardiac mass and open into all four heart chambers.

The flow within the coronary blood vessels is quite interesting, because the majority of the blood flow occurs during ventricular diastole and the flow almost ceases during systole. This is the reverse of what happens in most other vascular beds. The reason for this reversed flow (compared with the majority of locations in the systemic circulation) is that during ventricular systole the cardiac muscle contracts, causing compression of the coronary blood vessels. This compression is so severe that the resistance to blood flow through these vessels increases significantly and the blood flow pressure gradient is not large enough to overcome the resistance to flow because of compression of the cardiac muscle mass. During diastole, the cardiac muscle relaxes and relieves the constriction of the coronary blood vessels. Therefore, the resistance to blood flow reduces and blood can begin to actually flow through the coronary circulation. This is especially prevalent in the blood vessels that supply the left ventricular muscle mass compared with the right ventricular muscle mass, because the muscle contraction is much stronger within the left ventricle compared with the right ventricle.

Coronary artery disease remains the leading cause of death in the Western world. Coronary artery disease lumps together pathological conditions that lead to a reduction in coronary blood flow, which can eventually lead to myocardial infarction (see [Section 5.7.2](#)). In the United States, one of the most common causes of coronary artery disease is atherosclerosis. Atherosclerosis can be initiated by genetic factors or lifestyle choices (such as eating foods high in cholesterol), and these risk factors tend to be a combination of both modifiable and nonmodifiable components. Modifiable components are those that, at least theoretically, one can make a choice to be exposed to, for instance, primary exposure to tobacco smoke. Nonmodifiable are those risk factors that patients have little to no control over, for instance, genetic predisposition toward a disease or some environmental factors. Regardless, of the factors the patient is exposed to, atherosclerosis initiates through the deposition of large quantities of cholesterol within the subendothelial space. When significant cholesterol deposits within the subendothelial space, there is a bulging of blood vessel material into the luminal space of the blood vessels. Interestingly, cholesterol deposits can be found throughout the body, but many vascular beds can adapt to the altered and somewhat reduced blood flow (at least to a certain point; this is due to safety factors that are

intrinsic within the vascular system). Because of the fact that the coronary arteries are not as adaptable as other vascular beds and that the heart requires a large quantity of blood at all times, any cholesterol deposition within the coronary blood vessels can have potential major problems for the patient. This becomes even more prevalent under conditions of physical (exercise, extreme cold temperature) or emotional stress.

After cholesterol deposition occurs, there are a few processes that proceed in parallel. The first process that can happen is for cholesterol molecules to coalesce, forming larger deposits. As this occurs, macrophages can invade the subendothelial space to ingest the cholesterol deposits. Macrophages that ingest a large quantity of cholesterol transform into foam cells. These cells are full of fat/cholesterol and have negligible function in the subendothelial space. In addition to the lack of function, foam cells are large and are unable to migrate out of the subendothelial space. Along with these two processes, fibrous tissue and smooth muscle cells (that both naturally surround the blood vessels) begin to proliferate and sometimes can become calcified. This occurs in response to the increased macrophage population in the subendothelial space. The net result of these three processes (cholesterol coalescence, foam cell production, and vascular cell proliferation) is that a plaque forms that extends into the blood vessel lumen. A blockage of the vessel lumen (partial or complete) decreases blood flow through that vessel, because the blockage itself increases the resistance to flow through that section of the vascular system. To maintain the same flow through the vessel, the blood pressure may increase, which has its own pathological effects and will be discussed in [Section 6.14.1](#). If the blood vessel becomes calcified, it becomes less pliant, hence more brittle, and if this change is severe enough, the vessel potentially cannot withstand the normal-pressure forces exerted by the fluid. This can lead to the vessel bursting and is especially concerning when the blood pressure increases.

One of the first clinical manifestations of coronary artery disease is *angina pectoris*, which is a term that refers to chest pain resulting from oxygen deficiency in a region(s) of the heart. Oxygen deficiencies occur when oxygen demand surpasses oxygen supply for an extended period or when there is an overall decrease in the oxygen delivery. Angina is most commonly associated with coronary artery diseases and atherosclerosis of the coronary arteries, but other pathological conditions of the heart have been shown to induce angina. Cardiomyocyte oxygen demand can increase if the myocardial tension increases (this is a function of blood pressure), the heart rate increases, or the contractility of the heart increases.

One of the most common ways to detect the presence of coronary atherosclerosis is through the use of arteriography. Arteriography is conducted by injecting a radiopaque contrasting agent into the blood. This is followed by imaging techniques, typically x-ray fluoroscopy, to allow for the visualization of the inside diameter of the contrasted blood vessels. Using this technique, physicians can classify the extent of plaque formation and make a determination of whether an intervention surgery is needed. For the most part, physicians will not recommend an intervention if the luminal diameter is constricted to 70% or less of the normal diameter. Reports have shown that a constriction of 50%, which is defined as an important luminal diameter constriction, can alter the coronary blood flow under exertion, but the resting coronary blood flow is not altered. This is direct evidence that the vascular system has developed/evolved with a significant safety factor allowing for reductions in

blood flow. A luminal diameter reduction of 70% or more is defined as a significant luminal diameter constriction and can alter both the coronary blood flow under exertion and the resting conditions. Most physicians will recommend intervention surgery under these significantly reduced blood flow conditions (e.g., angioplasty or grafting), unless other clinical parameters would interfere with the disease or treatment plan.

Atherosclerosis development is very common in the first few centimeters of the coronary arteries. This is most likely caused by the 3D structure of the coronary arteries (see [Fig. 5.17](#)). Immediately downstream of the branches with the aorta, there is a high degree of tortuosity (twists/bends) and tapering within the coronary vessels. Since the blood flow in these vessels is very fast, these rapid geometrical changes induce localized regions of turbulence with the blood vessel. Regions of turbulence can be characterized by flow separation, stagnation points, and recirculation zones, in which the flow rate is reduced, allowing cholesterol enough time to migrate into the subendothelial space. Recall from our earlier discussions that this is not true turbulence, even though some localized mixing may be observed. The turbulence-like flows observed in these regions are not self-sustaining and dissipate very quickly.

Reduced blood flow throughout the coronary vessels is devastating to the muscle mass of the heart (see [Section 5.7.2](#)). However, if the blockage is not severe enough or if it progresses slowly enough, the coronary arterioles can protect the heart tissue for some time, through an innate protection mechanism. At the time of an upstream blockage, the dilation of the downstream coronary arterioles can counterbalance the flow restriction for approximately 24 to 48 hours. With an increasing diameter, the blood flow will slow in these vessels, more blood will be present in these vessels, and the overall resident time for blood in these vessels increases. This allows for an increased time for exchange and for the majority of the cardiac muscle mass to survive because the cardiac tissue will still obtain enough oxygen. For a long-term solution, the coronary collateral circulation will adapt to supply the undernourished tissue with blood. The collateral circulation of the coronary vessels is a unique feature of this vascular bed that allows for a large redundancy of flow to one particular region of cardiac muscle. This suggests that at a minimum two large arterioles supply the same capillary bed with blood. If one of these arterioles is blocked, the second arteriole (and potentially others in the vicinity) will remodel so that the blood flow to that region returns to approximately 100% of the normal value. In most cases, atherosclerotic lesions progress slow enough to allow for a dilation of downstream arterioles and a remodeling of collateral vessels to occur. These two processes potentially allow a patient with a coronary lesion to survive for years after the onset of the disease. It is even possible that patients do not realize or notice a difference in their activity level because of these safety mechanisms.

Some of the interesting phenomena regarding the coronary collateral circulation is the recruitment of these vessels during a time of need. In the most simplistic relationship, the flow through a vessel is a function of the pressure gradient and the resistance within that vessel. Under most cases, the resistance to flow is so large in the collateral circulation that the vast majority of flow proceeds through the normal coronary circulation. However, as atherosclerotic lesions begin to develop, the resistance to flow shifts between the normal coronary circulation and the collateral circulation, allowing for an overall shifting of blood to where more blood is needed. Emerging evidence suggests that as new shear forces are

applied to the coronary collateral vessels (as the resistance to flow shifts) mechanisms that initiate and are responsible for the remodeling processes that occur under pathological conditions are instigated.

5.7.2 Myocardial infarction

One of the immediate effects of a blocked coronary artery is decreased blood flow into the region downstream of the blockage. If the muscle that is being supplied by the blocked vessel can no longer maintain normal cardiac contractions, this region will become infarcted. Clinically, this is typically defined as irreversible cellular injury that leads to necrosis (cell death) as a consequence of prolonged ischemia (reduced oxygen). Without a blood supply for 1 to 2 hours, cardiac muscle cells begin to die. As stated earlier, blood flow can return to the infarcted area through changes to the collateral circulation, but the response time for the collateral circulation to return blood flow to normal levels may not be fast enough under extreme conditions. However, because significant tissue damage may have been done, blood has little purpose there because the damaged cells cannot contract as strongly as before, if they can contract at all, and thus the oxygen demand of these cells may not be as large as previously. Blood that enters an infarcted region stagnates because the major vessels have been closed off from circulation through a separate remodeling process that we have not discussed. The presence of this stagnated blood in the infarcted area alters the contractile and mechanical properties of the heart. In extreme cases, the endothelial cells become very permeable and leak blood into the heart wall.

There are two major mechanisms by which myocardial infarction occurs; the first is a prolonged increase in myocardial oxygen demand with a significant decrease in coronary artery flow (which is common during coronary artery atherosclerotic lesion formation and was discussed earlier) and the second is a decrease in the oxygen delivery to the myocardium. The second cause of myocardial infarction is typically found in patients with hypotension (low blood pressure that cannot overcome the resistance to flow) or spasms of the coronary artery (which can alter the fluid dynamics through the coronary circulation). These issues can be identified in patients with an ECG, in which it is common to observe a significant Q wave (greater than 0.04 second in duration), a reduced amplitude of the R wave (e.g., by 30% or more) or a more prominently peaked T wave. A second, slightly more specific manner in which the occurrence of myocardial infarction can be diagnosed is through the presence of myocardial-specific creatine phosphokinase (MB-CPK). The increase in MB-CPK peaks at approximately 10 hours after an acute myocardial infarction event and can be observed within approximately 1 hour after the myocardial event. However, a downside of MB-CPK as a marker is that the concentration of MB-CPK returns to normal levels approximately 24 hours after the initial coronary event.

With a minor block in the coronary vessels, it is unlikely that cardiac tissue will become infarcted. Cardiac tissue is supplied with approximately four times as much blood as it needs to survive. Thus, even with a blockage that reduces blood flow by half, it is unlikely that muscle tissue will die immediately through a lack of oxygen supply. The lack of oxygen becomes a significant problem when the collateral circulation does not return the flow to normal levels after a vessel becomes blocked. However, if the blockage is severe enough or the collateral

circulation does not supply the newly infarcted region with enough blood, the muscle tissue will begin to die.

Once a large region of the heart becomes infarcted, there are four likely outcomes that can each independently lead to death. The first two outcomes are consequences of the heart not pumping enough blood to the systemic circulation. As stated earlier, an infarcted region of the heart does not contract as strongly as is necessary. If the region of the heart that is infarcted is large, it is possible that the total cardiac output reduces. A lower cardiac output can and does affect many locations throughout the body, including the coronary and/or cerebral circulation. A decreased blood supply to any organ will change its function and potentially lead to death. In addition, when the ventricular muscle mass is not moving enough blood through the vascular system, the blood must collect somewhere. Because the total blood volume does not change and the arterial system is not highly compliant, the excess blood is typically held within the veins and/or the pulmonary circulation and may even back up into the heart. When the blood volume in the venous and pulmonary circulation systems increases significantly, the overall pressure of the cardiovascular system increases (see [Section 6.14.1](#)). This becomes especially detrimental when the capillary pressure increases and blood and nutrients within blood cannot be delivered to the body tissues. If the heart begins to “store” some blood, the cardiac output severely reduces, lowering the overall efficiency of the vascular system.

The remaining two outcomes are problems associated with the heart as a result of the lack of nutrients being supplied to the infarcted region. A common cause of death associated with myocardial infarction is ventricular fibrillation. With zero or negligible quantities of blood supplied to the cardiac tissue, there is a rapid reduction of potassium ions from the muscle cells. Without potassium ions, a cell cannot become repolarized after an action potential has occurred. This leads to a basic breakdown in the membrane potential because the ionic concentration gradients are incorrect, causing the cells to not function properly. Furthermore, a lack of potassium would likely increase the membrane potential and either bring the membrane potential closer to an action potential threshold level (for excitable cells) or even surpass the action potential threshold level. Therefore, the cells would contract in an irregular and constant manner, which is termed and observed as a *fibrillation of the tissue*. The last major possible occurrence is rupture of the cardiac tissue. An infarcted region by definition is composed of dead muscle cells. A few days after the infarction occurs, the tissue will begin to degenerate and thin. If the majority of the heart remains to function at its optimal capacity, it is likely that the thinned region will become unable to withstand the pressure generated by cardiac contraction. At the onset of this process, the infarcted region begins to bulge outward, and, eventually, if not corrected, the infarcted region can burst. Blood would then pool in the pericardial space and begin to compress other regions of the heart. In a short time, the weaker atria will collapse and little to no blood will enter into the ventricles or be pumped out by the ventricles. The patient would eventually die of a reduction in cardiac output if uncorrected.

5.7.3 Heart valve diseases

As discussed previously, the heart valves regulate the flow of blood through the heart and prevent the backflow of blood into the various heart chambers. A disease of the heart valves

obstructs these functions. There are two common ways for a disease of the heart valves to develop. The first is associated with rheumatic fever, and the second is associated with an increased calcium concentration in the body. Rheumatic fever is a disease in which a bacterium enters the body and produces a variety of proteins. These proteins are similar to some of the innate proteins within the body, and, therefore, antibodies produced by the host's immune system attack the bacterial proteins and some innate and important proteins. The heart valve leaflets are likely to be attacked by these antibodies, causing severe damage to their structure. Normally, the mitral valve leaflets and the aortic valve leaflets are the first to be attacked because they are exposed to more flow, faster flow, and larger mechanical disturbances during normal functioning (because of the higher pressure forces acting on these valves). If the disease progresses far enough, it is common to see lesions within the tricuspid and the pulmonary valves.

There are two stages of valve leaflet destruction that can occur during rheumatic fever. During the early stages of the disease, the leaflets of adjacent valves can become stuck together as a result of the protein destruction and remodeling. In this case the leaflets can typically close fully, but they cannot open fully, causing a stenosed valve. During these conditions, blood is not ejected as efficiently through a stenosed valve as through a normal valve. Clearly, if the valve is stenosed enough, not enough blood will enter the ventricles and/or the systemic or pulmonary circulation, which can have serious repercussions for oxygen transport and cardiac output. During later stages of rheumatic fever, scar tissue can form along valve leaflets because of the extensive destruction of their protein structure. As the reader knows, scar tissue is mechanically stiffer than the very pliant valve leaflets. This prevents the valve leaflets from opening and closing fully. A valve that does not close properly causes backflow of blood into the atria and/or the ventricles. A valve experiencing backflow is said to be experiencing regurgitation. Regurgitation occurs during the cardiac cycle when the valves should be closed but they are not fully closed. The end product of a regurgitating valve is a reduced cardiac output. In most cases of rheumatic fever, there is some degree of valve stenosis along with regurgitated flow.

Another common heart valve disease occurs when the valve leaflets become calcified. The mechanism behind this phenomenon is currently not clear. However, what occurs is the formation of a bonelike matrix (i.e., hydroxyapatite) within the valve leaflets. Similar to the rheumatic fever disease scenario, calcified valve leaflets are much stiffer compared with normal leaflets. This will induce some combination of valve stenosis and regurgitation flow through the valve and effectively reduce the cardiac output.

Other consequences of heart valve disease must be taken into consideration as to which valve has become diseased and which chamber of the heart must compensate by undergoing hypertrophy or dilation. When a semilunar valve becomes stenotic or regurgitant or when an AV valve is regurgitant the primary burden is placed on the appropriate ventricle (depending on which side of the heart is experiencing the disease). With aortic stenosis, there are major changes to the pressure waveform in the systemic circulation, which alters the delivery of blood throughout the entire systemic circulation and will thus have major repercussions. If the mitral valve is regurgitant, there are major secondary effects observed in the venous pulmonary circulation, and there is a reduction in oxygenated blood delivery to the systemic circulation. Stenotic AV valves place a larger primary burden on the atrium, and there are secondary effects observed within the corresponding venous circulation. For instance,

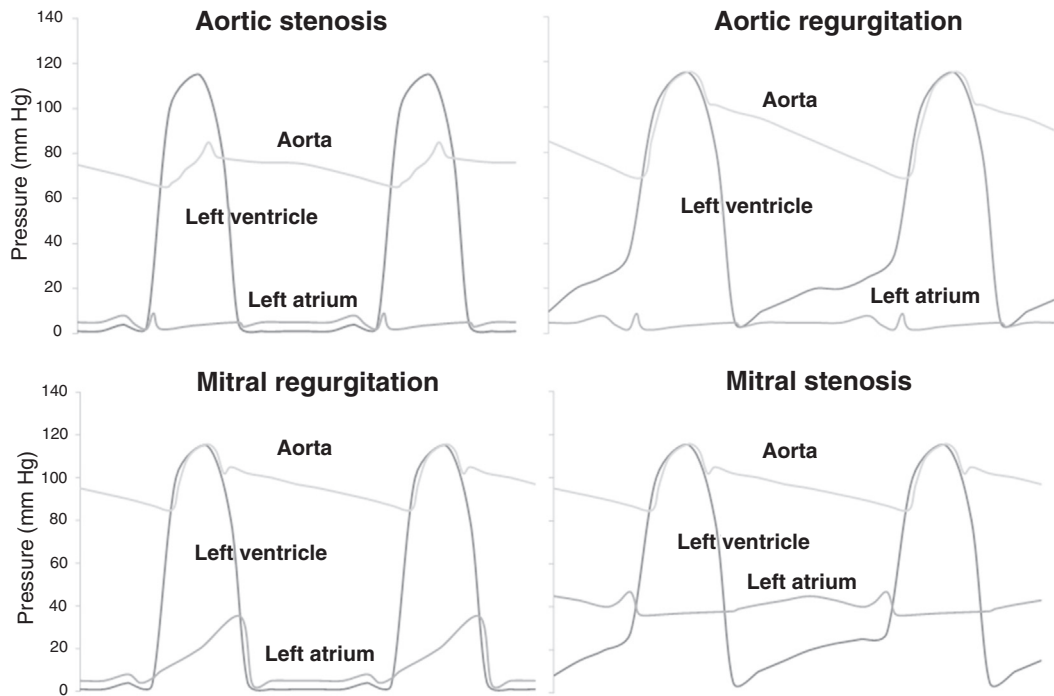


FIG. 5.18 Pressure relationship in the left side of the heart and in the aorta during valve diseases of the left side of the heart. The normal relationship for the pressure waveforms can be found in [Fig. 5.10](#). The pathological conditions associated with aortic stenosis (aorta pressure reduction) and mitral regurgitation (left atrium pressure increase) are predominately observed during ventricular systole, whereas the pathological conditions associated with aortic regurgitation (left ventricle pressure increase/aortic pressure decrease) and mitral stenosis (left atrium pressure increase/left ventricle pressure increase) are predominately observed during ventricular diastole.

when the tricuspid valve becomes stenotic, there is a systemic increase in the venous circulation pressure.

Changes observed to the pressure waveforms on the left side of the heart under various heart valve diseases are shown in [Fig. 5.18](#). Under aortic stenosis conditions, the left ventricular pressure waveform appears normal, but the aortic pressure does not mimic the left ventricle waveform during ventricular systole. This primarily leads to left ventricular hypertrophy, altered coronary blood flow, and altered myocardial oxygen demand. Under aortic valve regurgitation conditions, both the aortic and left ventricular pressure waveforms are altered from the normal conditions. The backflow of blood into the left ventricle significantly increases the left ventricular pressure while reducing the aortic pressure. Therefore, the ejection period of blood during ventricular contraction is increased and an overload of blood within the ventricle is observed. Mitral valve regurgitation puts an excessive burden on the left ventricle, because there is a leak between the ventricle and the atrium during ventricular systole. The heart has to increase its stroke volume (and cardiac output potentially through heart rate changes) to make up for the loss of blood volume to the systemic circulation. There is also a large abnormal increase in the left atrium pressure waveform during

ventricular systole. Mitral stenosis progressively elevates the atrial pressure and somewhat reduces the ability for the ventricle to maintain a normal stroke volume. The atrial contraction cannot overcome the incompressibility of blood, and thus the atria lose ability to act as a primer pump. As one can imagine, the downstream effects of these changes on the corresponding vascular beds are numerous, including systemic vasoconstriction, with a decrease in the ability to maintain temperature and cyanotic peripheral tissue. The changes on the right side of the heart will be analogous to those discussed on the left side of the heart, except that the pressure is approximately six times less within the pulmonary circulation than in the systemic circulation.

We will now focus a little more specifically on the aortic valve and two diseases that result in a reduction in the stroke volume of the heart. Aortic stenosis is characterized by a narrowing of the aortic valve along with a reduction in the ability for the left ventricle to empty. The second disease, aortic regurgitation, is when the aortic valve does not close properly and blood returns from the aorta into the ventricle. In both cases, it is observed that the left ventricular muscle mass hypertrophies because of the increased workload to eject blood out of the heart. When regurgitation is experienced, this change is coupled with an increase in the ventricle size to hold the extra blood. Recordings of intraventricular pressure of 400 mmHg have been recorded during aortic stenosis. This massive increase in pressure is required to overcome the excessive resistance from the stenosed valve. Similarly, during regurgitation, an increase in systolic stroke volume has been observed, but over 75% of the ejected blood volume can return back into the left ventricle, thus the efficiency of ventricular contraction is severely reduced. Volumes of 250 mL have been reported to be ejected with approximately 200 mL of this volume returning back into the left ventricle.

Similar findings have been observed during mitral valve stenosis and regurgitation. During mitral valve stenosis, the flow of blood into the left ventricle is impeded, whereas in mitral valve regurgitation, significant blood flows from the left ventricle into the left atrium. For either of these diseases, there is a net increase of blood and blood pressure within the left atrium. It is common to observe significant pulmonary edema when this disease progresses significantly enough (left atrium pressure on the order of 30 to 40 mmHg). The pulmonary vascular pressure will not increase significantly; therefore, the driving force of fluid flow can reverse and cause a build-up of fluid in the lungs. However, the lungs do have an extensive lymphatics system that can accommodate changes in left atrial pressure to an extent. It is also common to observe an increase in atrial fibrillation during these disease cases. To accommodate the extra blood in the atrium and the increased pressure, it is common for the atrium to increase in size. This increases the distance that the cardiac electrical signals must traverse. With a significant increase in distance the timing of the contraction is no longer correct and eventually leads to atrial fibrillation.

5.7.4 Congenital heart diseases

Congenital defects are those that are associated with a malformation during fetal development. In the context of the heart, there are three main congenital defects that can lead to various heart diseases. These defects are (1) an abnormality that allows blood to flow backward from the left side of the heart (or aorta) to the right side of the heart (or pulmonary

artery), termed *left-to-right shunt*; (2) an abnormality that allows blood to flow directly from the right side of the heart into the left side of the heart bypassing the pulmonary circulation, termed *right-to-left shunt*; and (3) an abnormal stenosis within the heart or one of the major blood vessels. A congenital stenotic vessel or component of the heart results in pathological conditions similar to those in general stenotic vessels that were discussed previously. In general, there is an increase in pressure upstream of the stenosis, combined with a distention of either of the vessels or heart chambers upstream of the stenosis. This will be coupled to a reduced flow through the stenosis and possible pathological conditions associated with reduction in blood delivery to the downstream locations.

The blood pressure in the fetal circulation is vastly different from what we have discussed so far. The lungs and the pulmonary circulation are collapsed and thus provide a very high resistance to flow. In parallel to this, the pressure in the aorta is lower than normal (because the flow through placenta has a lower resistance) and is at a lower nominal value than the blood pressure in the pulmonary circulation. These differences require that arterial blood flows through an artery, which is normally present only during fetal development, which directly connects the pulmonary artery directly with the aorta. This special vessel is termed the *ductus arteriosus* and has the function of bypassing the lungs (remember that fetal blood is oxygenated by the placenta and not the lungs). Under normal conditions, at birth the blood flow begins to reverse in the ductus arteriosus because of the lungs and lung vasculature inflating and the aortic pressure increasing. After a few hours, the vessel becomes occluded and eventually blood flow ceases through this bypass. However, for 1 in every approximately 5000 to 6000 births, this bypass does not close properly, inducing a left-to-right shunt (termed patent ductus arteriosus).

In the presence of this shunt, blood from the aorta can continually flow into the pulmonary arteries. In fact, with the large pressure differential between these vessels, the ductus arteriosus continues to enlarge, inducing more significant problems as the child ages. It has been shown that at least 50% of the aortic blood flows into the pulmonary circulation. These patients typically experience a higher left ventricular output (approximately 2.5 times the normal cardiac output) to accommodate the reduced flow to the systemic circulation. Patients with this pathological condition are especially susceptible to fainting during moderately strenuous and strenuous activities, and thus it is recommended for them to avoid such activities that increase heart rate and demand a higher cardiac output. If this pathological condition remains uncorrected, patients will typically survive until early adulthood; however, there is a surgery to remedy this left-to-right shunt, and luckily this surgery is relatively simple. Either the shunt is ligated or split and sutured. This was one of the first heart surgeries performed successfully in 1938 by two independent physicians, Robert Gross in the United States and Emil Frey in Germany.

One of the most common right-to-left shunts is termed *tetralogy of Fallot* and is one of the causes of “blue baby.” This pathological condition is characterized by four congenital defects in the heart that happen simultaneously, resulting in the majority of blood bypassing the pulmonary circuit, and thus, the arterial blood in the systemic circulation is largely deoxygenated. The first defect is that the aorta originates from the right ventricle or that the position of the aorta blocks the closure of a hole in the septum. Regardless of which of these pathological conditions occurs, the aorta receives blood from the right ventricle and no (or little) blood from the left ventricle. In parallel to the first defect, the pulmonary artery becomes stenosed,

causing an increased resistance to flow through this vessel and shunting additional blood away from the pulmonary circuit into the aorta and systemic circuit. Third, blood flow through the heart becomes quite complicated, because blood can pass between the right and left side of the heart somewhat freely. This can alter the heart anatomy depending on the exact complications faced earlier and overall causes a mixing of blood that prevents normal oxygenation. Finally, the right side of the heart becomes enlarged because it must work against a pressure gradient greater than normal. Heart contraction would be associated with a greater workload, would have higher energy demands, and may compete with the left ventricle for proper pumping function.

It is common under these conditions for two-thirds to three-quarters of the blood that enters the right side of the heart to pass directly back into the systemic circulation, bypassing the pulmonary circulation. These pathological conditions are fairly easy to diagnosis because the child's skin becomes cyanotic (blue) almost immediately after birth. Combining this observation with ventricular pressure recordings can confirm the presence of a right-to-left shunt. If the pathological condition remains untreated, the child will normally not survive for more than 3 to 5 years. However, surgical intervention can be undertaken to open the stenosed pulmonary artery, close the septal wall, and rearrange the aortic flow as necessary. This can significantly increase the life expectancy of patients with these defects.

The causes of congenital heart defects are somewhat complicated but have been linked to both genetics and viral infections. Identical twins have been observed to have the same congenital defect; furthermore, it has been observed that the defects can be passed from generation to generation within one family, suggesting a genetic link. It has been estimated that children of parents with congenital defects have a 10 to 15 times higher chance of having a congenital defect as well. Mothers who contract a viral infection during the first trimester of pregnancy, when the heart is forming, have an increased likelihood to have a child born with a congenital defect. Although a direct cause has not been identified, mothers who contract German measles (rubella) during the first trimester are especially susceptible to having a child with a congenital heart defect (approximately 85% of children born when a mother becomes infected with rubella during the first 12 weeks of pregnancy develop a congenital defect; this probability drops sharply over the next few weeks of pregnancy).

Summary

- 5.1. The human heart consists of two separate pumps that work in synergy to transport deoxygenated blood to the pulmonary circulation and oxygenated blood to the systemic circulation. Each pump is composed of a primer pump, the atrium, and an active pump, the ventricle. The cardiac muscle cells are highly interconnected to allow for the transfer of electrical signals between the muscle cells and to prevent the heart muscle from tearing itself apart. Troponin and tropomyosin are present within cardiac muscle to regulate actin–myosin cross-bridge formation, in a manner similar to that of skeletal muscle. The major difference between cardiac muscle tissue and skeletal muscle is that cardiac muscle contains voltage-gated calcium channels that help elongate the depolarization phase of the cardiac action potential. This elongation

allows the atria to contract as one and then the ventricles to contract as one, instead of having a wave of contractions through the cardiac tissue. The work that the heart undergoes to contract can be depicted by the pressure–volume relationship of each heart chamber. The area within this closed-loop circuit describes the work of heart contraction.

- 5.2. The cardiac action potential is generated in the SA node, which is a highly specialized structure that is surrounded by extracellular fluid with an abnormally high sodium concentration. This sodium continually enters the cells that make up the SA node and approximately every 60 seconds generates an action potential. The cells of the SA node are directly connected with neighboring cardiac myocytes to allow for the coupling of the atria with the SA node. There are three pathways along the right atrium wall, which help pass the action potential signal from the SA node to the AV node. The AV node is responsible for initiating ventricular contraction, but the AV node slows the conduction speed of the cardiac action potential so the atria can finish contraction before ventricle contraction. The action potential passes from the AV node to the Purkinje fiber system, which rapidly transmits the action potential to the apex of the heart and then penetrates into the ventricular muscle mass. This causes the inferior portion of the ventricle to contract first, pushing the blood toward the valves located superior to the ventricle. The ECG is a common way to measure the electrical potential within cardiac tissue. The ECG signal is composed of three waves: the P wave, which is associated with atrial contraction; the QRS complex, which is associated with ventricular contraction; and the T wave, which is associated with ventricular repolarization. Changes in the intervals between these waves, the lengths of the waves, and the electrical potential of these waves can help physicians diagnose various cardiac conditions.
- 5.3. The cardiac cycle describes all of the events that occur during one heartbeat and is divided into two phases, diastole and systole (typically related to ventricular relaxation and contraction, respectively, but it can be discussed regarding the specific contraction sequences of the atria as well). Diastole is characterized by cardiac myocytes that are not actively contracting, whereas systole is characterized by active cardiac myocyte contraction. During ventricular diastole, there is a rapid reduction in the intracardiac pressure and there is a rise in the blood volume for the chambers within the heart. During ventricular systole, there is a rapid increase in cardiac pressure accompanied by a rapid decrease in the blood volume.
- 5.4. During active contraction, the entire heart moves in 3D space, which can be modeled by changes in the forces/pressures within the heart. A.V. Hill modeled the heart contraction as a three-component model that is composed of the active contraction mechanism (actin–myosin), a viscoelastic relaxation, and a parallel resistive element. The Hill model can be used to calculate the force generated during contraction. The solid mechanics of the heart are also very important to understand when modeling heart motion. Assuming that the heart is a perfect spherical shell with homogeneous material properties, the radial stress and the circumferential stress generated within the cardiac tissue can be described by

$$\sigma_r(r) = \frac{p_o b^3 (r^3 - a^3)}{r^3 (a^3 - b^3)} + \frac{p_i a^3 (b^3 - r^3)}{r^3 (a^3 - b^3)}$$

$$\sigma_{\theta}(r) = \frac{p_o b^3(2r^3 + a^3)}{2r^3(a^3 - b^3)} - \frac{p_i a^3(2r^3 + b^3)}{2r^3(a^3 - b^3)}$$

respectively.

- 5.5. There are four valves present within the heart: the mitral valve (between the left atrium and left ventricle), the tricuspid valve (between the right atrium and right ventricle), the aortic valve (between the left ventricle and the aorta), and the pulmonary valves (between the right ventricle and the pulmonary artery). The function of the mitral and tricuspid valves is very similar, and the same is true for the function of the aortic and pulmonary valves. The mitral and tricuspid valves remain open for approximately 75% of the cardiac cycle, so that blood flows freely from the atria to the ventricles. As the ventricles begin to contract, these valves will close and the aortic and pulmonary valves will open. The mitral and tricuspid valves are connected to the chordate tendineae and the papillary muscles, which prevent the valves from bulging (and potentially opening) into the atria. The most important function of the valve leaflets is to determine the direction of blood flow through the heart. The pressure–tension relationship for the valve leaflets can be represented as

$$p_i - p_e = \frac{T_i}{r_i^2} + \frac{T_e}{r_e^2}$$

The Gorlin equation can approximate the aortic valve area as a function of physiological parameters as

$$\text{Valve area} = \frac{\text{Cardiac output}}{44.3 (\text{Heart rate})(\text{Systolic ejection period})(\sqrt{\text{Mean pressure gradient}})}$$

- 5.6. The cardiac valves work passively. The AV valves are very thin compared with the much heavier and thicker semilunar valves. AV valves have a much slower and softer closing, whereas the semilunar valves snap shut quickly, and the sounds associated with this closing can be heard by stethoscope. The surface on the upstream side of the valve is elastin rich. The downstream side of the valve is composed primarily of a dense collagenous layer. These two surfaces sandwich a core composed of loose connective tissue. The dynamics of valve leaflet motion have been correlated to the mechanical properties of the leaflets and the blood flow motion across the valves. The motion of heart valves also has been shown to be quite complex; however, significant work related to the motion of valves has been completed for the valves on the left side of the heart and there is still room for investigating the motion of the valves on the right side of the heart.
- 5.7. Coronary artery disease is characterized by a reduction in the coronary artery blood flow, which can eventually lead to cardiac muscle tissue death. The coronary arteries are responsible for supplying the cardiac tissue with the oxygen and nutrients it needs

to contract during the entire cardiac cycle. Myocardial infarction is characterized by a section of cardiac tissue that begins to die because it does not receive enough blood. This region will not contract as strongly as possible, and this can have a drastic effect on the blood delivery to the vascular system (depending on the size of the infarcted region). Heart valve disease is characterized by a destruction of the heart valves, which can potentially affect blood flow through the heart. If the valves do not open fully, there will likely be a reduction in blood flow to the cardiovascular system, and if the valves do not close fully, there is the likelihood for backflow of blood into the heart. This can be observed by changes to the pressure waveforms within the heart chambers and/or the respective vessels. Note that there are defects of the heart that are congenital as well and can be genetic related or related to environmental exposures.

Homework problems

- 5.1. Blood returning to the human heart in one of the pulmonary veins will drain first into the_____, after which it passes into the_____ and then enters the_____ circulation.
- 5.2. The occurrence of cardiovascular diseases depends on the country of origin. For instance, Greece has a much lower cardiovascular disease rate than the United States. List a few possible reasons for this dependence. Would it be possible to test the reasons you list and how would you test them?
- 5.3. During diastole, heart chambers experience
 - a. contractions that push blood into the downstream chamber.
 - b. a decrease in pressure, associated with muscle relaxation.
 - c. an opening of the left and right semilunar valves.
 - d. an increase in intracellular calcium.
- 5.4. Discuss the differences between the cardiac muscle and skeletal muscle. Why are the action potentials different in these two types of muscle?
- 5.5. Do the chordae tendineae play an active role in heart valve motion? What is the purpose of these structures?
- 5.6. You are sitting outside on a warm day and are losing a great deal of fluid volume through sweat. You decide to have your blood pressure taken and find that it is higher than normal. Why is this?
- 5.7. If your alarm clock wakes you up and you rise rapidly, why may you feel light-headed? Under other conditions, such as voluntary waking without an alarm clock, this does not occur, why?
- 5.8. A patient with congestive heart failure (severe myocardial infarction) has swollen ankles and feet. What is the relationship between heart failure and fluid loss from the vascular system?
- 5.9. A patient has an ECG, and the physician finds that there are two P waves, followed by the QRS complex and then the T wave. What is a possible reason behind this?
- 5.10. What are the principle valves in the heart and what are their functions?
- 5.11. Describe the salient aspects of the cardiac cycle.

Homework problems (cont'd)

- 5.12. Under normal physiological conditions, the pressure–volume relationship for the heart is described in Fig. 5.7. Approximate the work associated with the left ventricle under these conditions. Also, what is the cardiac work associated with a patient who is experiencing high blood pressure, whose pressure–volume relationship phase 1 starts at 2 mmHg and ends at 8 mmHg. Phase 2 ends when the left ventricular pressure reaches 110 mmHg, and at this point the aortic valve opens. The maximum pressure associated with phase 3 reaches 175 mmHg and ends at a pressure of 125 mmHg, and follows a path similar to that described in Fig. 5.7. Phase 4 closes the work loop. Assume that the volumes under the disease condition remain the same.
- 5.13. Discuss the time rate of change experienced in the left ventricular volume filling curve during the cardiac cycle. Would this temporally varying quantity differ during a disease condition?
- 5.14. A patient has a murmur in the ventricle that produces a loud gushing sound at the beginning of systole. Which valve is most likely causing this sound and what is a possible remedy for this murmur?
- 5.15. Calculate and plot the radial and circumferential stress distribution in the left ventricle at the end of systole ($p = 80$ mmHg; assume that the ventricle is a spherical shell). The inner radius of the heart is 3.2 cm and the outer radius of the heart is 3.8 cm. The external pressure surrounding the heart is -1 mmHg. Under a disease condition in which the heart muscle thickens, calculate the radial and circumferential stress distribution in the left ventricle at the end of systole. Under these conditions the pressure at the end of systole remains the same, but the inner wall radius is 3 cm and the outer wall radius is 4.2 cm. Compare this to normal conditions and comment.
- 5.16. Recalculate the stress distribution through the cardiac wall with an inner radius of 3.5 cm and an outer radius of 4 cm; however, the internal pressure during peak systole is 150 mmHg. All other conditions are as listed in Problem 5.15.
- 5.17. Use the Cartesian Navier–Stokes equations to approximate the flow through the left ventricle during peak systole. Assume that the gravitational effects on the flow are negligible and that the opening orifice for blood to flow through is 25 mm (aorta). The width of the left ventricle can be approximated as 2 cm and the total length from the apex of the heart to the aortic valve as 4 cm. Determine the maximum velocity at both the aorta and within the ventricle. Blood viscosity is 3.5 cP; assume that the pressure gradient across this flow is -1 mmHg/cm.
- 5.18. During heart valve degeneration, the thickness of the valves can decrease. Calculate the tension on the inner leaflet to maintain the valve in a closed position. Assume that during valve closure, there is a pressure difference of 3 mmHg, with an atrial pressure of 5 mmHg. The radii of curvature for the principal directions of the valve leaflets are 1 cm and 1.05 cm. There is a uniform width of 3 mm across the leaflets. Assume that the leaflet is approximately one-third of the sphere.

Continued

Homework problems *(cont'd)*

- 5.19. Under a condition in which the heart valves stiffen, the tension that they can withstand reduces to 2 mN on the exterior surface and 0.5 mN on the interior surface. What is the radius of curvature needed for the leaflets to maintain this pressure? Assume that all pressure conditions and geometrical considerations are the same as in Problem 5.18.
- 5.20. *Modeling:* Design a two-dimensional aortic valve geometry (including the aorta) using a computational fluid dynamics program. Compute the velocity field behind the valve at peak systole (assume that the pressure gradient is 15 mmHg across the section of the valve shown in Fig. 5.16).
- 5.21. What is the cardiac output of a person with an aortic root area of 0.5 cm^2 , heart rate of 72 beats per minute, ejection period of 0.3 second and a pressure gradient of 45 mmHg?
- 5.22. The answer to the previous question somewhat underestimates the cardiac output of a person: (1) illustrate the dependence of cardiac output approximation on both the ejection period and the pressure gradient, using the aortic root area and heart rate as provided in Problem 5.21; (2) discuss your findings for (1); and (3) discuss the meaning of the constant of proportionality in the Gorlin equation (e.g., 44.3).
- 5.23. The cardiac conduction system is designed with some very specific considerations as to the speed of conduction from the SA node to the apex of the heart. Knowing the conduction delay between the various segments within the cardiac conduction system, estimate the conduction speed through each portion of the cardiac conduction system. Estimate the length of each segment.

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Blood flow in arteries and veins

LEARNING OUTCOMES

- Differentiate the anatomy/physiology of the arterial system and venous system
- Explain the distinct layers that compose the blood vessel wall
- State the general path of blood through the systemic circulation
- Describe the function of the venous valve system
- Discuss how blood moves through the venous system
- Compare the characteristics and functions of cells that compose the cellular component of blood
- Explain the different constituents of the plasma component and describe their function
- Compare the different types of white blood cells
- Interpret various characteristics of blood and how they play a role in rheology
- Define the relationships among pressure, flow, and resistance in the arterial system
- Calculate the volumetric flow rate using the Hagen–Poiseuille formulation
- Develop a relationship among the pressure, the flow, and the resistance in the venous system
- Formulate relationships for the volumetric flow rate of blood within veins
- Apply the Windkessel model to blood flows
- Discuss wave propagation in the arterial circulation
- Compare the wave speed within the arterial vessel wall with different assumptions
- Interpret the cause of pressure changes at bifurcations
- Calculate the optimal design for bifurcations
- Illustrate flow separation and how flows skew at bifurcations
- Use the pressure gradient to determine the likelihood for flow separation
- Model flow through blood vessels using a taper or steps
- Identify and express the critical components within the Navier–Stokes equations for a tapered blood vessel
- Analyze pulsatile blood flow conditions
- Explain the mathematical principle behind turbulent flows
- Define and apply the Womersley solution to various applications
- Discuss oscillatory blood flow and calculate important parameters associated with oscillatory blood flow
- Categorize common disease conditions that affect the vascular system

6.1 Arterial system physiology

The entire cardiovascular system is composed of the heart (see Chapter 5) and blood vessels, which have the primary function of transporting blood throughout the entire body. In this textbook, we will divide the blood vessels into three main categories: the arteries, the veins (for vein physiology, see [Section 6.2](#)), and the capillaries (see Chapters 7 and 8). It is interesting to note the distribution of blood within these systems. Under normal conditions, approximately 7% of the blood volume is held within the heart, approximately 10% of the blood volume is in the arteries (including the aorta), approximately 10% of the blood volume is in the arterioles/capillary beds, approximately 10% of the blood volume is in the pulmonary circulation, and the remaining approximately 60% of the blood volume is held within the venous system. Therefore, the vast majority of the blood in the entire body is in the venous system, which therefore acts as a blood reservoir. More about the venous system will be discussed in [Section 6.2](#).

An artery is defined as any vessel that transports blood away from the heart (note that this does not mean that the blood within an artery has to be oxygenated; i.e., the pulmonary arteries carry deoxygenated blood away from the heart). The term *artery* comes from the Greek word *αηρτηρευν*, which literally translates to “to contain air.” Before the knowledge of blood, it was thought that the arteries (and thus the vasculature) transported air throughout the body. Within both the systemic and pulmonary circulatory systems, arterial transport is carried out under high pressure, compared with their respective venous systems. As discussed in the previous chapter, this high pressure is primarily generated from the contraction of the heart muscle during the cardiac cycle and the lower compliance of arteries compared with veins. The pressure pulse generated during heart contraction applies a large amount of force throughout the cardiovascular system that acts on the arteries, along with the typical pressure that acts as a driving force for flow. To be able to withstand these high-pressure forces generated by the heart, arteries are composed of thick and relatively muscular walls.

In fact, the arterial wall is composed of three distinct layers: the tunica intima, the tunica media, and the tunica adventitia ([Fig. 6.1](#)). The tunica intima is the interior layer of the blood vessel wall and therefore is the only layer in contact with blood (under normal conditions).

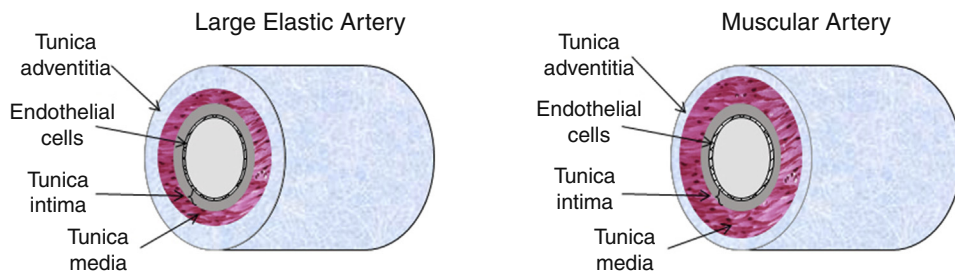


FIG. 6.1 Anatomical structure of large elastic arteries and muscular arteries, respectively. In both of these types of blood vessels, the tunica media, which is composed of smooth muscle cells, is thick to withstand the high pressures within the arterial system. The tunica adventitia is composed of elastic fibers and helps to anchor the blood vessel to the surrounding tissue. The internal layer, the tunica intima, is composed of endothelial cells that are in contact with blood.

This layer is composed of endothelial cells and a small connective tissue layer. The connective tissue within the tunica intima is mostly composed of elastic fibers and helps secure the endothelial cells in place. In most arteries, this layer is not smooth, because of the constant contraction and dilation (anatomical response to the heart pressure pulse) and the elastic recoil of the blood vessels; arteries must expand in response to heart contraction. The material that allows for this expansion must be present in the nonexpanded form. The tunica media is composed of smooth muscle cells organized in concentric rings. These muscle cells are responsible for altering the blood vessel diameter in response to neuronal input and local humoral control and maintaining the integrity of the blood vessels while exposed to the high pressures. The tunica media is typically the thickest layer within the arterial wall (especially for large and medium-sized arteries), allowing the arteries to have sufficient mechanical properties to withstand the large pressure forces generated by the heart. The tunica adventitia is composed of connective tissue, mainly collagen and elastin. In tissues, this arterial wall layer is responsible for anchoring the blood vessel to adjacent tissue. The tunica adventitia is normally nearly as thick as the tunica media layer in larger arteries. [Fig. 6.1](#) illustrates a large artery (left panel) and a muscular artery (right panel).

The systemic circulation begins at the ascending aorta, immediately distal to the aortic valve ([Fig. 6.2](#)). Within a few centimeters, the aorta makes a 180-degree turn (this is called the *aortic arch*) that leads to the descending aorta. The aortic arch contains branches for blood flow to the head (carotid arteries) and the arms (subclavian arteries). As the aorta descends

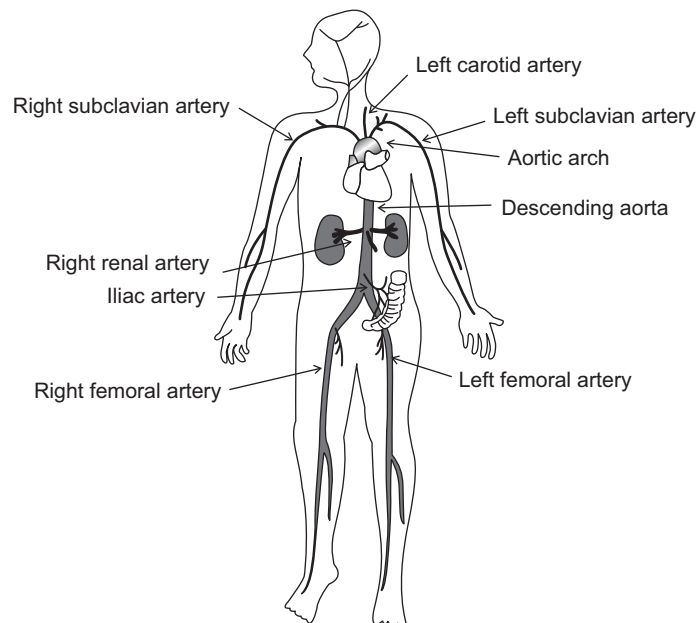


FIG. 6.2 A schematic of the major arteries within the systemic circulation. After passing from the heart, into the aorta, oxygenated blood can enter the carotid arteries (feed the head), the subclavian arteries (feed the arms), the renal arteries (feed the kidneys), the iliac arteries (feed the pelvic region), or the femoral arteries (feed the lower limbs). There are other vessels that branch off the aorta that are not included within this figure.

toward the pelvis, it continually tapers and directly branches to deliver blood to many of the major abdominal organs (e.g., renal arteries, hepatic arteries, and bronchial arteries). At the pelvic region, the aorta branches into the left and right iliac arteries, which supply the legs with blood, and the sacral artery. The aorta can be described as twisting (e.g., moves through different planes), tapering, and branching throughout its entire length, and therefore, the blood flow through the aorta is complex. Furthermore, blood velocity and pressure are normally the highest in this vessel and the mechanical compliance of the aorta is relatively low. In contrast, nearly every other artery, including all of the secondary arteries to the smallest arterioles and every artery in between, are fairly straight (at least in two dimensions, radial and theta (θ); blood vessels can and tend to vary in the z-dimension) and do not taper significantly until there is a branching point. At every branching point, the diameter of the branching vessel(s) (termed daughter vessel[s]) and the diameter of the main branch are reduced. The reduction in blood vessel diameter is not constant (e.g., the vessel diameter is not always halved at a branch point or reduced by some other common factor) at each branch point, and in many instances the daughter branches do not have the same diameter among themselves. For a comparison, the diameter of the ascending aorta is approximately 30 mm in humans. The diameter of the descending aorta, immediately distal to the aortic arch, is approximately 27 mm. By the time the aorta passes the diaphragm, the diameter has reduced to approximately 20 mm. As a comparison, the iliac and carotid arteries have a diameter of approximately 10 mm and these vessels maintain a diameter similar to this until the first branch point along its length. Therefore, within a relatively short length (approximately 30 cm), the aorta experiences a reduction in diameter of approximately one-third and therefore an approximate five-ninths reduction in the cross-sectional area. This is significant for the flow conditions throughout the vessel. Again, the secondary arteries maintain a fairly constant diameter until a daughter vessel branches off from the original vessel.

After blood has passed through the arteries, it enters the smaller arterioles, which are the last branches of the arterial system before blood entering the microcirculation. The arterioles are also under high pressure (approximately 40 to 80 mmHg), and they experience the largest pressure gradient across their length compared with all of the other classes of blood vessels. This is designed to aid in the rapid movement of blood through the arteriolar system and into the capillaries. These vessels are also found to be composed of a thick muscular layer. Not only do the muscles in the arterioles act to maintain the integrity of the blood vessel under high pressure; they also regulate blood flow into the capillary beds. As a side note, the muscles in the larger arteries do not regulate blood flow (e.g., they do not actively contract and dilate to dictate microvascular perfusion); they only act to maintain the blood vessel integrity under the extreme pressure loading conditions of the arterial circulation and have a minor role in dictating the capacity of blood the vessels can contain. In contrast, when the arteriolar muscles contract, blood flow can be halted in that vessel and shunted to another region that has a larger blood demand. Physically, blood is shunted from the region that has undergone a contraction, because of an increase in the vessel resistance without a significant change in the pressure gradient. The region that the blood has been shunted to typically has a lower resistance, and thus flow would proceed to that region. Under a dilatory relaxation, the arteriolar diameter can be increased by three to four times, which significantly increases the blood flow to its downstream capillary bed (see [Sections 6.5–6.6](#) for details on flow resistance). To some extent, these vessels are the controllers/regulators of blood flow throughout the entire body.

Blood velocity through the arterial circulation is directly proportional to the aggregate cross-sectional area of the particular vascular bed. This is a direct application of the conservation of mass formulation. Note that we stated that it is proportional to the aggregate cross-sectional area of the vascular bed and not the cross-sectional area of a representative blood vessel. Under conservation of mass, if the cross-sectional area decreases, the flow velocity should increase, and vice versa. However, we know that the blood flow is slower in smaller vessels compared with the feeding larger vessels. This is because one must account for the total aggregate cross-sectional area of all similar blood vessels. For instance, there is one aorta with an average cross-sectional area of approximately 3 cm^2 . Combining all of the small arteries in the body (diameter range from 0.5 to 1.5 cm), there is an average aggregate cross-sectional area of approximately 25 cm^2 . Combining all of the arterioles in the body (diameter range from 20 to 500 μm), there is an average aggregate cross-sectional area of approximately 50 cm^2 . For comparison, capillaries account for a combined cross-sectional area of greater than 2000 cm^2 , with the total combined venules accounting for an aggregate cross-sectional area of approximately 250 cm^2 and the large veins (vena cava) accounting for a cross-sectional area of approximately 10 cm^2 . For quantity comparisons, one aorta branches into approximately 200 arteries (large and small), which eventually branch into approximately 160,000 arterioles, which branch into 35 billion capillaries, which converge into approximately 10 million venules, which converge into 50 veins, which lead to 1 inferior vena cava and 1 superior vena cava.

6.2 Venous system physiology

A vein is defined as any blood vessel that transports blood toward the heart (note that this does not mean that the blood within a vein is deoxygenated; i.e., the pulmonary veins carry oxygenated blood toward the heart). The venous system as an entity also performs the critical task of acting as a reservoir for blood within the circulatory system (remember that approximately 60% of the total blood volume is housed within the venous system). In contrast to the arterial circulation, venous transport is carried out under much lower pressures (typically less than 5 mmHg, but this can vary slightly under different physiological or pathological conditions). Because of the low pressure in the venous system, the blood vessel walls in the venous circulation are thinner than walls of arteries at the same level in the vascular tree, but they are still relatively muscular. The diameter of veins is normally smaller but relatively comparable to that of arteries at the same location within the vascular tree. Contraction and dilation of muscles within the venous wall alter the amount of blood that can be held in the individual vessels and hence within the venous reservoir, but this does not regulate blood velocity or vascular perfusion as significantly as it does in the arterial circulation. In the venous circulation, blood flows much slower and most often in response to skeletal muscle contraction (as we will discuss later in this section).

Similar to the arterial wall, the venous wall is composed of three layers, the tunica intima, the tunica media, and the tunica adventitia (Fig. 6.3). These layers have the same general anatomical composition as the arterial layers described previously, with the following differences. The endothelial layer within the tunica intima is typically smooth because veins do not experience significant dilatory or contraction responses as often as arteries. The tunica

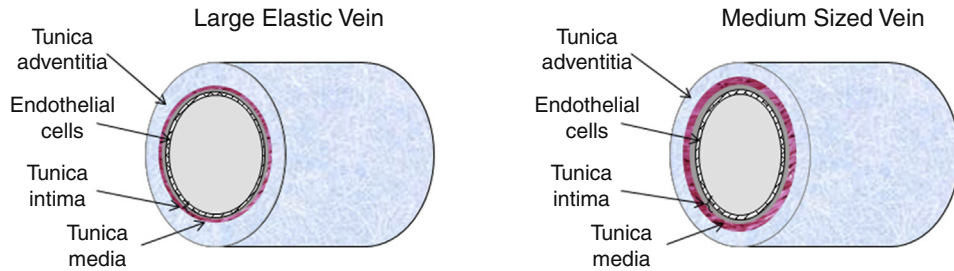


FIG. 6.3 Anatomical structure of large elastic veins and medium-sized veins, respectively. The tunica adventitia is composed of elastic fibers and helps anchor the blood vessel to the surrounding tissue. This is the thickest layer in veins. The tunica media is composed of smooth muscle cells and is smaller in veins compared with arteries because they are under a lower pressure. The internal layer, the tunica intima, is composed of endothelial cells that are in contact with blood.

media is relatively thin, compared with the arterial wall, and it is composed of smooth muscle cells and collagen. This layer is still responsible for controlling blood vessel diameter; however, the internal blood pressures are much lower in the veins than the arteries. The tunica adventitia is the thickest layer and is composed of collagen, elastin, and some smooth muscle cells. This layer is responsible for vessel anchoring to nearby tissues.

Although there is a common structure between arteries and veins, there are some important differences to discuss. Generally, the walls of arteries are thicker than those of veins. This difference is primarily manifested in the tunica media because arteries are composed of significantly more smooth muscle cells and more elastic fibers compared with veins. Again, however, the veins have a size similar to that of the paired arteries (e.g., the vessels that are at the same location within the vascular tree). Arteries are normally cylindrical, whereas veins do not have a typical structure because of the low hydrostatic pressure throughout the system. When under high pressure, it is more beneficial for blood vessels to have a uniform (or regular) circular geometry, so that the pressure forces are equally distributed at all locations along the vessel wall. Under uniform circular cross-sectional areas one location will not experience an extremely high load compared with other locations along the vessel wall. If this is the case, the vessels would be more susceptible to failure as a result of this uneven distribution of forces. Veins do not have as high a pressure force to distribute across the vessel wall, compared with arteries, and thus can take a more irregular shape without significant consequences. Finally, veins contain valves to prevent the backflow of blood toward the capillary beds. Again, because the venous system is under low pressure and a significant portion of venous flow is from the lower extremities upward toward the heart, blood would tend to pool within the lower limbs because the intravascular pressure gradient is not large enough to overcome the hydrostatic pressure gradient. Thus, blood would preferentially pool within the low regions of the limbs.

Venous circulation begins as blood passes out from the capillary beds and enters the venules. These particular blood vessels collect and store blood and pass the blood along to the large veins. Therefore, venous flow is convergent flow, meaning that two (or more) blood vessels combine to form a larger venous blood vessel (in contrast, arterial flow is generally divergent flow). This convergence of vessels continually occurs within the venous system until blood enters the heart by the superior (blood from the head and upper torso) or inferior (blood from the lower torso) vena cava.

Large veins have very little resistance to flow when they are fully open. However, under normal conditions, the veins in the chest cavity are compressed to some extent. Compression of veins occurs as a result of the low pressures within the venous system, the higher pressure from other surrounding organs or the interstitial space acting on the veins, and veins bending over bones or other stiffer biological materials (e.g., the subclavian vein bends over the first rib bone). This compression partially regulates venous return into the heart by increasing flow resistance; however, contraction of local muscles can overcome this resistance to allow for venous return to occur. As discussed in Chapter 3, the venous flow is also a function of the hydrostatic pressure within the fluid, because the pressure head (driving force ∇P) for flow is relatively low, the hydrostatic pressure gradient becomes very important. An average adult in a standing position experiences a pressure difference between the heart and the toes of approximately 100 mmHg. The forcing dynamic pressure head (∇P) in the venous system cannot overcome this pressure difference by itself, and that is why if you stand still and upright for an extended period, your lower limbs can cramp, blood will pool in the lower limbs, and/or the “pins and needles” feeling occurs upon new motion because of reperfusion of the tissue. Conversely, when an average adult is in a standing position, the hydrostatic pressure of blood in an average cranial space is approximately 10 mmHg lower than the hydrostatic pressure experienced in the right atrium. This aids in constant blood flow from the head back to the heart, and therefore, there is little pooling of the blood in the cranium and neck and a constant circulation of nutrients and wastes to and from the head. As you should know, increased pressure on the brain, including blood pressure, can have dramatic effects that can lead to death and/or improper brain function.

To help blood flow from the lower limbs back toward the heart, the venous system can act as a pump. We want to caution the reader that the term *pump* usually elicits the connotation of an active mechanism to move fluid throughout a system. However, there is no active mechanism within the venous circulation to move blood throughout the system. The term *venous pump* refers to more of a passive mechanism that forces blood to move in one direction (usually toward the heart), when functioning properly. Specifically, the venous pump uses the valves that were discussed briefly to prevent the backflow of blood toward the capillary beds. In fact, without the valve system, it would be nearly impossible for blood in the venous circulation to ever flow back toward the heart when a person is in a normal upright position. The opening and closing of the venous valves help regulate and induce blood flow through the majority of the venous system. This valve movement is facilitated by skeletal muscle contraction (which provides the active portion of the pump) and the increase in local fluid pressure induced by skeletal muscle contraction. Every time a skeletal muscle contracts, it compresses the veins that are in close proximity to that particular muscle, forcing the blood to flow through the downstream valves. Similar to the heart valves, the venous valves are designed in such a way that blood flows unidirectionally toward the heart and not toward the capillary beds (Fig. 6.4). As the blood evacuates one of the isolated venous chambers (a section of vessel between two valves), the overall pressure of that portion of the venous blood vessel is lowered, which facilitates blood flow into that section from the upstream venous chamber during the next muscle contraction. This pumping action is efficient under normal conditions, so that enough blood returns back to the heart and so there is not an excess of blood stored in the venous system. As a side note, when the valves within the venous system do not function properly, it is common for a person to develop varicose veins.

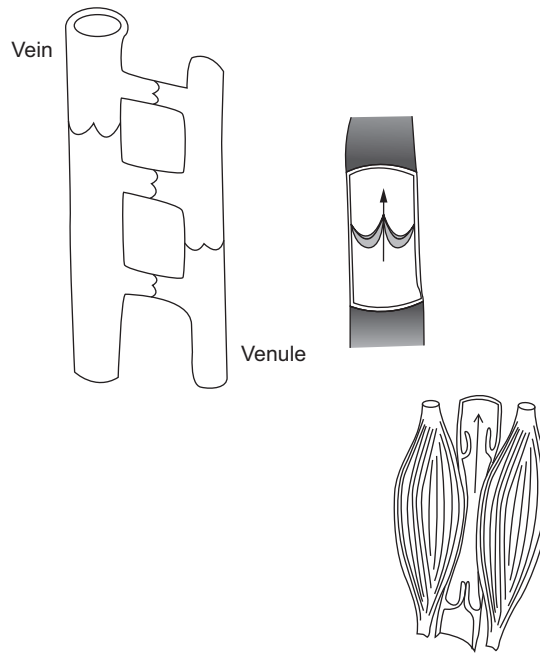


FIG. 6.4 Venous valves determine the direction of blood within the venous system, preventing blood flow back toward the capillaries. Skeletal muscle contraction helps to transiently increase the pressure within veins to propel blood toward the heart. Arrows depict blood flow direction. The venous valve system is useful in the lower extremities when normally the blood pressure cannot overcome the hydrostatic pressure to propel blood toward the heart.

Varicose veins are characterized by an overall increase in the diameter of the veins that causes the valves to not close properly. Therefore, under these conditions, blood can flow toward the capillary beds and then the hydrostatic pressure continually increases within the damaged venous section. Skeletal muscle contraction cannot overcome this increased pressure in severe cases, and therefore, blood begins to pool within the damaged venous section. Pooled blood causes distention of the vein beneath the skin, and this is what is seen as varicose veins.

6.3 Blood cells and plasma

Blood is composed of two major components: the cellular component and the plasma component (Table 6.1). In an average adult, the blood volume is approximately 5 L, of which approximately 55% to 60% is plasma and the remaining portion is cellular. More than 99% of the cellular component is composed of red blood cells. The most common way to quantify the percent of blood that is cellular is by quantifying the packed red blood cell volume, which is termed *hematocrit*. Red blood cells can be packed by centrifugation, which forces the heavier cells to one location in a test tube and the lighter fluid to a different location. Since the white blood cells and platelets make up a small percentage of the cellular volume and are not readily visible after centrifugation, the packed red blood cell volume is typically

TABLE 6.1 Blood composition

Cellular component (~40%)	Cell type	Cell concentration	Characteristic shape/ dimensions
	Red blood cell (erythrocyte: ~99.7%)	~5 million/ μL	Biconcave discs/8 μm diameter 2.5- μm thickness
	White blood cell (leukocyte: ~0.2%)	~7500/ μL	Spherical 20–100 μm diameter
	Platelet (thrombocyte: ~0.1%)	~250,000/ μL	Ellipsoid 4 μm long axis 1.5 μm short axis
Plasma component (~60%)	Composition	Major contributors	Function
	Water (~92%)	H ₂ O	Reduce viscosity
	Plasma proteins (~7%)	Albumin (~60%)	Osmotic pressure
		Globulins (~35%)	Immune function
		Fibrinogen (~3%)	Clotting
		Others (~2%)	Enzymes/hormones
	Other solutes (~1%)	Electrolytes	Homeostasis
		Nutrients	Cellular energy
		Wastes	Excretion

quantified as the hematocrit. The hematocrit for a male adult is typically greater than that of a female adult, approximately 43% for males and approximately 40% for females. Some research groups have speculated that the reason that heart disease is more common in males is the increased hematocrit compared with females (these groups suggest that a higher iron concentration is correlated with and can induce various cardiovascular disease; a second thought is that the altered balance between testosterone and estrogen may lead to altered cardiovascular disease responses). Anemia (or reduced red blood cell volume) can be easily diagnosed by hematocrit measurement. Patients with anemia can have a hematocrit that ranges from 10% to 35%. Anemia, although it is characterized by a low red blood cell count, is also associated with decreased transport of oxygen and difficulties in maintaining core body temperature. Our discussion will continue with a discussion on the salient aspects of blood, starting with the cellular component and then the plasma component.

Red blood cells (or erythrocytes) have multiple functions in the body, but one of the most critical functions these cells perform is the delivery of oxygen to and the removal of carbon dioxide from all cells of the body. This function is performed through the use of hemoglobin (which is a metallo-organic protein) and carbonic anhydrase, which are both proteins associated with and contained within red blood cells. Hemoglobin is the primary transporter of oxygen within the red blood cells. Red blood cells can be considered to be cells filled with hemoglobin molecules. Carbonic anhydrase, an enzyme that resides within red blood cells,

catalyzes the conversion reaction of carbon dioxide to water. This allows the blood to carry carbon dioxide in the form of bicarbonate ions (HCO_3^-). As you should be aware, oxygen and carbon dioxide exchange occurs within the capillaries of the systemic and pulmonary circulatory systems and will be discussed in detail in Chapters 8 and 10. Details of oxygen transport and function of carbonic anhydrase are provided within those discussions. Another important function that the red blood cells perform is the maintenance of the blood pH, through the use of hemoglobin as a buffer. The buffering capacity of hemoglobin is relatively large, and it is able to maintain the blood pH between 7.35 and 7.45 by associating with any free hydrogen ions and/or releasing those ions under basic conditions.

Red blood cells are biconcave discs with a mean diameter in the range of $8\text{ }\mu\text{m}$ and a thickness of approximately $2.5\text{ }\mu\text{m}$ at the thickest point and approximately $0.8\text{ }\mu\text{m}$ in the center (which is normally the thinnest point) (Fig. 6.5). Although we have not discussed capillaries yet, the average diameter of capillaries is approximately $6\text{ to }8\text{ }\mu\text{m}$. Therefore, the shape and orientation of red blood cells can and must change for these cells to squeeze through capillaries (a complete discussion on capillaries and red blood cell perfusion of capillaries can be found in Part 3 of this textbook). Because of the normal biconcave shape of red blood cells, there is an excess amount of red blood cell membrane allowing the cell to deform into many shapes different than the standard biconcave structure. Under normal conditions, there are approximately 5 million red blood cells/ μL of blood (males tend to have a concentration slightly higher than this quantity, and females tend to have a concentration slightly lower than this quantity). Under normal conditions, the quantity of hemoglobin per red blood cell is maintained at its maximum (i.e., saturated), to efficiently and effectively transport oxygen throughout the cardiovascular system. The quantity of hemoglobin within the red blood cell should not limit the rate of oxygen transport in the vascular system under

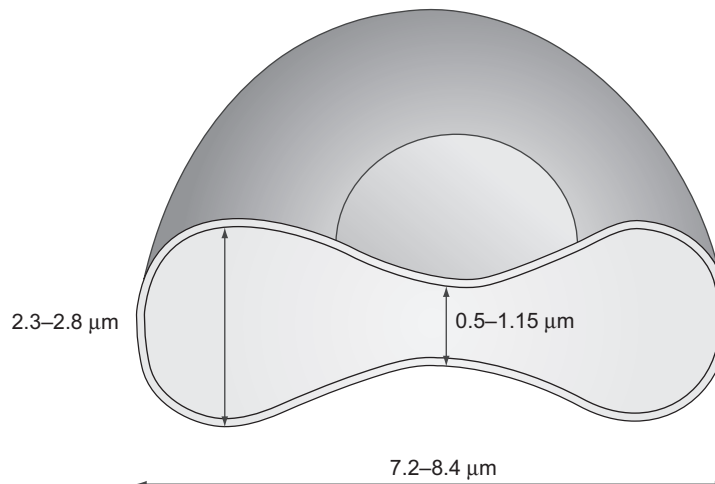


FIG. 6.5 Cross-sectional view of a mature red blood cell. We also include the average range for various dimensions of a mature red blood cell. Each red blood cell contains hemoglobin molecules that facilitate the transport of oxygen and carbon dioxide throughout the cardiovascular system. There are approximately 5 million red blood cells/ μL of blood, and each red blood cell remains in circulation for approximately 120 days.

physiological conditions. In fact, the quantity of hemoglobin within the red blood cell is limited only by the production of hemoglobin (in the liver) and not the transport of hemoglobin to form red blood cells. At its maximum production rate, the concentration of hemoglobin in each red blood cell is approximately 30 g/dL. The average red blood cell can stay in circulation for approximately 120 days before the cell (especially the hemoglobin and other proteins) is recycled.

The majority of red blood cells are produced in the marrow of bones during adult life (during fetal development, the liver, spleen, and yolk sac produce the majority of red blood cells). In contrast to what many think, most of the red blood cells are produced in the vertebrae and sternum during later stages of life (older than 20 to 25 years); only during the early stages of life does the marrow of long bones produce significant quantities of red blood cells. All blood cells are formed from hematopoietic stem cells, which differentiate and specialize into specific committed stem cells, which individually develop into different blood cell types. The major regulator of red blood cell production in the body is erythropoietin, which is a 34-kDa cytokine. Under hypoxic conditions (low tissue oxygenation), the formation of erythropoietin is increased within the kidneys and liver. Erythropoietin circulates to the red blood cell producing marrow and induces the differentiation of hematopoietic stem cells into proerythroblasts, which differentiate into erythrocytes within 1 to 2 days. For the complete differentiation of proerythroblasts into erythrocytes, vitamin B₁₂ and folic acid are required cofactors for this conversion reaction. Both of these vitamins are needed for DNA synthesis, which prevents nuclear maturation in the proerythroblast stage (red blood cells do not contain nuclei). Without these two vitamins, erythrocyte-like cells can be produced, but they can stay within circulation for only 30 to 40 days (in contrast to the approximate 120 days for typical red blood cells), inducing a form of anemia caused by a production of “inefficient” and high-turnover red blood cells. Causes of low tissue oxygenation are anemia, destruction of hemoglobin, and reduced blood flow, among others, all of which have been shown to lead to increases in erythropoietin production. When there is a high tissue oxygenation level, the production of erythropoietin is slowed, so that an excess of red blood cells/hemoglobin is not circulating within the cardiovascular system.

White blood cells (or leukocytes) are the primary cells that protect the body from foreign particles. There are two ways that leukocytes can perform this task: leukocytes can directly destroy foreign particles, or leukocytes can produce antibodies that aid in the immune response. There are six types of white blood cells in the body, each with its own specialized function. These six cell types are neutrophils, lymphocytes, monocytes, eosinophils, basophils, and plasma cells (some include platelets as a specialized type of white blood cell; however, for clarity we will separate the discussion on platelets). There are approximately 7000 to 8000 white blood cells per 1 μ L of blood. Of those cells, neutrophils account for more than 60% of the total, lymphocytes account for approximately 30%, monocytes account for approximately 5%, eosinophils account for approximately 2.5%, basophils account for 0.5%, and plasma cells approximately 0.1%. All white blood cells are formed in the bone marrow, except for lymphocytes and plasma cells, which are formed in lymph glands and spleen (see Chapter 9). Compared with red blood cells, white blood cells have a relatively short circulation time span, which is typically only 5 days. The exceptions to this are monocytes and lymphocytes; monocytes can migrate into tissues within 1 day of being in the blood, and lymphocytes can continually migrate between the blood and the tissue for approximately 1 month.

Monocytes that enter the tissue can swell and become macrophages and can stay in the extracellular space for months. Some plasma cells are an exception as well.

We will now briefly describe the immune responses of these cells, but for a more complete and detailed discussion, please refer to other textbooks more focused on inflammatory processes. Neutrophils and monocytes engulf invading particles directly through phagocytosis. These cells contain many lysosomes to digest and destroy the foreign particles. Lymphocytes play a role in acquired immunity, which is the inflammatory reaction against specific invading particles within the body. Some specialized lymphocytes have a memory for foreign particles that have previously entered into the body. Eosinophils exhibit a phagocytotic response toward parasites and release hydrolytic enzymes to neutralize the parasite invasion. Basophils play an important role in allergic reactions and can release histamine, serotonin, and heparin directly into the bloodstream. Plasma cells are antibody-producing cells and act in response to specific antigens. Each plasma cell can form one antibody, and they also can serve as a memory for the immune system. Depending on the type of plasma cell, they can reside in the circulation for months or within the bone marrow for years (termed long-lived plasma cells). Loss or low counts of white blood cells do not typically affect the inflammatory response because the function of many of these cell types overlaps. Therefore, if one cell type is not functioning properly, a second type of white blood cell can take up the slack. Leukemia is a cancer characterized by the overproduction of white blood cells within the body. Unfortunately, these cells do not function properly and therefore multiple inflammatory processes are lost. The extent of leukemia dictates the amount of inflammatory reactions that are lost.

Platelets (or thrombocytes) are the primary “cells” for hemostasis (note that some people define platelets as cells, whereas others do not). They are cellular fragments of megakaryocytes, which are derived from the same hematopoietic stem cells that lead to the formation of red blood cells and white blood cells. Platelets are typically ellipsoid with a long axis of approximately 4 μm and a short axis of approximately 1.5 μm . The normal blood platelet concentration is in the range of 250,000 platelets/ μL but can vary somewhat from this value and still be considered within the physiological normal range (platelet concentrations in the approximate range of 150,000 to 400,000 platelets/ μL are considered normal). Platelets do not contain nuclei or many of the other common cellular organelles, but they do contain a large intracellular concentration of calcium, adenosine diphosphate, prostaglandins, and coagulation cofactors; most of these are stored within specific granules structures. The platelet cell membrane may be the most important structure of the platelet. It contains many glycoproteins, which adhere to other platelets, endothelial cells, extracellular proteins, and proteins during clot formation. In addition, the charge of the cell membrane can accelerate or decelerate coagulation kinetics. The average life span of platelets is approximately 10 days within circulation, at which time they are removed by the spleen.

Hemostasis is a complex process that culminates in the formation of insoluble fibrin. Once insoluble fiber is produced, a fibrin protein mesh forms within the blood (or along the blood vessel wall) that is similar in structure to gauze. This mesh acts to seal off the wound within the blood vessel, further preventing blood loss. The coagulation cascade is a series of enzymatic reactions in which an active enzyme cleaves an inactive zymogen into its active form. The newly activated enzyme cleaves another zymogen into its active form and so on. This process continues until thrombin cleaves soluble fibrinogen into insoluble fibrin,

forming the mesh to prevent blood loss. Platelets are integral in these coagulation reactions because they provide multiple necessary cofactors for these reactions to occur (many of these are stored in the granule structures). For instance, platelets provide a negative phospholipid membrane surface (only from the activated cell membrane of platelets, which express the negative phospholipids that typically reside on the inner leaflet of the cell membrane) for coagulation complexes to form on (coagulation complexes include an activated enzyme and the specific inactive zymogen that the enzyme can activate and any possible cofactors). Platelets also provide particular protein and chemical cofactors to accelerate the coagulation reactions (especially factor Va and calcium). This helps in localizing the coagulation factors needed for clot formation and helps increase the kinetics of the reactions within a localized region. Without these two critical roles that platelets play, fibrinogen will not be cleaved to fibrin rapid enough to prevent a major loss of blood. Finally, platelets can aggregate with each other and various plasma proteins, forming a temporary mesh until the fibrin mesh has stabilized through the actions of factor XIII. Negative feedback on hemostasis include the removal of platelets that are participating in these processes and antithrombotic proteins that cleave and deactivate activated coagulation zymogens. If the platelet count is low, coagulation does not proceed as rapidly as normal and injuries that should be minor can cause severe blood loss. This is analogous to classic hemophilia (loss or low concentration of factor VIII), which is characterized by prolonged bleeding. It is important to note that shear stress can alter the platelet physiology significantly and that under disturbed blood flow conditions (e.g., high shear stresses, recirculation zones, oscillating stresses), platelets may accelerate cardiovascular disease progression.

The second major component of blood is plasma (see [Table 6.1](#)). Plasma includes everything in blood with the exception of the cellular matter. The major component of plasma is water. The remaining components are mostly electrolytes, sugars, urea, phospholipids, cholesterol, and proteins. The plasma concentration of electrolytes is very similar to that of the interstitial fluid because these compartments are only separated by the very permeable capillary wall (discussed in detail in Part 3). Therefore, these different compartments (the interstitial fluid and the capillary) reach or approach equilibrium relatively quickly along the capillary length. Sodium ions are the most abundant positively charged ions in the plasma (although potassium, calcium, and magnesium are not negligible). Chloride is the most abundant negatively charged ion (but bicarbonate, phosphate, and sulfate are also present). The total plasma osmolarity is approximately 300 mOsm/L H₂O. Approximately 2% of plasma osmolarity is accounted for by sugars within the plasma. Cholesterol contributes 4% to 5% of the plasma osmolarity (in a normal diet) and phospholipids contribute approximately 6% to 7% to the plasma osmolarity. Proteins account for approximately 1 mOsm/L H₂O of plasma but account for 7% of the total composition of plasma. The most crucial and most abundant protein within the blood is albumin, which accounts for over 60% of the total plasma protein concentration. Albumin has the primary function of maintaining the osmotic pressure of blood, because under normal conditions albumin should not diffuse across/through the capillary wall. Thus, albumin acts to balance the mass transfer across the capillary wall (see Chapter 8). The next major protein contributors to plasma are the family of globulins, which account for approximately 35% of the plasma protein concentration. Antibodies (immunoglobulins) and transport globulins are the major constituents of this component of plasma. Antibodies play a role in immunology, and transport globulins can bind to hormones,

metallic ions, and steroids, among others, to transport these molecules throughout the body. The majority of the remaining plasma protein composition is made up of fibrinogen (approximately 3%) and all of the other proteins. Fibrinogen is the precursor to fibrin and forms a mesh during clot formation, as discussed previously. The other plasma proteins have a wide range of functions but include insulin, thyroid-stimulating hormone, and all of the coagulation proteins.

The liver is the primary organ that synthesizes plasma proteins, including albumin, fibrinogen, and some of the hormones. Antibodies are produced by white blood cells, as discussed earlier. The other components of plasma are typically synthesized in cells, transported between cells, or ingested through the digestive system. The relative concentration of these components is regulated tightly but can change relatively fast depending on many factors. For instance, after eating a candy bar, your blood glucose levels can increase significantly. However, under normal conditions, the body regulates this concentration closely, and the blood glucose level should return back to its normal level rather quickly. Thus, it is typical to see transient spikes in plasma concentrations of various food molecules immediately after a meal.

Plasma does not have a function per se because it is an amalgam of many different biologically active components. In general, the water portion of plasma is used to reduce the viscosity of the cellular component of blood. This in effect reduces the resistance to flow and even can be considered to allow for blood flow to occur (i.e., cellular matter itself would not “flow”). A major function of the remaining plasma components is to maintain equilibrium with the interstitial space, which aids in homeostasis. Furthermore, sugars are used as the nutrient source for cells. Cholesterol can be used within the cell membrane to locally increase its rigidity so the cell can withstand forces better. Also, it is thought that highly specialized signaling occurs within this cholesterol-rich area of the cell membrane and these more rigid areas may provide a more stable structure in which the membrane-bound proteins function. Proteins have specific functions, and each protein may have a different task. Therefore, plasma in effect has a very critical function for the human body. Serum is a special component of plasma in which the protein fibrinogen has been removed. This is most likely the result of clot formation but can be made in the laboratory to study various properties of plasma.

6.4 Blood rheology

Rheology is the study of flowing materials combined with the study of the physical properties of the particular flowing material. In this section, we will discuss a more accurate way to model the viscosity of blood, which will account for some of the rheological properties of blood. As we have seen in previous chapters, blood is a special non-Newtonian fluid and is also composed of at least two phases. Recall that blood is a combination of cells, proteins, and electrolytes, among other compounds, all suspended in a fluid medium. Each of these phases can be accounted for differently or lumped together within the analysis. Plasma (the portion of blood not including cells) behaves as a Newtonian fluid (e.g., constant viscosity under shear forces) under physiological conditions and has a viscosity of approximately 1.2 cP. Whole blood, however, does not have a constant viscosity, exhibits a yield

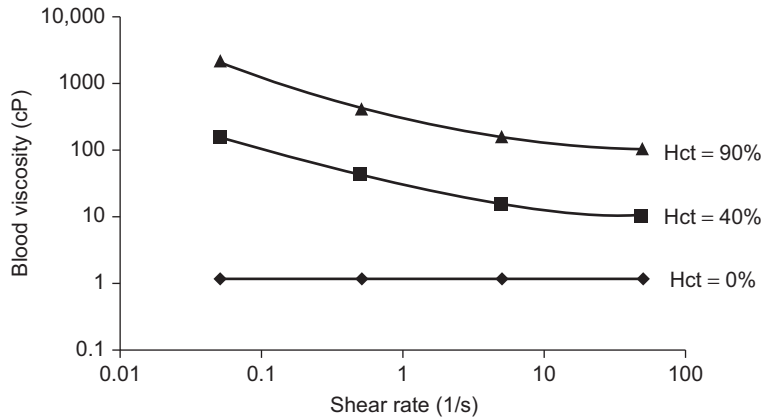


FIG. 6.6 The variation in blood viscosity as a function of shear rate and blood hematocrit (Hct). This figure illustrates that without the cellular component the blood viscosity remains constant, at approximately 1.2 cP, over the range of shear rates depicted on the figure. When cells are present in the blood, the viscosity is no longer constant and increases with decreasing shear rate. This figure is a summary of data collected by Chien et al.

stress, and is composed of many different constituents, as described previously. Many investigations have shown that the viscosity of whole blood varies with shear rate, hematocrit, temperature, and disease conditions (Fig. 6.6), and these changes are predominantly the result of the presence of cells in plasma, the interaction of the cells with each other and the fluid medium, and the presence of other charged compounds within the fluid. Fig. 6.6 illustrates (1) that plasma ($Hct = 0$) has a constant viscosity within the shear rate tested, (2) viscosity increases with increasing hematocrit, and (3) viscosity decreases with increasing shear rate when cells are present. Furthermore, many of these investigations have supported the idea that the presence of cells and charged molecules is the most significant contributor to blood behaving as a non-Newtonian fluid. Importantly, many groups have tried to determine the yield stress for blood, but have observed that it is difficult to quantify blood motion as the shear rate approaches zero. There are many reasons for this difficulty, including settling of cells because of gravity, the settled cells interacting with each other in different and possibly more complicated ways, and the controls of the experimental systems (e.g., to exclude other physical properties) tend to be quite difficult. Even with these difficulties, using a Casson model for blood flow combined with measured values for shear stress at given shear rates, the yield stress for blood can be extrapolated. The Casson model was first introduced in 1959 for a classic fluid mechanics application and was observed to fit blood flow well because it accounts for the interaction of solid and fluid particles as a two-phase fluid. This model incorporates both a yield stress for blood and the shear-thinning viscous properties of blood. The Casson model for blood can be represented by

$$\sqrt{\tau} = \sqrt{\tau_y} + \sqrt{\eta \dot{\gamma}} \quad (6.1)$$

Eq. 6.1 is a relationship that can be used to describe the dependence of shear stress on shear rate ($\dot{\gamma}$), a yield stress (τ_y) (which varies based on blood hematocrit), and apparent viscosity (η), which is an experimentally fit constant to approximate the fluid's viscosity (note that the

Casson formulation can be applied to other flow scenarios and is used for blood motion quite frequently). Under most physiological conditions, the yield stress of blood can be approximated as 0.05 dyne/cm^2 . Therefore, when a shear stress less than 0.05 dyne/cm^2 is applied to blood, blood will not flow or will only flow as a rigid body.

We have already learned that under normal laminar, steady, fully developed flow conditions in a cylindrical tube, the shear stress at the centerline is zero. Therefore, blood at the centerline would be forced to move as a rigid body, because this shearing force has not exceeded the yield stress for blood (in fact this would be theoretically true for all fluids, regardless of how small the yield stress is for that particular fluid). Extending this thought further, the shear stress experienced by blood will surpass 0.05 dyne/cm^2 (the assumed yield stress of blood) at a finite distance from the vessel centerline. For modeling purposes, we will assume that blood is flowing fully developed through a perfectly cylindrical channel with a constant radius. Under these conditions, we can state that at a distance of r_y , the shear stress will exceed τ_y . Therefore, blood that is further from the centerline than this location (e.g., closer to the vessel walls and having a numeric value greater than r_y) will flow as a "normal" viscous fluid. Fluid that is at a location closer to the centerline, compared with r_y , will flow as a rigid body. Thus, the combination of these two different flow characteristics will lead the fluid to have a pseudoparabolic velocity profile that has a blunted centerline velocity (Fig. 6.7). This altered parabolic velocity profile is caused by the principle that the blood viscosity will be zero (or stated otherwise that blood can be modeled as an inviscid fluid) when the yield stress within the flow field has not been surpassed. Under these conditions blood will flow as a rigid body. This becomes very apparent and important within the microcirculation, where red blood cells (which are semirigid objects) stream toward the centerline of the blood vessel and are thus suspended within blood that acts like a rigid body.

Mathematically, the phenomenon that we have been describing can be represented using the Casson model. We already know from previous discussions that

$$\tau = -\frac{r}{2} \frac{dp}{dx}$$

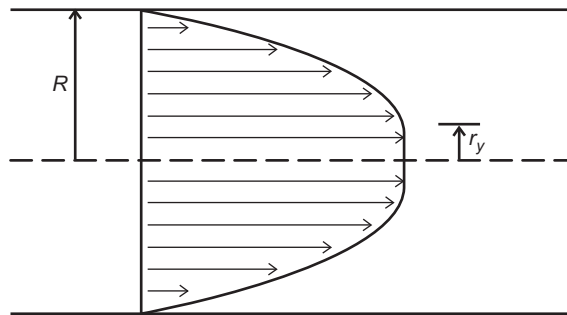


FIG. 6.7 The velocity profile of blood flowing through a cylindrical vessel using the Casson model. The profile is blunter than a purely Newtonian fluid's velocity profile because the fluid that is between the centerline and r_y flows as a solid. At r_y , the shear stress surpasses the yield stress of the fluid (τ_y) and the viscous forces take effect.

and, therefore, the Casson model (Eq. 6.1) can be rewritten as

$$\sqrt{-\frac{r}{2} \frac{dp}{dx}} = \sqrt{\tau_y} + \sqrt{\eta} \sqrt{\dot{\gamma}} \quad (6.2)$$

Solving Eq. (6.2) for shear rate we can obtain the following

$$-\frac{du}{dr} = \dot{\gamma} = \frac{1}{\eta} \left(\sqrt{-\frac{r}{2} \frac{dp}{dx}} - \sqrt{\tau_y} \right)^2 \quad (6.3)$$

If we integrate Eq. (6.3) from r_y to R (tube radius), over the appropriate reduced cross-sectional area (e.g., the cross-sectional area is not πR^2 , but it can be represented with $\pi(R^2 - r_y^2)$), we can obtain the following function for the velocity profile, keeping in mind that the fluid velocity is constant between the centerline ($r = 0$) and r_y .

$$u(r) = \begin{cases} -\frac{1}{4\eta} \frac{dp}{dx} \left(R^2 - r^2 - \frac{8}{3} r_y^{0.5} (R^{1.5} - r^{1.5}) + 2r_y(R - r) \right) & r_y \leq r \leq R \\ -\frac{1}{4\eta} \frac{dp}{dx} (\sqrt{R} - \sqrt{r_y})^3 \left(\sqrt{R} + \frac{1}{3} \sqrt{r_y} \right) & r \leq r_y \end{cases} \quad (6.4)$$

To obtain this formulation, we make use of many of the same assumptions that were discussed in previous sections for blood flow through vessels (e.g., constant cross-sectional area, constant apparent viscosity, rigid containing vessel, the flow is steady). Remember that when using these assumptions, r_y is a particular constant value and describes the radial location where the fluid shear stress exceeds the fluid yield stress. Note that the fluid velocity is constant for r values of r_y or less. Deriving from Eq. (6.4), the velocity profile of a fluid can be modeled with the Casson approximation and can be represented by Fig. 6.7.

The Casson model is a very useful representation of blood flow through the arterial system, but it tends to complicate the computations by hand. The following sections discuss methods to simplify the calculations, but these methods may not accurately represent the blood flow conditions.

A second approximation for blood flow characteristics that has become popular is the power law model for fluid flow applied to blood. This model also takes into account the non-Newtonian properties of the fluid, which include approximations for shear thinning and yield stress behavior. The power law for blood flow can be represented by

$$\tau = a \dot{\gamma}^b \quad (6.5)$$

where a and b are empirically defined power law constants for the particular flow conditions. The consistency index for fluids is represented within a ; as a increases, the viscosity of the fluid also increases. Non-Newtonian characteristics are represented in b ; as b diverges from a value of 1, the fluid exhibits more non-Newtonian characteristics. Eq. (6.5) is similar in

form to Eq. (2.39), where $b > 1$ would describe a shear-thickening fluid and $b < 1$ would describe a shear-thinning fluid. The power law for blood flow does not represent the yield stress of blood flow. The Herschel–Bulkley model extends the power law relationship to include a yield stress and can be represented as

$$\begin{aligned} \tau &= a\dot{\gamma}^b + \tau_y & \tau &\geq \tau_y \\ \dot{\gamma} &= 0 & \tau &\leq \tau_y \end{aligned} \quad (6.6)$$

where the variables in Eq. (6.6) represent the same quantities as discussed for Eqs. (6.1) and (6.5). This model is very similar to the Casson model for blood flow and has been used in many biological fluid flows.

Because plasma behaves as a Newtonian fluid (as shown in Fig. 6.6, when the hematocrit is set to 0), the non-Newtonian fluid properties are more than likely attributed to the cellular component of blood. Recall that by definition, plasma contains all of the dissolved solutes that are found in blood (e.g., proteins, ions, sugars, fats, etc.). The first contributing factor to non-Newtonian behavior is the ability of red blood cells, the majority of the cellular component, in the fluid phase to form aggregates termed *rouleaux* (Fig. 6.8). Interestingly, the presence of *rouleaux* in the blood depends on the shear rate at which the fluid is flowing, hematocrit, and temperature. At lower shear rates, *rouleaux* are more prevalent, likely because of the greater time that cells can come into contact with each other and/or proteins in the blood. It has been speculated that as the shear rate approaches zero, blood will act as a viscoelastic solid, because all of the red blood cells will form into one large aggregate. As you may recall from solid mechanics courses, viscoelastic solids have a definite yield stress, which may account for the yield stress of blood. In addition, at low shear rates, the formation of *rouleaux* consumes energy when they tumble through the fluid. This can be recorded as an effective increase in the viscosity of blood, whereas at higher shear rates, when the *rouleaux* break apart, the apparent viscosity of blood decreases.

A second contributing factor to the non-Newtonian behavior of fluids is the deformability of red blood cells. The deformability of red blood cells arises because of the composition of

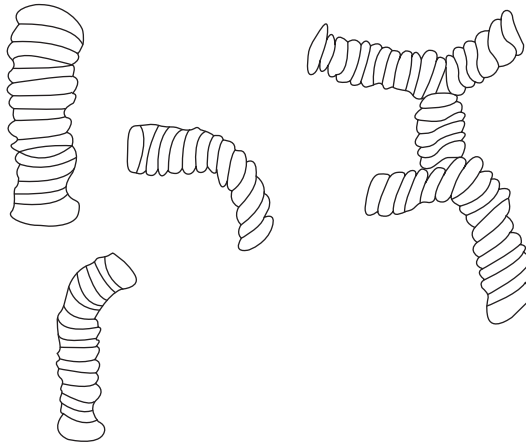


FIG. 6.8 Red blood cell aggregates termed *rouleaux*, which can form linear or branched structures. The number of red blood cells in a *rouleaux* can vary from 2 to approximately 50. Red blood cells in the microcirculation typically traverse through capillaries within *rouleaux* structures.

the cell membrane and the overall rigidity of the cytoskeleton. Although many model red blood cells as solid particles within the fluid phase, red blood cells exhibit many viscoelastic and fluid properties themselves. A report by Goldsmith investigated the effects of particle rigidity and particle concentration (or hematocrit) on the fluid's apparent viscosity. This report showed that at a shear rate sufficient to prevent aggregation ($>100 \text{ s}^{-1}$), a suspension consisting of rigid latex particles in water, rigid rubber discs in glycerol, red blood cells in blood, or sickled red blood cells in blood (all particles had a size similar to that of red blood cells) exhibited an increase in the apparent viscosity as the percent of particles within the fluid increased. However, for high hematocrit ratios, all suspensions, excluding those of normal red blood cells, approached an apparent viscosity of infinity, whereas normal red blood cells at a hematocrit of 0.9 approached a viscosity of 20 cP. This suggests that red blood cells can deform to allow for fluid motions to occur and even at very high concentrations of cells the presence of red blood cells does not completely impede motion. The data from this report is redrawn in Fig. 6.9. It also has been observed and shown that the deformability of red blood cells is a function of the red blood cell membrane and the intrinsic properties of the membrane. Unlike many droplets and suspended particles, the pressure that acts on the internal cell membrane and the external cell membrane must be equal because of the biconcave shape of the cell, if we assume that the bending rigidity of the cell membrane is negligible. Under this scenario, the cell membrane in the normal biconcave shape is under negligible (or zero) stress. The shape of the red blood cell also suggests that large deformations can be accomplished without stretching the cell membrane and without the input of significant energy. The packing density of red blood cells, because of the deformability and the unique shape, can be higher with less energy input than suspended particles.

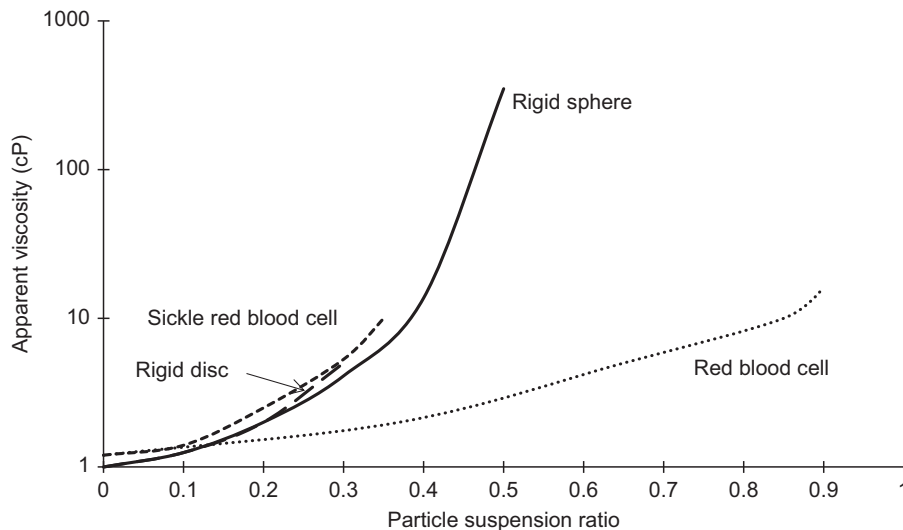


FIG. 6.9 Investigations to determine the apparent viscosity of a suspension at a given shear rate. It has been shown that as the particle suspension ratio (e.g., the hematocrit for blood) increases, the apparent viscosity of the solution also increases. Investigations into the mechanical properties of the red cell membrane have shown that the fluid properties of the membrane prevent a massive increase in apparent viscosity, with marginal increase in particle suspension ratio. Rigid spheres or rigid discs, with a similar size/area as red blood cells show this large increase in apparent viscosity with small changes in suspension ratio. Additionally, sickle red cells lose their fluid-like properties.

6.5 Pressure, flow, and resistance: arterial system

This and the following sections will reiterate some of the important formulas that govern the flow behavior within the arterial system and the venous system (Section 6.6) from the previous chapters. Our goal for these two sections is to discuss some of the common simplifying assumptions that are made when modeling flows through the arterial and the venous circulation. In the simplest case, the flow through a blood vessel (Q) is determined by the pressure difference across the vessel (ΔP) and the resistance to flow throughout the vessel (R). This relationship follows an Ohm's law type of formulation, where a driving force (ΔP , in our case) is proportional to the flow through the system (Q , in our case).

$$Q = \frac{\Delta P}{R} = \frac{P_1 - P_2}{R} \quad (6.7)$$

Under normal resting conditions, the blood flow rate is approximately 5 L/min. This means that all of the blood within the body traverses the circulatory system once a minute and that the flow through any given section of the cardiovascular tree must equate to 5 L/min. This statement assumes normal physiological flow conditions for an adult human. Pressure difference is something that we have discussed numerous times before in this text. Pressure is relatively easy to measure and is typically in units of millimeters of mercury. Recall that the pressure that we are discussing here is the driving force for flow and not the static pressure difference across the tissue. Resistance to flow, however, is something that cannot be measured; it can, however, be directly calculated from Eq. (6.7). Be cautioned that there are many properties that will affect Q and R , and Eq. (6.7) is overly simplified to some extent. Some of the assumptions that are built into Eq. (6.7) are that the fluid flow and fluid properties have no temporal variation and that there is a constant uniform circular cross-section within a rigid blood vessel.

Example 6.1

Calculate the resistance to blood flow within the descending aorta and the inferior vena cava. Assume that the pressure difference between the distal portion of the aortic arch and the iliac arteries is 20 mmHg. The pressure difference within the inferior vena cava is 3 mmHg. Assume that the flow rate through both vessels is 4.5 L/min.

Solution

Descending Aorta	Inferior Vena Cava
$R = \frac{\Delta P}{Q} = \frac{20 \text{ mmHg}}{4.5 \text{ L/min}}$	$R = \frac{\Delta P}{Q} = \frac{3 \text{ mmHg}}{4.5 \text{ L/min}}$
$R = 355.5 \text{ dyne} \cdot \text{s/cm}^5$	$R = 53.3 \text{ dyne} \cdot \text{s/cm}^5$

Example 6.1 illustrates that to maintain the same flow rate at a higher pressure gradient, the resistance to flow must be larger. If the resistance to flow was the same in the two cases illustrated in Example 6.1, the flow would have to be much greater with a larger pressure gradient; this is clearly an oversimplification of the biological processes, but it can provide some insight into the flow through the cardiovascular system and may be helpful in understanding other fluid mechanics principles that the reader may encounter.

A more useful approximation for volumetric flow rate (Q) is Hagen–Poiseuille’s law. The general Poiseuille solution is obtained by solving for the volumetric flow rate for laminar fluid flow within a cylindrical tube. Recall from Chapter 3 that the general velocity profile for pressure-driven cylindrical flow, with constant fluid properties and a rigid containing vessel, is given by

$$v_z(r) = \frac{R^2}{4\mu} \frac{\partial p}{\partial z} \left(\left(\frac{r}{R} \right)^2 - 1 \right)$$

The volumetric flow can be calculated by integrating the velocity profile over the cross-sectional area of the vessel, as in

$$\begin{aligned} Q &= \int_0^R 2\pi r v_z(r) dr = \int_0^R 2\pi r \left[\frac{R^2}{4\mu} \frac{\partial P}{\partial z} \left(\left(\frac{r}{R} \right)^2 - 1 \right) \right] dr = 2\pi \frac{R^2}{4\mu} \frac{\partial P}{\partial z} \int_0^R r \left[\left(\frac{r}{R} \right)^2 - 1 \right] dr \\ &= \frac{\pi R^2}{2\mu} \frac{\partial P}{\partial z} \int_0^R \left(\frac{r^3}{R^2} - r \right) dr = \frac{\pi R^2}{2\mu} \frac{\partial P}{\partial z} \left[\frac{r^4}{4R^2} - \frac{r^2}{2} \right]_0^R = \frac{\pi R^2}{2\mu} \frac{\partial P}{\partial z} \left[\frac{R^4}{4R^2} - \frac{R^2}{2} - 0 + 0 \right] \quad (6.8) \\ &= -\frac{\pi R^4}{8\mu} \frac{\partial P}{\partial z} \end{aligned}$$

As the partial derivative in space approaches the tube length (which is what can be measured), the spatial partial derivative of pressure becomes measurable with conventional equipment. Mathematically this can be represented as

$$\partial z \rightarrow L: \frac{\partial P}{\partial z} \rightarrow -\frac{\Delta P}{L}$$

where

$$\Delta P = P_1 - P_2$$

and

$$\partial P = P_2 - P_1$$

Therefore the volumetric flow rate can be approximated as

$$Q = \frac{\pi \Delta P R^4}{8 \mu L} \quad (6.9)$$

where $\Delta P/L$ is the pressure gradient across a tube of length L and radius R . To clearly state the assumptions that were used to derive this formulation, the fluid within the tube must have a constant viscosity of μ and a uniform circular cross-sectional area over the entire length, L . Additionally, none of the fluid properties can vary with time; however, this formula can be used for one discrete period of a temporally varying flow. As we have seen, the Hagen–Poiseuille solution is derived from integrating the velocity of the fluid (solved by using the Navier–Stokes equations) with respect to blood vessel cross-sectional area. In other words, this is a weighted average (weighted based on area) for each section of fluid that has the same velocity. The lamina of fluid alongside the vessel wall would be characterized by the circumference of the vessel (or total arc length of an irregularly shaped container) and would have an assumed velocity of zero. The lamina along the centerline of a circular vessel would have a differential circular area characterized by the maximum velocity of the fluid. Using the generalized integral relationship, one can derive a formula for volumetric flow rate for any shaped container under pressure-driven flow. From Eq. (6.9), one can define resistance R from Eq. (6.7) as

$$R = \frac{8 \mu L}{\pi R^4} \quad (6.10)$$

What is interesting to note about Eqs. (6.9) and (6.10) is that small changes in the vessel radius cause very large changes in the flow rate by altering the resistance significantly. A doubling of the blood vessel radius would be associated with a 16-fold increase in the volumetric flow rate throughout the vessel, assuming that all of the other parameters remain the same. This is not a trivial or hypothetical discussion, because radius doubling is quite possible when a blood vessel passes from a maximally constricted state to a maximally dilated state. It is common for the resistance blood vessels (arterioles) to experience changes in vessel diameter on the order of four fold (again this would be maximally constricted to maximally dilated), which theoretically would increase the volumetric flow rate 256 times. In addition, what one can infer from this is that the blood vessel radius does not have to change significantly to increase (or decrease) flow to a region that has nonnormal (low or high) tissue oxygenation. This is important for energy usage (or consumption) and storage for the smooth muscle cells (you may recall from other classes that the cell cannot effectively store energy in the form of ATP, it is almost a use-it or lose-it scenario). If the blood flow rate did not change rapidly with small changes in vessel diameter, blood vessels would need to dilate or constrict significantly to counterbalance the tissue oxygenation level changes. These changes would be associated with large energy demands that would effectively deplete the smooth muscle cells of energy, and then they would be unable to respond to changes in the tissue needs in the near future. Instead, the biological system is designed so that minimal energy is required to allow for changes in blood flow. Furthermore, these changes can be accomplished very rapidly.

Example 6.2

Calculate the volumetric flow rate within an arteriole with a length of 100 μm and a radius of 35 μm . The pressure difference across the arteriole is 10 mmHg. Also calculate the change in radius needed to reduce the volumetric flow rate by 5% and to increase the volumetric flow rate by 10%. In this vessel, the effective blood viscosity is 2.8 cP. Assume that when the radius changes there are no other changes in the other fluid parameters.

Solution

Using Hagen–Poiseuille’s formulation to calculate the volumetric flow rate, we get

$$Q = \frac{\pi \Delta P R^4}{8 \mu L} = \frac{\pi (10 \text{ mmHg}) (35 \mu\text{m})^4}{8 (2.8 \text{ cP}) (100 \mu\text{m})} = 0.168 \text{ mL/min}$$

5% of this flow rate is 0.00842 mL/min; therefore

5% Reduction	10% Increase
$Q = 0.160 \text{ mL/min}$	$Q = 0.185 \text{ mL/min}$
$R = \sqrt[4]{\frac{8Q\mu L}{\pi \Delta P}}$	$R = \sqrt[4]{\frac{8Q\mu L}{\pi \Delta P}}$
$= \sqrt[4]{\frac{8(0.160 \text{ mL/min})(2.8 \text{ cP})(100 \mu\text{m})}{\pi(10 \text{ mmHg})}}$	$= \sqrt[4]{\frac{8(0.185 \text{ mL/min})(2.8 \text{ cP})(100 \mu\text{m})}{\pi(10 \text{ mmHg})}}$
$= 34.5 \mu\text{m}$	$= 35.8 \mu\text{m}$
$\Delta R = 0.5 \mu\text{m}$ (1.5% change)	$\Delta R = 0.8 \mu\text{m}$ (2.3% change)

The previous problem illustrates that relatively small changes in an arteriole radius (e.g., a 1.5% change) can significantly affect the flow rate (5% change). The take-home message is that very small changes in vessel diameter can cause large changes in flow.

We would like to revisit the Casson model of blood flow to show that the volumetric flow rate associated with this more accurate approximation of blood rheology obtains a solution that is analogous to the Hagen–Poiseuille solution. If we compute the volumetric flow rate of the Casson velocity profile (Eq. (6.4)), as given by

$$Q = 2\pi \int_0^R u(r) r dr$$

we obtain

$$Q = \frac{\pi R^4}{8\eta} \frac{dp}{dx} F(\Psi) \quad (6.11)$$

The function of Ψ is defined as

$$F(\Psi) = - \left(1 - \frac{16}{7}\Psi^{0.5} + \frac{4}{3}\Psi - \frac{1}{21}\Psi^4 \right) \quad (6.12)$$

and

$$\Psi = \left(\frac{2\tau_y}{R} \right) \left(-\frac{dp}{dx} \right)^{-1} \quad (6.13)$$

Comparing Eqs. (6.9) and (6.11), we can see that by using the Casson model of blood flow, the volumetric flow rate becomes a function of the fluid yield shear stress. This would be anticipated because if the shear stress applied to the fluid was below this threshold, the fluid would not flow or would move as a rigid body. However, there are distinct similarities between Eqs. (6.9) and (6.11). If we can assume that our fluid has a negligible yield stress, the Hagen–Poiseuille solution may be applicable (if the other assumptions are valid). Also note that if the fluid has no yield stress ($\tau_y = 0$), we would obtain the exact Hagen–Poiseuille solution as shown in Eq. (6.8) (if $\tau_y = 0$, then $\Psi = 0$ and $F(\Psi) = -1$).

We have already learned that the pressure variation in a normal human aorta is approximately 80 to 120 mmHg. A comparison between blood pressure and mass shows that as the mass of the animal increases, the mean systolic blood pressure also increases (Fig. 6.10). As we discussed with changes in heart rate based on animal mass, correlations for this variation can be made based on the activities and evolutionary history of the animals.

6.6 Pressure, flow, and resistance: venous system

The mathematical formulation that was derived in the previous section for volumetric flow rate through the arterial system can be used to approximate the volumetric flow rate in the

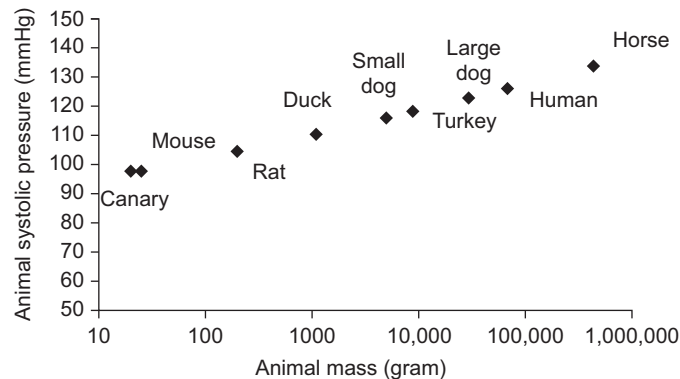


FIG. 6.10 The relationship between animal mass and mean systolic pressure. As the mass of the animal increases, there is a general increase in systolic pressure. The relationship between these two measurements can be correlated to many different properties of the animal, as described in the text.

venous system, as well. However, it is critical here to determine whether the assumptions that have been made in deriving Hagen–Poiseuille’s law are still valid. In most instances, veins and venules are not circular, and therefore, this formulation will provide only an approximation to the volumetric flow rate. However, like in arteries, the approximate radius along the vessel length is relatively constant between converging branches. We want to remind the reader that veins are not as rigid as arteries and experience a much lower pressure, compared with arteries, and thus the cross-sectional area can change drastically and is typically irregular. Therefore, let us revisit the derivation of the volume flow rate. Using cylindrical coordinates the velocity profile within a vein would become

$$v_z(r) = \frac{r^2}{4\mu} \frac{\partial P}{\partial z} + c_1 \ln(r) + c_2 \quad (6.14)$$

by solving the cylindrical Navier–Stokes equations (if $v_z(r)$ is a function of radius only) and assuming that flow is only pressure driven. The integration constants can be found only if the boundary conditions of the particular flow conditions are known (we typically assumed that the shear rate along the centerline was zero, $\frac{dv_z}{dr}(r = 0) = 0$ and that the velocity along the wall was zero $v_z(r = R) = 0$). When the cross-sectional area of the object is not regular or the vein appears to be a randomly shaped object, the second boundary condition may become difficult to define and may become a function of θ . Furthermore, if the cross-sectional area is not constant over the tube length, the centerline of the channel varies along the axial length of the channel, making the first boundary condition difficult to determine. For instance, in Fig. 6.11, which depicts an irregularly shaped vein, the blood velocity along the entire wall is zero but the radial coordinate that describes the wall is not constant with changes in the angular, θ , direction. Therefore the solution for the volumetric flow rate would become

$$\int_A \left(\frac{r^2}{4\mu} \frac{\partial p}{\partial z} + c_1 \ln(r) + c_2 \right) dA \quad (6.15)$$

which may be approximated for laminas of a particular thickness if the velocity can be assumed to be uniform within that lamina and the velocity changes with θ are negligible.

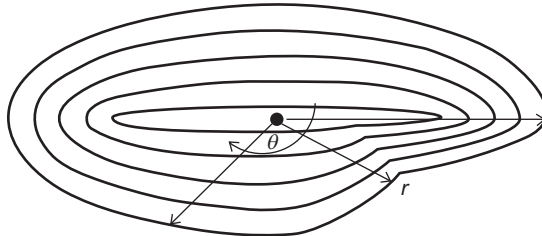


FIG. 6.11 Schematic of a vein with a nonstandard geometry, shown by varying radial’s length at various angles, θ . The method of choosing laminae of known average velocities still applies to these vessels; however, one would need to account for the different areas of each lamina. Additionally, one would need to consider whether or not the fluid properties change as a function of the different radial directions.

This would use a weighted average formulation. The key here is that we must be able to neglect changes in velocity in the angular direction to apply this type of approximation and that we must be able to approximate sections of the vessel area with a “uniform” velocity (e.g., small laminae with similar velocity contributions and a somewhat calculable area).

Example 6.3

Calculate the average volumetric flow rate for the following blood vessel that is represented as an ellipse. The blood vessel has known average velocity values and geometrical values for specific laminae of fluid (r_L is the radius for the long axis and r_S is the radius for the short axis, Fig. 6.12).

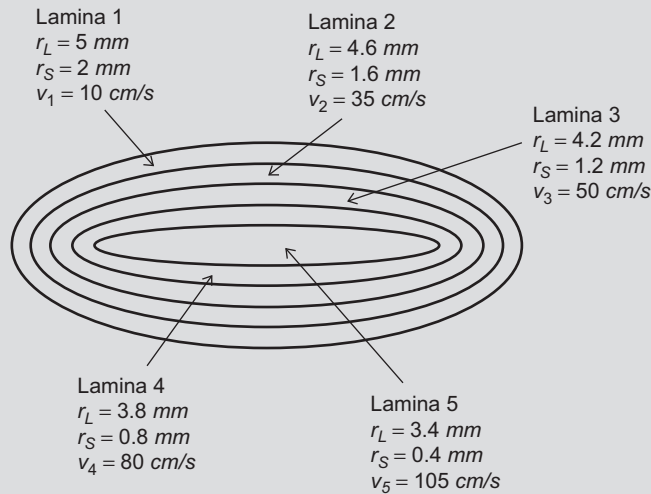


FIG. 6.12 Figure associated with Example Problem 6.3.

Solution

First, we will calculate the area associated with each fluid lamina

$$\begin{aligned}
 A_1 &= \pi(5 \text{ mm})(2 \text{ mm}) - \pi(4.6 \text{ mm})(1.6 \text{ mm}) = 8.29 \text{ mm}^2 \\
 A_2 &= \pi(4.6 \text{ mm})(1.6 \text{ mm}) - \pi(4.2 \text{ mm})(1.2 \text{ mm}) = 7.29 \text{ mm}^2 \\
 A_3 &= \pi(4.2 \text{ mm})(1.2 \text{ mm}) - \pi(3.8 \text{ mm})(0.8 \text{ mm}) = 6.28 \text{ mm}^2 \\
 A_4 &= \pi(3.8 \text{ mm})(0.8 \text{ mm}) - \pi(3.4 \text{ mm})(0.4 \text{ mm}) = 5.28 \text{ mm}^2 \\
 A_5 &= \pi(3.4 \text{ mm})(0.4 \text{ mm}) = 4.27 \text{ mm}^2
 \end{aligned}$$

Using the average velocity for each lamina, the volumetric flow rate can be found

$$\begin{aligned}
 Q &= Q_1 + Q_2 + Q_3 + Q_4 + Q_5 = v_1 A_1 + v_2 A_2 + v_3 A_3 + v_4 A_4 + v_5 A_5 \\
 Q &= 8.29 \text{ mm}^2(10 \text{ cm/s}) + 7.29 \text{ mm}^2(35 \text{ cm/s}) + 6.28 \text{ mm}^2(50 \text{ cm/s}) \\
 &\quad + 5.28 \text{ mm}^2(80 \text{ cm/s}) + 4.27 \text{ mm}^2(105 \text{ cm/s}) = 913.7 \text{ mL/min}
 \end{aligned}$$

Note that this type of approach likely oversimplifies the flow conditions, but would be necessary if the assumptions made when deriving the Hagen–Poiseuille formulation cannot be met.

Additionally, there are some known solutions for noncircular channels, which are commonly taught in more advanced fluid mechanics and/or biofluid mechanics courses. For interest, we include some of these formulas here, without derivations, so readers can compare results from various fluid parameters in circular channels with noncircular channels. If the reader is interested, derivations can be found in many fluid mechanics text, some of which are noted in our reference lists and Further Readings. For elliptical cross-sectional channels, where

$$\frac{y^2}{a^2} + \frac{z^2}{b^2} \leq 1$$

the velocity distribution (in the x -direction) and the volume flow rate have been found to equate to

$$u(y, z) = \frac{1}{2\mu} \left(-\frac{d\vec{p}}{dx} \right) \frac{a^2 b^2}{a^2 + b^2} \left(1 - \frac{y^2}{a^2} - \frac{z^2}{b^2} \right)$$

$$Q = \frac{\pi}{4\mu} \left(-\frac{d\vec{p}}{dx} \right) \frac{a^3 b^3}{a^2 + b^2}$$

In these equations the principal radii of the elliptical cross-sectional area are defined as a and b . Similar solutions for a concentric circular annulus have been developed (e.g., a torus shape in cross-section). For these flow situations, the inner radius b must be less than the outer radius a and the radius of interest for a particular flow conditions can be defined as

$$b \leq r \leq a$$

Under these cases, the velocity distribution (in the r -direction) and the volume flow rate have been found to be equal to

$$u(r) = \frac{1}{4\mu} \left(-\frac{d\vec{p}}{dx} \right) \left[a^2 - r^2 + (a^2 - b^2) \ln \frac{\left(\frac{a}{r} \right)}{\left(\frac{b}{a} \right)} \right]$$

$$Q = \frac{\pi}{8\mu} \left(-\frac{d\vec{p}}{dx} \right) \left[a^4 - b^4 - \frac{(a^2 - b^2)^2}{\ln \left(\frac{a}{b} \right)} \right]$$

Likewise, solutions for an eccentric annulus have been developed. These flows are of interest in biofluids problems in which a solid structure may be threaded through the vascular system and that structure is not centered in the flow channel. To define the geometry, an eccentric annulus has an interior (solid) circle of radius b and an external circle of radius a , which can support flow. The center of the interior and exterior are off-set by a linear distance

of c . In the case that $c = 0$, the solution will equate exactly to the concentric annulus. Under these eccentric annulus conditions the volumetric flow rate can be found from

$$Q = \frac{\pi}{8\mu} \left(-\frac{d\vec{p}}{dx} \right) \left[a^4 - b^4 - \frac{4c^2 M^2}{\beta - \alpha} - 8c^2 M^2 \sum_{n=1}^{\infty} \frac{ne^{-n(\beta+\alpha)}}{\sinh(n\beta - n\alpha)} \right]$$

where

$$M = (F^2 - a^2)^{\frac{1}{2}} \quad F = \frac{a^2 - b^2 + c^2}{2c}$$

$$\alpha = \frac{1}{2} \ln \frac{F+M}{F-M} \quad \beta = \frac{1}{2} \ln \frac{F-c+M}{F-c-M}$$

One interesting fluid parameter is to evaluate the volumetric flow rate for eccentric annulus and a concentric annulus. The ratio of the volumetric flow rates can be shown to equate to something relatively simple for the ratio of the flow rate through an eccentric annulus to a concentric annulus (the radii a and b must be the same under these conditions)

$$\frac{Q_{\text{eccentric annulus}}}{Q_{\text{concentric annulus}}} = \frac{Q_{c \neq 0}}{Q_{c=0}} = 1 + \frac{3}{2} \left(\frac{c}{a-b} \right)^2$$

The exact solutions for volumetric flow rate and velocity distribution have been obtained for many different shapes, many of which are not applicable to the majority of biofluid mechanics questions. These also tend to be quite complicated solutions (as can be seen from the three relatively simple examples given previously). Many of these more complicated solutions can be found in classic graduate-level fluid mechanics textbooks, which are referenced throughout this book.

6.7 Windkessel model for blood flow*

The previous two sections discussed one of the simplest ways to model the flow of blood through the circulation, that is, by relating only the pressure, flow, and resistance within particular sections of the vascular tree. However, this analysis is somewhat overly simplified considering the magnitude of biological phenomenon that can occur that can potentially alter the flow properties through blood vessels. In addition, this analysis ignores the physical properties of the blood vessel, changes in those same properties, and that the cells and their functions and interactions cannot be modeled very accurately (or at all) within these approaches. Many of the original theories of blood flow focused on the arterial circulation and the majority of them started with the assumption that the arterial circulation can be modeled as perfectly elastic pressure chambers. The rationale for this assumption was the knowledge that blood flow out of the heart was pulsatile but blood flow into the tissues

*This section is considered advanced and can be skipped without a loss of continuity.

was largely nonpulsatile. Therefore, the vessels that transport blood from the heart to the peripheral tissue must have the ability to dampen the pulsatility introduced into the circulation by the heart contraction. The most simplistic of these models would make the assumption of a purely perfect elastic pressure chamber. This type of analysis is referred to as the *Windkessel model*, after the German word for air compression chamber. In classic fluid mechanics applications, air compression chambers can be used to damp pulsatility within the flow field.

The first assumption of the Windkessel model is that the arterial tree is composed of a series of interconnected tubes, each with its own capacity to store blood. The inflow of each tube is provided by a time-varying inflow rate. It is assumed that the outflow of each tube is steady and that the outflow properties are governed by the inflow, the overall blood vessel resistance, the capacity for the blood vessel to accommodate more blood, the properties of the blood vessel, and the pressure gradient across the vessel, only. An overall schematic of arterial flow based on the Windkessel model assumptions is shown in Fig. 6.13. To begin an analysis of blood flow using the Windkessel model, we start with a mass balance across the volume of interest. In this case the mass balance can be summarized as

$$\text{Inflow} - \text{Outflow} = \text{Time Rate of Change of Blood Accumulation} \quad (6.16)$$

$$Q_i(t) - Q_o = \frac{da}{dt}$$

Under these conditions, the inflow would need to be a given and would typically be represented as a function of time. If we assume that the outflow is into the peripheral tissue, where the pulsatility is damped, the Hagen–Poiseuille formulation can be used to quantify the outflow rate as (although this equation has its own intrinsic assumptions)

$$Q_o = \frac{\Delta P}{R}$$

The time rate of change of blood accumulation is a little more complex to analyze. First, we would have to be able to relate the pressure and volume changes to the mechanical properties of the blood vessel. This is typically quantified in terms of a distensibility value (D), which is traditionally defined as

$$D = \frac{dV}{d\Delta P} \quad (6.17)$$

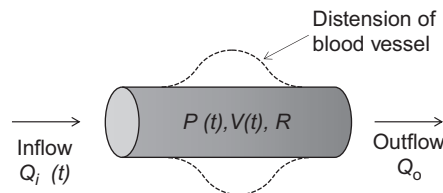


FIG. 6.13 Schematic of a distensible arterial tree that can accommodate increases in blood flow by an increased volume. If we assume that the outflow rate has little variation in time, we can analyze this type of vessel using a Windkessel approach as outlined in the text.

The time rate of change of blood accumulation (a) can be defined from the time rate of change of the blood vessel volume. Using some mathematical manipulations and substitutions the rate of accumulation can equate to

$$\frac{da}{dt} = \frac{dV}{dt} = \frac{dV}{d\Delta P} \frac{d\Delta P}{dt} = D \frac{d\Delta P}{dt} \quad (6.18)$$

Therefore the overall Windkessel formulation, with the assumption that the outflow has no pulsatility, can be mathematically represented as

$$Q_i(t) - \frac{\Delta P}{R} = D \frac{d\Delta P}{dt} \quad (6.19)$$

This equation is a differential equation in terms of time and pressure. Therefore, to solve this problem, the inflow function would need to be given to obtain a solution for how the pressure varies as a function of time through the section of vessel that is being analyzed.

Example 6.4

Calculate the pressure variation in the arterial circulation using the Windkessel model for blood flow. Assume that the inflow pressure waveform can be represented by the following piecewise continuous function.

$$Q_i = \begin{cases} \sin\left(\frac{\pi t}{0.3}\right) & 0 \leq t \leq 0.3s \\ 0 & 0.3 < t \leq 0.9s \end{cases}$$

Assume that the pressure gradient is equal to P_S at the beginning of the systolic phase of the flow (first phase of the piecewise continuous function, e.g., when t is 0.3 seconds or less) and P_D at the beginning of the diastolic phase of the flow (second phase of the piecewise continuous function). The distensibility and resistance are constant values over the time of this problem.

Solution

First, we will set up the governing equation for this system and write the known initial conditions for the *systolic phase* of the waveform. We have assumed that the outflow has no pulsatility because this section of the blood vessel will dampen any incoming pulsatility before the outflow.

$$\begin{aligned} Q_i(t) - \frac{\Delta P}{R} &= D \frac{d\Delta P}{dt} \\ \sin\left(\frac{\pi t}{0.3}\right) - \frac{\Delta P}{R} &= D \frac{d\Delta P}{dt} \\ \Delta P(0) &= P_S \end{aligned}$$

This can be rewritten as the following, which may help with the analytical solution.

Example 6.4 (cont'd)

$$\frac{d\Delta P}{dt} + \frac{\Delta P}{DR} - \frac{1}{D} \sin\left(\frac{\pi t}{0.3}\right) = 0$$

This equation is a first-order linear differential equation, which can be solved with various methods. We have chosen to use the Laplace transform and the convolution principle to arrive at a solution (if you are more familiar with other solution methods, feel free to apply those instead). We will not go through all of the calculations here, but some of the major steps are shown. After taking the Laplace transform and rearranging the terms, we get

$$\overline{\Delta P} = \frac{1}{s + \left(\frac{1}{DR}\right)} \left(\frac{\pi/0.3}{s^2 + \left(\frac{\pi}{0.3}\right)^2} \right) + \frac{P_s}{s + \left(\frac{1}{DR}\right)}$$

where $\overline{\Delta P}$ represents the time-varying pressure waveform in the Laplace domain. The second term on the right side of the equation has a relatively common inverse Laplace transform, but the first term on the right side requires the use of the convolution principle to find its inverse Laplace transform. In this case the convolution of the first term on the right side can be represented as

$$\Delta P(t)_{\text{term 1-RHS}} = \frac{1}{D} \left[e^{-\frac{t}{DR}} * \sin\left(\frac{\pi t}{0.3}\right) \right] = \frac{1}{D} \int_0^t e^{-\frac{t-\tau}{DR}} \sin\left(\frac{\pi \tau}{0.3}\right) d\tau$$

If one works through this convolution, which would require two “integration by parts stages,” one finds that this equation “simplifies” to

$$\frac{1}{1 + (0.3/DR\pi)^2} \left[\left(\frac{-0.3}{\pi} \right) e^{\frac{t}{DR}} \cos\left(\frac{\pi t}{0.3}\right) + \frac{1}{DR} \left(\frac{0.3}{\pi} \right)^2 e^{\frac{t}{DR}} \sin\left(\frac{\pi t}{0.3}\right) + \frac{0.3}{\pi} \right]$$

Incorporating this term as the inverse Laplace transform of the first term on the right side of the equation in the Laplace domain, we can get a function for the change in pressure with respect to time, during the systolic phase of the cardiac cycle. This includes the inverse Laplace transform of the second term on the right side of the equation as well (which is the last quantity in the forthcoming equation). The time-varying pressure waveform, transformed back into the time domain from the Laplace domain is

$$\Delta P(t)_{\text{systolic}} = \frac{1}{1 + (0.3/DR\pi)^2} \left[\left(\frac{-0.3}{\pi} \right) e^{\frac{t}{DR}} \cos\left(\frac{\pi t}{0.3}\right) + \frac{1}{DR} \left(\frac{0.3}{\pi} \right)^2 e^{\frac{t}{DR}} \sin\left(\frac{\pi t}{0.3}\right) + \frac{0.3}{\pi} \right] + P_s e^{-t/DR}$$

Using a similar procedure for the diastolic phase, we start by writing the governing equation

$$\begin{aligned} Q_i(t) - \frac{\Delta P}{R} &= D \frac{d\Delta P}{dt} \\ 0 - \frac{\Delta P}{R} &= D \frac{d\Delta P}{dt} \\ \Delta P(0.3) &= P_D \end{aligned}$$

Example 6.4 (*cont'd*)

This differential equation can be solved by using a separation of variable method as follows

$$\begin{aligned}
 -\int_{0.3}^t \frac{dt}{DR} &= \int_{0.3}^P \frac{d\Delta P}{\Delta P} \\
 -\left(\frac{t-0.3}{DR}\right) &= \ln\left(\frac{P}{P_D}\right) \\
 P(t)_{\text{diastolic}} &= P_D e^{-(t-0.3)/DR}
 \end{aligned}$$

Therefore, the pressure waveform over one cardiac cycle can be represented as

$$P(t) = \begin{cases} \frac{1}{1 + (0.3/DR\pi)^2} \left[\left(\frac{-0.3}{\pi}\right) e^{\frac{t}{DR}\pi} \cos\left(\frac{\pi t}{0.3}\right) + \frac{1}{DR} \left(\frac{0.3}{\pi}\right)^2 e^{\frac{t}{DR}\pi} \sin\left(\frac{\pi t}{0.3}\right) + \frac{0.3}{\pi} \right] + P_s e^{-t/DR} & 0 \leq t \leq 0.3 \\ P_D e^{-(t-0.3)/DR} & 0.3 < t \leq 0.9 \end{cases}$$

The function that was obtained for Example 6.4 can be plotted against time for one cardiac cycle to see how the pressure waveform changes as a function of the variables (Fig. 6.14). We plotted various cases, but what can be observed is that (1) there is essentially no transition between the systolic and diastolic pressure waveforms under normotensive conditions; (2) under hypertensive conditions, the curves are slightly changed (and shifted upward) and there is a small transition at systolic and diastolic values (this can be removed by altering the peak systolic and diastolic values, which we did not attempt to do to smooth the curve); (3) with an increased distensibility (increased by 50%), the pressure does not dissipate as quickly because the vessel is less likely to accommodate changes in the pressure forces, and (4) with a decreased distensibility (decreased by 50%), the pressure dissipates quickly because the vessel is more likely to accommodate changes in the pressure forces. Note that the jumps at the beginning of diastole are caused because we left the diastolic value the same for all of the plotted cases and thus will only be “smooth” for the normotensive case. However, if one could change the pressure waveform curves to piecewise continuous functions (by finding a peak diastolic value that matches the pressure value at the end of systole), then the changes in the pressure waveform curves would be more pronounced.

Although the Windkessel model can provide us with analysis techniques that can be used for flow through the arterial tree, there are a number of limitations to this modeling approach. First, the Windkessel model assumes that changes to the pressure waveforms are transmitted instantaneously (e.g., there is no wave propagation) and that reflectance of the waveform does not occur (we did not include a bifurcation in this model, but could). Additionally, all elastic properties of the blood vessel are summarized in the distensibility and need to be known. The blood vessels cannot exhibit viscoelastic properties. We also assumed that the resistance and the distensibility were not time varying (e.g., include the viscoelastic properties). The Windkessel model can be extended to these more complex scenarios but

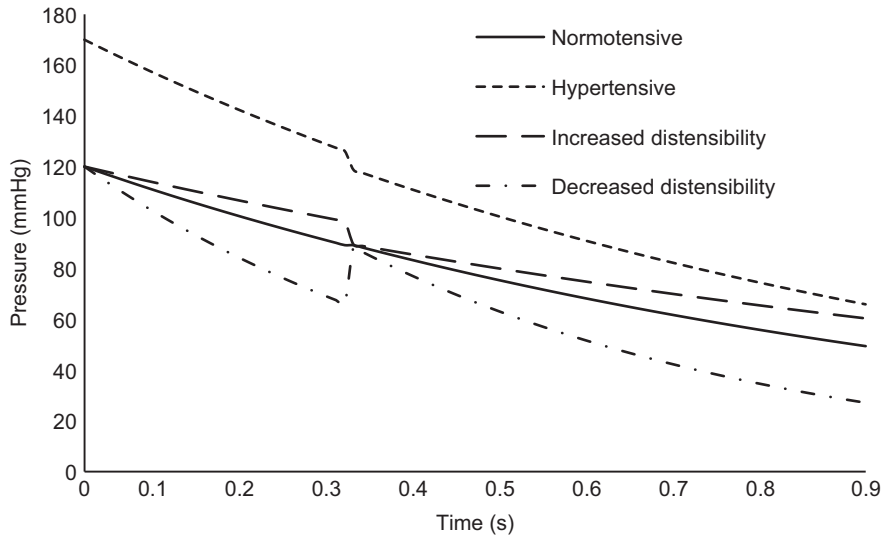


FIG. 6.14 Figure associated with the Example Problem 6.4. Note that the pressure values were set to $P_S = 120$ mmHg and $P_D = 80$ mmHg for all cases, except the hypertensive case ($P_S = 170$ mmHg and $P_D = 120$ mmHg). The distensibility was either increased or decreased by 50% to arrive at the other curves.

the computations associated with the model would likely need computational algorithms to solve. However, as with some of the earlier models, the Windkessel model provides a somewhat accurate approximation of the pressure variations in the arterial tree.

6.8 Wave propagation in arterial circulation

Wave propagation in arteries is primarily concerned with the displacement of the arterial wall in response to the progression of pressure/velocity waves through the blood vessel. This displacement is primarily due to the elasticity of the vessel wall combined with the large pressure variances observed in the arterial tree. To fully represent this condition, a fairly complex set of mathematical equations must be solved simultaneously. This solution would describe an instance of fluid structure interactions, where the fluid forces impact the wall and the wall responds to these changes (solutions that make few assumptions are discussed in Chapter 15). Additionally, the recoil, motion, and other mechanical properties of the vessel wall will affect the flow conditions. This coupling occurs at all instances in time and may have drastic effects on the overall fluid conditions. To begin to understand the concepts of wave propagation, let us first consider a blood vessel that is cylindrical and straight with wall mechanical properties that are homogeneous and elastic. Also, we will first make the assumption that the fluid is incompressible, inviscid, and relatively slow (in the main direction of flow). A pressure pulse at one end of the blood vessel will cause a geometrical change in the vessel cross-sectional area that propagates along the tube length at a particular speed. The speed of this propagation depends on the mechanical properties of the fluid and the blood vessel wall. In most instances, the wavelength is much larger than the wave amplitude, which allows us to assume that the flow velocity is still one-dimensional (1D).

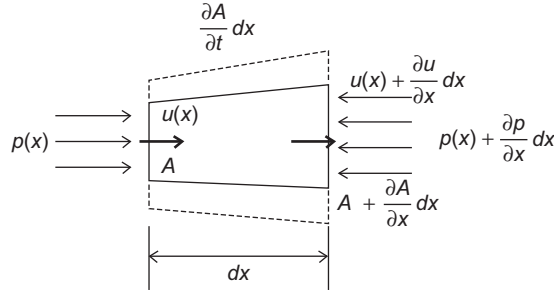


FIG. 6.15 Wave propagation within a deformable homogenous artery. With a deformable boundary, one would need to take into account the change in area, with time, of the fluid element. The material properties of the arterial wall need to be included within this formulation as well.

If the amplitude of the wave is large, with respect to the wavelength, fluid would need to enter/leave the space created/removed when the wave passed through the blood vessel wall, and this velocity typically would not be in the same direction as the majority of the fluid flow. Therefore, a coupled Navier–Stokes solution would be required to determine the velocity profile (e.g., instead of solving the Navier–Stokes in one direction, you would need to solve the problem in multiple directions).

Combining all of these assumptions and using the continuity equation and the Navier–Stokes equation, one can determine the speed of wave propagation in an artery. First we should consider the forces acting on the blood vessel during the pressure pulse through the vessel (Fig. 6.15). We will assume that the forces balance in the y -direction, and therefore, they are not considered on this figure. In the x -direction, the summation of the pressure forces is

$$\sum F_x = p_{\text{inlet}}A_{\text{inlet}} - p_{\text{outlet}}A_{\text{outlet}} + p_{\text{walls}}A_{\text{walls}}$$

$$p(x)A - \left[p(x) + \frac{\partial p}{\partial x} dx \right] \left[A + \frac{\partial A}{\partial x} dx \right] + p(x) \frac{\partial A}{\partial x} dx = -A \frac{\partial p}{\partial x} dx \quad (6.20)$$

if the second-order differential terms are ignored. The pressure acting on the walls may be a component of the pressure forces that act perpendicular to the flow. Using Newton's second law of motion, the net force acting on a differential element is equal to the mass multiplied by the acceleration of the object. Writing this in equation form, we get (using density/volume in lieu of mass)

$$-A \frac{\partial p}{\partial x} dx = (\rho A dx) \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} \right)$$

Rearranging terms we can get

$$0 = \frac{1}{\rho} \frac{\partial p}{\partial x} + \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} \quad (6.21)$$

which is a simplified form of the Navier–Stokes equation (weight acts in the y -direction on this figure but can be extended to other directions as needed). The conservation of mass on this element must take into account the increase in area of the element during time. Assuming the density remains constant within the entire element (e.g., our assumption that the fluid is incompressible), conservation of mass states (again neglecting second-order terms), where u is the x -velocity

$$uA = \left(u + \frac{\partial u}{\partial x}dx\right)\left(A + \frac{\partial A}{\partial x}dx\right) + \frac{\partial A}{\partial t}dx$$

$$uA = uA + u\frac{\partial A}{\partial x}dx + A\frac{\partial u}{\partial x}dx + \frac{\partial A}{\partial t}dx \quad (6.22)$$

$$u\frac{\partial A}{\partial x} + A\frac{\partial u}{\partial x} + \frac{\partial A}{\partial t} = \frac{\partial A}{\partial t} + \frac{\partial}{\partial x}(uA) = 0 \quad (6.23)$$

The first term in Eq. (6.22) is the inflow conservation of mass balance, the second term is the outflow mass balance, and the last term accounts for the increase in area as a function of time. To determine the wave propagation throughout the blood vessel, the material properties of the vessel wall must be known and related to the fluid properties. In some instances, we can make the assumption that the changes in the blood vessel radius (r_i) is linearly proportional to the blood pressure acting on the vessel wall (p_i), using the following relationship

$$r_i = r_{i,0} + \alpha p_i \quad (6.24)$$

where $r_{i,0}$ is the radius of the blood vessel at a zero external pressure and α is a constant that describes the material properties of the blood vessel. Note that Eq. (6.24) may not be the best representation of how the vessel geometry is altered by pressure under other conditions. As the complexity of this relationship increases, the mathematics that describe the relationship and mathematics required to solve the relationships will likely increase as well. Eqs. (6.21), (6.23), and (6.24) govern the wave propagation speed throughout a blood vessel (with the assumptions that we have made, note that Eq. (6.24) is overly simplifying the biological mechanical properties/responses to forces, but this gives us a starting point for the analysis of the wave propagation through the vessel). Substituting the area into Eq. (6.23) and remembering that the fluid velocity is relatively slow, Eqs. (6.21) and (6.23) simplify to

$$0 = \frac{1}{\rho} \frac{\partial p}{\partial x} + \frac{\partial u}{\partial t} \quad (6.25)$$

$$0 = \frac{\partial(\pi r_i^2)}{\partial t} + \frac{\partial}{\partial x}(u\pi r_i^2) = 2\pi r_i \frac{\partial r_i}{\partial t} + u\pi \frac{\partial r_i^2}{\partial x} + \pi r_i^2 \frac{\partial u}{\partial x} = 2\pi r_i \frac{\partial r_i}{\partial t} + \pi r_i^2 \frac{\partial u}{\partial x} = \frac{2}{r_i} \frac{\partial r_i}{\partial t} + \frac{\partial u}{\partial x} \quad (6.26)$$

For clarity, the two appropriate assumptions are that the blood velocity is close to zero ($u = 0$) and that the wave amplitude is much smaller than the wavelength. Combining Eq. (6.24) with Eq. (6.26), we get

$$0 = \frac{2}{r_i} \frac{\partial r_i}{\partial t} + \frac{\partial u}{\partial x} = \frac{2}{r_i} \frac{\partial}{\partial t} (r_{i,0} + \alpha p_i) + \frac{\partial u}{\partial x} = \frac{2\alpha}{r_i} \frac{\partial p_i}{\partial t} + \frac{\partial u}{\partial x} \quad (6.27)$$

To solve this in the form of the wave equation, we must take the temporal derivative of Eq. (6.27) and subtract this from the spatial derivative of Eq. (6.25). With some algebraic modifications of the proportionality constants, we can get the wave speed (c)

$$\begin{aligned} \frac{\partial}{\partial x} \left[0 = \frac{1}{\rho} \frac{\partial p_i}{\partial x} + \frac{\partial u}{\partial t} \right] &\rightarrow 0 = \frac{1}{\rho} \frac{\partial^2 p_i}{\partial x^2} + \frac{\partial^2 u}{\partial x \partial t} \\ \frac{\partial}{\partial t} \left[0 = \frac{2\alpha}{r_i} \frac{\partial p_i}{\partial t} + \frac{\partial u}{\partial x} \right] &\rightarrow 0 = \frac{2\alpha}{r_i} \frac{\partial^2 p_i}{\partial t^2} + \frac{\partial^2 u}{\partial t \partial x} \\ 0 = \frac{1}{\rho} \frac{\partial^2 p_i}{\partial x^2} + \frac{\partial^2 u}{\partial t \partial x} - \frac{2\alpha}{r_i} \frac{\partial^2 p_i}{\partial t^2} - \frac{\partial^2 u}{\partial t \partial x} &= \frac{1}{\rho} \frac{\partial^2 p_i}{\partial x^2} - \frac{2\alpha}{r_i} \frac{\partial^2 p_i}{\partial t^2} = \frac{\partial^2 p_i}{\partial x^2} - \frac{2\alpha\rho}{r_i} \frac{\partial^2 p_i}{\partial t^2} \end{aligned} \quad (6.28)$$

Putting Eq. (6.28) into the form of the wave equation

$$\begin{aligned} 0 &= \frac{\partial^2 p_i}{\partial x^2} - \frac{1}{c^2} \frac{\partial^2 p_i}{\partial t^2} \\ c &= \sqrt{\frac{r_i}{2\alpha\rho}} \end{aligned} \quad (6.29)$$

where ρ is the blood density. Using the same analysis, we can derive the equation for wave speed in various types of blood vessels. For instance, if the blood vessel wall is purely elastic and relatively thin compared with the diameter and perfectly circular, the wave speed is

$$c = \sqrt{\frac{Eh}{4\rho r_i}} \quad (6.30)$$

where E is the elastic modulus of the vessel wall, ρ is the blood density, and h is the wall thickness. Eq. 6.30 is commonly referred to as the *Moens-Korteweg formula* and is used in many biofluid mechanics simulations. If more of the assumptions are relaxed, we can develop more realistic approximations for the wave propagation speed within an arterial wall, but that is beyond the scope of this discussion.

Example 6.5

Calculate the wave speed using Eqs. (6.29) and (6.30) to determine whether the assumptions that were made to obtain these formulas are acceptable. Assume that the blood density within a 12-mm-radius blood vessel with a wall thickness of 100 μm is 1.06 g/cm^3 . The compliance of this blood vessel is 6.7 $\mu\text{m}/\text{Pa}$, and Young's modulus is 15 kPa.

Solution

$$\begin{aligned}
 c &= \sqrt{\frac{r_i}{2\alpha\rho}} & c &= \sqrt{\frac{Eh}{4\rho r_i}} \\
 &= \sqrt{\frac{12 \text{ mm}}{2\left(6.7 \frac{\mu\text{m}}{\text{Pa}}\right)\left(1.06 \frac{\text{g}}{\text{cm}^3}\right)}} = 91.9 \text{ cm/s} & &= \sqrt{\frac{15 \text{ kPa}(100 \mu\text{m})}{4(1.06 \text{ g/cm}^3)(12 \text{ mm})}} = 24.3 \text{ cm/s}
 \end{aligned}$$

Considering that we are concerned only with the flow at one instant in time and we are neglecting the effects of slow velocity, the second approximation is more reasonable than the first solution. Also, we made many assumptions regarding the mechanical and geometrical properties of the blood vessel. In formulating Eq. (6.29), too many assumptions were made, and this calculation for wave speed within the blood vessel wall is not close to the physiological scenario. In vivo, wave speeds are on the order of 1 to 10 mm/s, so the second approximation is more reasonable compared with the first.

We will include a brief discussion on the dissipation of the pulsatility of the pressure and velocity waveforms in arteries resulting from the reflection and transmission of wave energy at bifurcations (and around turns). In large arteries, the discussion up to this point regarding wave propagation is relatively valid because of the thickness of the vessel wall and the relatively small wave amplitude compared with wavelength. Consider a standard bifurcating blood vessel (Fig. 6.16). The parent branch not only contains the incident wave but also

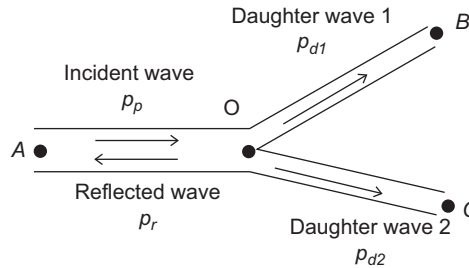


FIG. 6.16 Pressure wave reflectance and transmittance at a bifurcation. The pressure pulse is reflected back along the mother branch, but this is normally out of phase with the next incident wave and, therefore, the entire pressure would be reduced. The energy of the transmitted waves does not summate to the energy of the incident wave.

contains a portion of the wave that is reflected backward into the parent branch. For simplicity, consider this the portion of the velocity or pressure waveform that travels perfectly straight and hits the perfectly sharp point where the two daughter branches meet for this simplified geometry (in a “real” blood vessel there is a more significant area that the incoming pressure waveforms can impact). Each of the two daughter branches will contain a portion of the wave that is transmitted down the vascular tree. There will be some energy loss because of the energy used when the wave impacts the vessel wall, rebounds off the vessel wall, and causes a physical distortion to the vessel wall. Mathematically, the pressure (p) must have a single value at point O in Fig. 6.16, and the volumetric flow rate (Q) at this point must also be continuous. Therefore,

$$p_p - p_r = p_{d1} = p_{d2} \quad (6.31)$$

and

$$Q_p - Q_r = Q_{d1} + Q_{d2} \quad (6.32)$$

Equations (6.31) and (6.32) are basic conservation laws. The volumetric flow rate Q can be quantified as

$$Q = Au = \frac{A}{\rho c} p \quad (6.33)$$

under these conditions, where A is the cross-sectional area, u is the flow velocity, ρ is the blood density, c is the wave speed, and p is the pressure. The characteristic impedance (Z) of the blood vessel is defined as

$$Z = \frac{\rho c}{A} \quad (6.34)$$

Interestingly, if we use this new relationship for pressure-driven flow, we can calculate the amplitudes of the pressure waveforms immediately after a simple 2D bifurcation.

$$ZQ = p \quad (6.35)$$

$$\frac{p_p - p_r}{Z_p} = \frac{p_{d1}}{Z_{d1}} + \frac{p_{d2}}{Z_{d2}} \quad (6.35)$$

The impedance can be different within each vessel, primarily because of the area changes or the velocity within the channel. Therefore,

$$\frac{p_r}{p_p} = -\frac{Z_p^{-1} - (Z_{d1}^{-1} + Z_{d2}^{-1})}{Z_p^{-1} + (Z_{d1}^{-1} + Z_{d2}^{-1})} \quad (6.36)$$

$$\frac{p_{d1}}{p_p} = \frac{p_{d2}}{p_p} = \frac{2Z_p^{-1}}{Z_p^{-1} + (Z_{d1}^{-1} + Z_{d2}^{-1})} \quad (6.37)$$

Eqs. (6.35) through (6.37) show that there will be a reduction in the pressure pulse through the arterial system because of energy that is reflected back into the parent branch and is reflected through the daughter branches. This analysis can be extended for more complex bifurcating systems and more complex mechanical/physical properties (e.g., Eq. (6.34)).

6.9 Flow separation at bifurcations and at walls

Before we move into the discussion of flow separation, it is important to first discuss some of the important flow considerations at bifurcations. We have already learned that a very efficient way to control blood flow through the vascular system is through small changes in the blood vessel radius (Hagen–Poiseuille’s equation). Let us consider the simplest case, in which one vessel branches into two daughter vessels (Fig. 6.17). The flow in the main branch must be divided into the two daughter branches. The question remains as to how the bifurcation is designed to optimize the amount of work that the blood vessel completes to supply the tissue with sufficient blood compared with the rate of energy used by the tissue. Stated differently, how far can cells/tissue be from a capillary to efficiently receive nutrients from and transport wastes to that capillary?

The first and simplest way to optimize the delivery of blood through this bifurcation is for points *A*, *B*, and *C* (refer to Fig. 6.17) to all lie within one plane. If these points are in one plane, the blood vessels connecting each of these points to point *O* could potentially be aligned with that plane, thus minimizing the length of the vessel (however, realistically, points *A*, *B*, *C*, and *O* would not be in the same plane, and even if they were, the blood vessel centerline would not necessarily be in that same plane). What is also known is that the lengths of each vessel depend on the location of the center of the bifurcation point (e.g., point *O*). For instance, by moving the branch point (*O*) to the right (but keeping it in the same plane, which is represented by the textbook’s sheet of paper), branch 1 elongates and branches 2 and 3 reduce in length (assuming the simplest connections). At the same time,

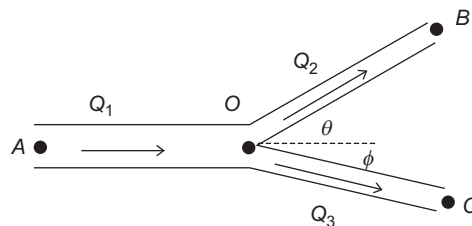


FIG. 6.17 Flow rate at a bifurcation would be divided into two daughter branches. The geometry (angles and radii) of the bifurcation determines the division of the flow within the two daughter branches. By assuming that the work of supplying tissue with oxygen for each vessel should be minimized, one can derive a relationship between the vessel organizations.

the branch angles, θ and ϕ , become larger. If the branch point is moved along the $\overline{OC}$ line or the $\overline{OB}$ line, various combinations of changes in the vessel lengths/angles can be obtained and optimized. In a study conducted in 1926, C.D. Murray proposed a mathematical representation to optimize the work at a bifurcation. These equations became known as Murray's law for the minimum work of a bifurcating network, and subsequently, they have been related to the vascular system. They are represented as

$$\begin{aligned}
 r_1^3 &= r_2^3 + r_3^3 \\
 \cos\theta &= \frac{r_1^4 + r_2^4 - r_3^4}{2r_1^2 r_2^2} \\
 \cos\phi &= \frac{r_1^4 - r_2^4 + r_3^4}{2r_1^2 r_3^2} \\
 \cos(\theta + \phi) &= \frac{r_1^4 - r_2^4 - r_3^4}{2r_2^2 r_3^2}
 \end{aligned} \tag{6.28}$$

These formulas have been validated with experimental physiological studies, and the fit is exceptionally good. Now the important point to remember is that, although we can optimize the work needed throughout a bifurcation, there are still many fluid dynamics principles that may not be optimized through the geometrical optimization.

Example 6.6

Calculate the radius of one daughter branch knowing that the radius of the parent vessel is $175 \mu\text{m}$ and the radius of the other daughter branch is $125 \mu\text{m}$. Draw the bifurcation, to scale, after calculating the bifurcation angles. Also, validate the last equation from Murray's law, which relates both bifurcation angles to the radii of the three blood vessels (Fig. 6.18).

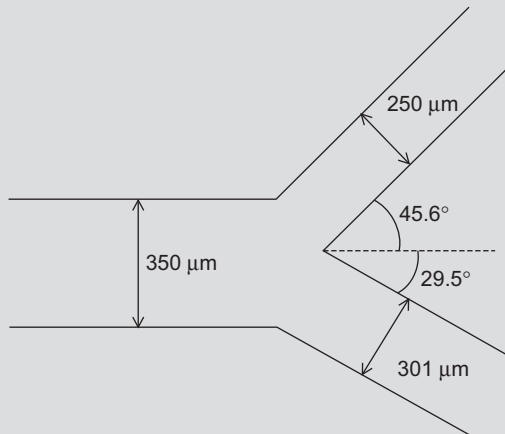


FIG. 6.18 Schematic of the bifurcation found in the sample problem.

Example 6.6 (cont'd)**Solution**

$$\begin{aligned}
r_1^3 &= r_2^3 + r_3^3 \\
(175 \mu\text{m})^3 &= (125 \mu\text{m})^3 + r_3^3 \\
r_3 &= \sqrt[3]{(175 \mu\text{m})^3 - (125 \mu\text{m})^3} = 150.5 \mu\text{m} \\
\theta &= \cos^{-1} \left(\frac{r_1^4 + r_2^4 - r_3^4}{2r_1^2 r_2^2} \right) = \cos^{-1} \left(\frac{(175 \mu\text{m})^4 + (125 \mu\text{m})^4 - (150.5 \mu\text{m})^4}{2(175 \mu\text{m})^2 (125 \mu\text{m})^2} \right) = 45.6^\circ \\
\phi &= \cos^{-1} \left(\frac{r_1^4 - r_2^4 + r_3^4}{2r_1^2 r_3^2} \right) = \cos^{-1} \left(\frac{(175 \mu\text{m})^4 - (125 \mu\text{m})^4 + (150.5 \mu\text{m})^4}{2(175 \mu\text{m})^2 (150.5 \mu\text{m})^2} \right) = 29.5^\circ \\
\cos(\theta + \phi) &= \cos(45.6^\circ + 29.5^\circ) = \cos(75.1^\circ) = 0.256 \\
\frac{r_1^4 - r_2^4 - r_3^4}{2r_2^2 r_3^2} &= \frac{(175 \mu\text{m})^4 - (125 \mu\text{m})^4 - (150.5 \mu\text{m})^4}{2(125 \mu\text{m})^2 (150.5 \mu\text{m})^2} = 0.256
\end{aligned}$$

Therefore

$$\cos(\theta + \phi) = \frac{r_1^4 - r_2^4 - r_3^4}{2r_2^2 r_3^2}$$

Flow separation is a common occurrence at bifurcations (especially within the arterial circulation, where the pressures/velocities are high) and at nearby wall locations when there are rapid geometrical changes that expand the cross-sectional area of the blood vessel. Flow separation is a phenomenon that occurs when the fluid pulls away from the containing wall forming a region that has very slow flow associated with it (Fig. 6.19) or perhaps flow that is in the reversed direction from the mainstream flow direction. The fluid in this region typically forms a recirculation pattern in which the fluid becomes trapped within that area. Flow separation occurs when the fluid velocity is relatively fast and cannot expand with the geometry rapidly. The formation of recirculation zones is a property of all viscous fluids and cannot be ignored in physiological settings. The fluid that is trapped within the recirculation zone stays within the recirculation zone because it cannot overcome the flowing fluid pressure to reenter the mainstream flow. Although diffusion of dissolved solutes may occur across the boundaries of the flow separation zone, fluid mass does not generally enter or exit from the separated zone. In general, flow separation occurs when the angle between the main fluid flow direction and the wall is relatively large.

Also, a common way to generate flow separation in biofluids mechanics problems is when there is an adverse pressure gradient causing convection throughout the fluid laminae. In a pressure-driven viscous flow, the momentum equation at the wall is (see Chapter 3 for the derivation of this equation)

$$\left. \frac{\partial^2 u}{\partial y^2} \right|_{y=0} = \frac{1}{\mu} \frac{\partial p}{\partial x} \quad (6.39)$$

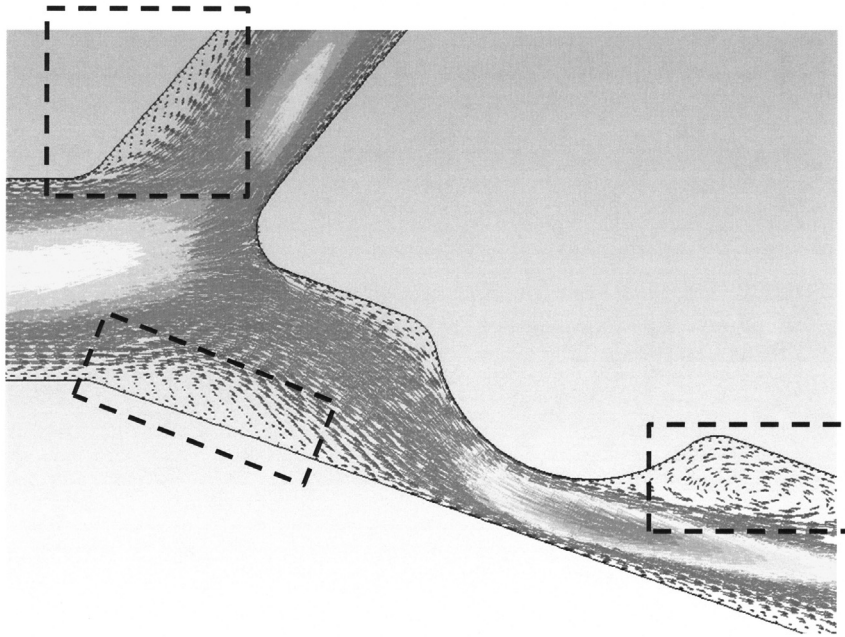


FIG. 6.19 Flow separation (region enclosed by *dashed lines*) downstream of a bifurcation and a stenosis (rapid area expansions). Flow separates from the wall partially because of the skewing of the velocity profile toward one of the walls of the blood vessel. By quantifying the pressure gradient along the wall, the likelihood for flow separation can be predicted.

To maintain the flow regime without recirculation zones, the wall curvature must have the same sign as the pressure gradient. Under normal conditions, the pressure gradient $\frac{\partial p}{\partial x}$ is negative, and therefore, the normal parabolic flow profile at the wall matches this sign, satisfying the momentum equation. However, as the pressure gradient approaches zero, the flow begins to separate from the wall because the signs of these two values no longer are the same. As the pressure gradient becomes positive, the flow will completely separate from the wall, forming a recirculation zone (Fig. 6.20). From this image we can see that flow separation tends to occur at a region where the near wall fluid flow rate decreases.

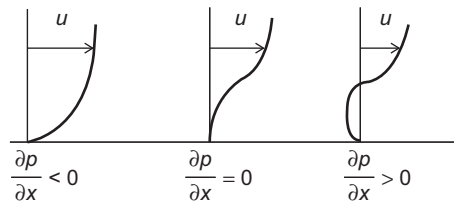


FIG. 6.20 Effects of a pressure gradient on the flow profile near the wall. With an adverse (or positive) pressure gradient along the wall, the flow would tend to separate. With a negative or zero wall pressure gradient, the flow would not likely separate.

Another interesting phenomenon that occurs at bifurcations is that the flow skews toward one of the walls, if the bifurcation angles and the fluid velocity are large enough. Because of the velocity of the fluid entering the bifurcation, more flow typically moves toward the inner walls of the bifurcation and therefore the fluid moves away from the outer walls (Fig. 6.21). In addition, the flow at the outer wall typically slows because the core flow is pushed toward the inner wall of this skewed velocity profile. Additionally, as can be observed in Fig. 6.21, there is a rapid spatial increase in the cross-sectional area of the blood vessel at a bifurcation (flow would decelerate), which then, just as rapidly, decreases again into the two (somewhat independent) cross-sectional areas of the daughter branch. The flow in these skewed regions is not fully developed; it does not have the typically parabolic flow profile. The highest velocity is no longer at the centerline but, as can be seen, moves closer to the inner bifurcation wall. The entrance length is a fluid property that quantifies the distance required for the fluid to become fully developed again after it has become skewed. As an approximation, if the vessel cross-sectional area remains constant after the bifurcation, within two to five tube diameters, the flow would be fully developed again. The significance of flow skewing at a bifurcation is that the wall shear stress is not what one would anticipate based on a fully developed flow. Along the inner wall the shear stress increases, and along the outer wall the shear stress decreases. This will be discussed in detail later, but cardiovascular diseases tend to initiate in locations where the shear stress diverges from the normal conditions (either heightened or reduced shear stress).

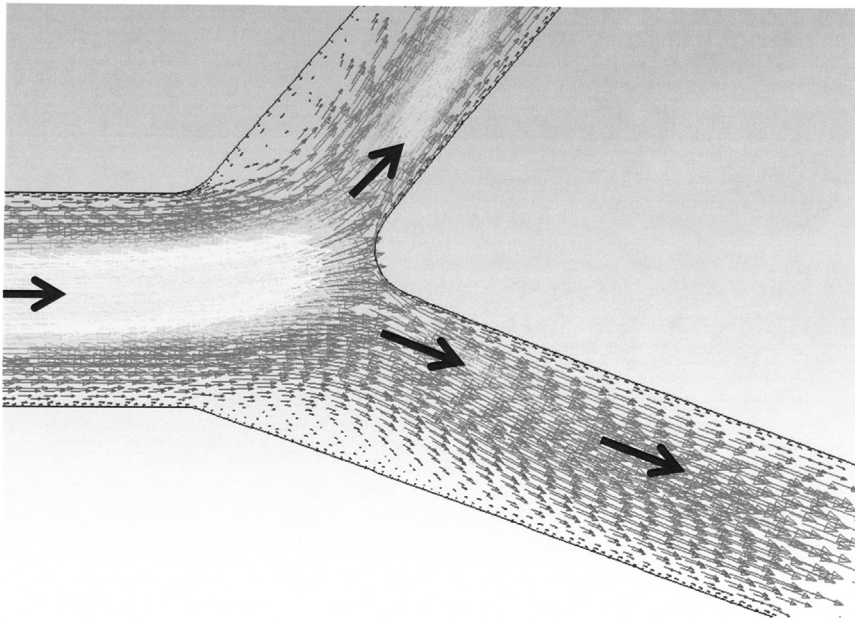


FIG. 6.21 Flow skew at a bifurcation, where the highest velocity blood flow is no longer at the centerline (highest velocity is marked by black arrows). The extent of flow skewing is determined by the geometry of the bifurcation.

6.10 Flow through tapering and curved channels*

In most of the examples that we have discussed in this chapter, we have made the assumption that the blood vessel is perfectly circular with a constant diameter and that the vessel remains straight within one plane (in Chapter 3, we illustrated some examples without these assumptions; however, the rate of change of the taper was not considered in those problems). Unfortunately, these assumptions do not match the physiological scenarios; most blood vessels experience some changes in diameter between bifurcations, do not have a perfectly circular cross-sectional area, and do not remain in the same plane in 3D space (although many blood vessels are relatively straight and thus not very twisted). In most blood vessels, the taper along the vessel length is relatively small until a branch point occurs; however, it is fairly easy to accommodate the effects of taper within our calculations if the taper can be approximated mathematically. In addition, the curves within vessels can be easily accounted for, as we have previously shown in Chapter 3. However, these additions may require the use of computational software to fully describe the flow profile. We will examine simple cases to illustrate some of the considerations that would be needed.

The first assumption that can be made about a tapered blood vessel is that it tapers in discrete known steps (Fig. 6.22). To model a taper with discrete instantaneous step changes in diameter, the assumption would be made that the velocity, pressure, shear stress, and other fluid parameters are all constant throughout each section at one instant in time. As we know, this is a drastic oversimplification of the flow conditions. With this assumption, the analysis of changes within these flow variables would need to be conducted only at the discrete steps, marked as 1, 2, and 3 on Fig. 6.22. Furthermore, these calculations can be carried out independent of each other (e.g., only the output flow variables of each step would be used to calculate the input flow variables within the next step). Common reasons that this type of discrete step analysis technique would be conducted instead of considering the exact blood vessel taper is because the change in area cannot be mathematically represented accurately or the change in area is too complicated to compute by hand and the use of numerical methods is needed.

To be able to model a taper and compute the fluid parameters of interest, one must use the same formulas for conservation of mass and conservation of momentum throughout the entire blood vessel, which were developed in previous sections. For a simple example,

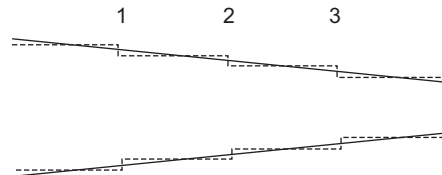


FIG. 6.22 The modeling of a continuous taper with evenly spaced steps. To calculate the velocity profile through a continuous taper, one would need to determine the exact taper function, which may not be as simple as the examples shown in the text. However, if the taper is complicated, it can be approximated with discrete steps or “simple” mathematical functions.

*This section is considered advanced and can be skipped without a loss of continuity.

a continuous taper that reduces the blood vessel radius by half over the entire vessel length can be modeled as

$$r(x) = r_i \left(1 - \frac{x}{2L}\right) \quad (6.40)$$

where L is the tube length and r_i is the blood vessel radius at the inlet. By using Eq. (6.40) within the conservation of mass, momentum, or energy formulation, quantities of interest can be easily calculated. In an analogous situation, the velocity of a fluid element at a particular location along the blood vessel length can be given as a function of position (instead of radius as a function of position), and the other fluid parameters of interest can be calculated from this given value.

Example 6.7

The velocity of a fluid element along the tapered channel's centerline (Fig. 6.23) is given by $\vec{v} = v_i \left(1 + \frac{2x}{L}\right) \hat{i}$, where v_i is the centerline inlet velocity. Calculate the acceleration of any particle along the centerline (i.e., as a function of x) and the position of a particle (as a function of time) that is located at $x = 0$ at time zero.

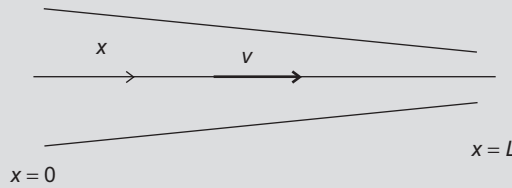


FIG. 6.23 Model of a continuous taper for Example Problem 6.7.

Solution

To find the acceleration of a particle, one must use the total derivative of velocity, developed in Chapter 2 (for the x -direction):

$$\frac{D\vec{v}}{Dt} = \frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z}$$

For this situation, u is only a function of x , and v and w are equal to zero. Thus

$$\begin{aligned} \frac{D\vec{v}}{Dt} &= u \frac{\partial u}{\partial x} = v_i \left(1 + \frac{2x}{L}\right) \left[\frac{\partial}{\partial x} \left(v_i \left(1 + \frac{2x}{L}\right) \right) \right] = v_i \left(1 + \frac{2x}{L}\right) \left[\frac{\partial}{\partial x} \left(\frac{2v_i x}{L} \right) \right] \\ &= v_i \left(1 + \frac{2x}{L}\right) \left(\frac{2v_i}{L} \right) = \frac{v_i^2}{L} \left(2 + \frac{4x}{L} \right) \end{aligned}$$

Continued

Example 6.7 (*cont'd*)

The acceleration of any particle along the centerline is

$$a_x(x) = \frac{v_i^2}{L} \left(2 + \frac{4x}{L} \right)$$

To determine the location of a particle, we first know that at time 0, the particle is located at position 0 (or at the inlet) and has a velocity of v_i . At some later time, the particle will be located at L and will have a velocity of $3v_i$. From Chapter 2, we learned that the velocity of a particle is the time derivative of its position. Using this relationship, we can develop a formula for the location of a fluid element as a function of time.

$$u_x = \frac{dx}{dt} = v_i \left(1 + \frac{2x}{L} \right)$$

To solve this equation, first we separate the variables.

$$v_i dt = \frac{dx}{\left(1 + \frac{2x}{L} \right)}$$

Integrate the previous equation with the bounds that at time zero the particle is located at a location of zero and at some time t the particle is located at some point x .

$$\begin{aligned} \int_0^t v_i dt &= \int_0^x \frac{dx}{\left(1 + \frac{2x}{L} \right)} \\ v_i t \Big|_0^t &= \frac{L}{2} \ln \left(1 + \frac{2x}{L} \right) \Big|_0^x \\ v_i t &= \frac{L}{2} \ln \left(1 + \frac{2x}{L} \right) \\ \ln \left(1 + \frac{2x}{L} \right) &= \frac{2v_i t}{L} \\ 1 + \frac{2x}{L} &= e^{\frac{2v_i t}{L}} \\ x(t) &= \frac{L}{2} \left(e^{\frac{2v_i t}{L}} - 1 \right) \end{aligned}$$

Example 6.7 illustrates the use of an exact solution for a tapering blood vessel.

As stated earlier, most blood vessels have a small taper and/or curvature in the body. Curving blood vessels do not add significant complexity to the problems discussed previously. Similar to the previous examples and the examples in Chapter 3, continuity, momentum conservation, and energy conservation can be used to calculate the velocity

profile, the forces needed to hold the particular vessel in place, the energy needed to maintain the flow, the pressure within the fluid, acceleration, shear stress, and others fluid properties. The Navier–Stokes equations can be used to determine the velocity profile as a function of geometrical changes. Example 6.8 illustrates the use of the Navier–Stokes equations to solve for the velocity profile in a curved tapering vessel.

Example 6.8

Determine the velocity profile in the three sections of the blood vessel shown in Fig. 6.24. Assume that the only portion that is tapering is within the curved section. In addition, assume that gravity acts only in the y -direction and that this is pressure-driven flow throughout the entire vessel.

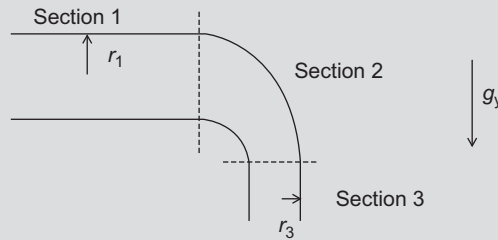


FIG. 6.24 Cross-section of a tapered curving blood vessel. This problem illustrates the difficulty of adding a tapering blood vessel with changes in orientation.

Solution

Blood vessel sections 1 and 3 should be relatively easy to solve because there is no taper and no bend in these sections. Also, the sections can be solved independently because we know that the outflow of one section will be the inflow of the subsequent section.

For section 1, if we choose the Cartesian Navier–Stokes equation

$$\begin{aligned} \rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= \rho g_x - \frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\ 0 &= - \frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial y^2} \right) \\ \frac{\partial^2 u}{\partial y^2} &= \frac{1}{\mu} \frac{\partial p}{\partial x} \\ \frac{\partial u}{\partial y} &= \frac{y}{\mu} \frac{\partial p}{\partial x} + c_1 \\ u(y) &= \frac{y^2}{\mu} \frac{\partial p}{\partial x} + c_1 y + c_2 \end{aligned}$$

Using the boundary conditions of

$$u(0) = 0 \quad \text{and} \quad u(2r_1) = 0$$

Continued

Example 6.8 (cont'd)

the solution of the velocity profile becomes

$$u(y) = \frac{y^2}{\mu} \frac{\partial p}{\partial x} - \frac{r_1}{\mu} \frac{\partial p}{\partial x} y$$

Using similar procedures, we can develop an equation for the flow profile by solving the Navier–Stokes equations for blood vessel section 3. In this case we will use the Navier–Stokes equation for the y -direction. The solution follows a similar approach as

$$\begin{aligned} \rho \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) &= \rho g_y - \frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\ 0 &= \rho g_y - \frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} \right) \\ \frac{\partial^2 v}{\partial x^2} &= \frac{1}{\mu} \frac{\partial p}{\partial y} - \frac{\rho}{\mu} g_y \\ \frac{\partial v}{\partial x} &= \left(\frac{1}{\mu} \frac{\partial p}{\partial y} - \frac{\rho}{\mu} g_y \right) x + c_1 \\ v(x) &= \left(\frac{1}{\mu} \frac{\partial p}{\partial y} - \frac{\rho}{\mu} g_y \right) \frac{x^2}{2} + c_1 x + c_2 \end{aligned}$$

Using the boundary conditions of

$$v(0) = 0 \quad \text{and} \quad v(2r_3) = 0$$

the solution of the velocity profile becomes

$$v(x) = \left(\frac{1}{\mu} \frac{\partial p}{\partial y} - \frac{\rho}{\mu} g_y \right) \frac{x^2}{2} + r_3 \left(\frac{\rho}{\mu} g_y - \frac{1}{\mu} \frac{\partial p}{\partial y} \right) x$$

Note that the one added difficulty of this solution is that the inflow conditions for this section would need to equate to the outflow conditions from section 2. The solution for blood vessel section 2 becomes more difficult because you would need to solve two coupled partial differential equations. For this particular section, u is a function of x and y and v is a function of x and y . The appropriate Navier–Stokes equations for this section of blood vessel are

$$\begin{aligned} \rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) &= \rho g_x - \frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\ \rho \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) &= \rho g_y - \frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\ \rho \left(u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} \right) &= -\frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) \\ \rho \left(u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} \right) &= \rho g_y - \frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} \right) \end{aligned}$$

Example 6.8 (*cont'd*)

The first two equations that are listed are the general Navier–Stokes equations for the two applicable directions. The second two equations for flow Section 2 are the reduced form of the Navier–Stokes equations, and, as the reader can see, these equations are coupled to each other; for example, as the x -velocity changes and the x -cross sectional area changes, this will alter the flow in the y -direction and vice versa. Furthermore, these equations would require the use of the outflow conditions from section 1 as the inflow conditions and it should be noted that the flow may not become fully developed in section 1 before the flow transitions to section 2. Regardless of whether the flow is fully developed at the end of section 1, because the cross-sectional area changes in section 2 and there is a curve in the flow, the flow field will have to develop again.

The easiest solution to the second set of two partial differential equations is through the use of numerical methods, which will not be addressed here. Because we did not provide the exact details about the flow properties, we will leave the discussion at this point. However, if you can make the assumption that the x -direction velocity component does not vary much with x (i.e., $\frac{\partial u}{\partial x} \approx 0$) and that the y -direction velocity component does not vary much with y (i.e., $\frac{\partial v}{\partial y} \approx 0$), this problem will simplify significantly. However, around a bend and considering that there is a taper in this particular vessel, these assumptions may not be the most accurate.

It is also important to point out that flow can skew around a curved branching point and it is common for a fully developed flow that enters a curved tube to no longer be fully developed within and/or directly distal to the curved branch. Thus, the velocity profile of the fluid may not be the typical parabolic profile. Part of the flow skewing is a function of the geometry of the curved branch, but it is also a function of the momentum contained within the flowing fluid. The readers may recall discussions on tangential acceleration and normal acceleration in an engineering mechanics class. In these classes, it was discussed that a rigid body moving along a curved path may have two types of accelerations (when one uses a normal-tangential coordinate system to characterize the motion). Under these conditions, the tangential acceleration is a measure of the time rate of change of the magnitude of velocity and the normal acceleration is a measure of the time rate of change of the direction of the velocity vector. In a constrained rigid system, the mass that is following this curved path would maintain on the curved path, by definition (e.g., if you spin a bucket over your head and the bucket is tied to a rope of constant length, the bucket follows the same curved path). In contrast, in a constrained system composed of a flowing fluid, the momentum associated with the accelerating fluid system can cause the fluid mass to shift away from the centerline (e.g., where it is fully developed) toward the outer wall of the curved constrained system. In this case the flow velocity would skew toward the outer wall as well. Remember that under full-developed conditions in a circular cross-section channel, the fluid mass and velocity are symmetrically distributed about the centerline of the channel. However, with curves in the channel the mass and velocity are typically no longer symmetrically distributed about the centerline, at least until the flow becomes fully developed again.

In contrast to the previous discussion, we identified an interesting phenomena, in which people “flowing” around a curved path do not skew toward the outside of the constrained system, but instead skew toward the inside. Although the angular momentum and accelerations that these people experience would suggest that they should flow toward the outer wall, they not only balance these forces but overcome them and flow toward the inner wall. Interestingly, however, with sufficient time and distance beyond the curved path, the distribution of people will normalize to a “fully developed” pattern (Fig. 6.25). Fig. 6.25A illustrates a set of steps in the old computer science building on the Stony Brook University Campus. We are looking at the staircase from the first landing down toward the first floor. People must enter this staircase (from either the top or bottom) by making a turn around a corner within a constrained system (e.g., the walls within the hallway). We can observe that both at the top and the bottom of the stairs, there is a distinct wear pattern toward the inside of the curve (highlighted with an arrow) and a much less significant wear pattern toward the outside of the curve (highlighted with a star). However, toward the center of the staircase, the wear pattern is more evenly distributed or “fully developed” (the geometrical center of the stairs is marked with a dashed line). Fig. 6.25B illustrates the second set of steps in this staircase looking from the second floor to the first landing. Similarly, people must enter these stairs by passing through a curve. We can see a second distinct skewing of the wear profile toward the inside of the curve that the walkers must follow (note that the inside curve for the first landing is on the right side of the figure, as marked, and the inside curve for the second floor is on the left side of the figure; in contrast, the inside curve is on the same side of the staircase for the portion shown in Fig. 6.25A). For the second staircase, the wear pattern never quite normalizes to a “fully developed” profile. This is likely because there are fewer steps in the second staircase compared with the first staircase (6 steps versus 14 steps).

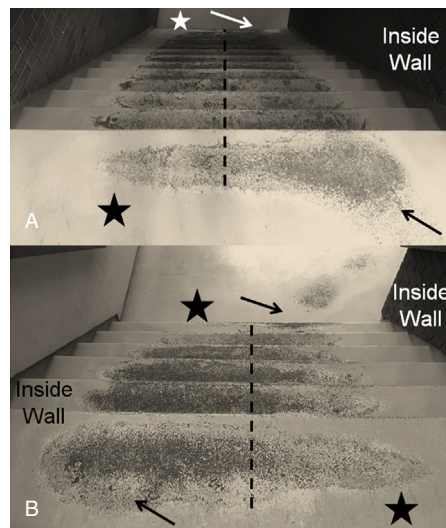


FIG. 6.25 Photographic evidence of “flow” skewing around a curved vessel. Note that this figure illustrates the wear pattern of walkers progressing along a staircase, where the walkers distinctly move closer to the internal curved wall, whereas fluid would move closer to the exterior wall. However, given enough time, the wear pattern normalizes in a process analogous to fluid becoming fully developed.

Analytical solutions for flow through tapering or curved channels have been obtained; however, the development/derivation of these equations and their use for an introductory-level course in biofluid mechanics is limited. There is one dimensionless number, the Dean number (Dn), which is important for characterizing the flow through curved pipes. Briefly, secondary flows (termed Dean vortices) may be observed for flows through curved channels. The Dean number helps predict the stability of these secondary flows. For low Dean number values ($Dn \cong 40 - 60$), flow through a curved channel remains unidirectional. For higher Dean number values ($75 < Dn < 200$), the secondary flows are relatively stable. For Dean number between 60 and 75 there is a transition where secondary flows are observed but they may dissipate. Turbulent flows through a curved channel tend to have very large Dean numbers ($Dn > 400$). The Dean number is defined as

$$Dn = \frac{\sqrt{\frac{1}{2}(\text{inertial forces})(\text{centripetal forces})}}{\text{viscous forces}} = Re \sqrt{\frac{D}{2\rho_c}}$$

after some analytic manipulations, where Re is the Reynolds number, D is the diameter of a circular channel (or characteristic length), and ρ_c is the radius of curvature of the bend.

6.11 Pulsatile flow and turbulence*

In most of the examples that we have discussed so far, we have always made the assumption that blood flow is steady. Because of the cardiac cycle (Section 5.3), the blood that is being ejected from the heart into the vasculature does not have a constant flow rate. In fact, the systemic blood flow generally mimics the left ventricular pressure waveform in time within the arterial circulation (Figs. 6.26 and 6.27). Fig. 6.26 illustrates that for a given location within the arterial vascular tree, the velocity waveform will mimic the cardiac output and will show a somewhat consistent waveform as a function of time. Fig. 6.27 illustrates the variation in the pressure waveform throughout the vascular tree. It is important to note that within the arterial circulation there is a pulsatility that is damped before the blood reaches the capillary circulation. In the large arteries, a significant variation in the blood pressure can be observed

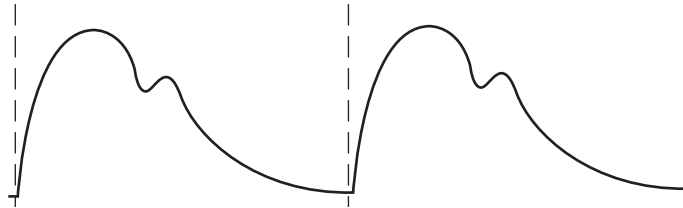


FIG. 6.26 A schematic of the velocity waveform in a large artery, such as the aorta, showing that the velocity changes temporally and is pulsatile. As we can see, this mimics the pressure pulse of the left ventricle, but is reasonably constant with time.

*This section is considered advanced and can be skipped without a loss of continuity.

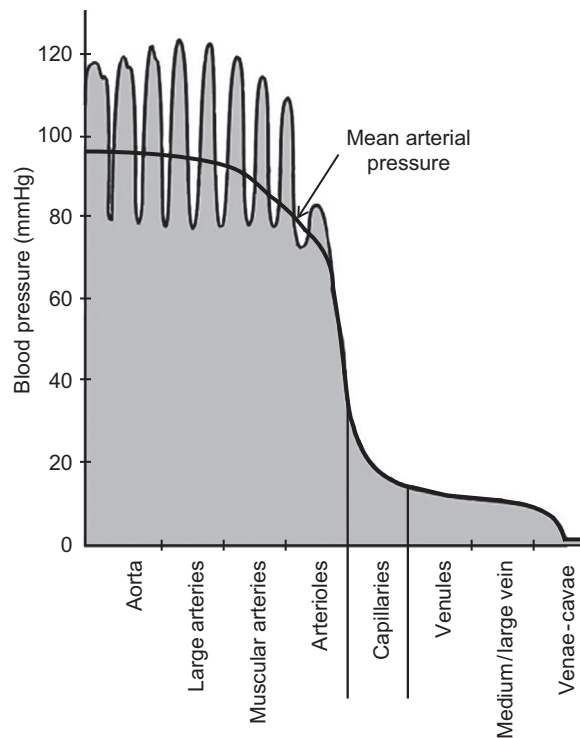


FIG. 6.27 Pressure variation within the systemic circulation, illustrating that (1) there is a variation in pressure spatially along the systemic circulation and (2) within a specific level within the systemic circulation, the pressure varies with the systolic and diastolic contractions of the heart. The mean arterial pressure is the effective pressure in the systemic circulation.

that has a range of approximately 40 mmHg under normal physiological conditions. The variation between the peak systolic pressure (typically around 120 mmHg) and the minimum diastolic pressure (typically around 80 mmHg) is termed the pulse pressure. The mean arterial pressure is the effective pressure in the vasculature and can be calculated as a time-weighted average of the peak systolic and minimum diastolic pressures, as follows

$$\text{Mean arterial pressure} = \text{Diastolic pressure} + \frac{\text{Pulse pressure}}{3} \quad (6.41)$$

However, to obtain the exact solution for mean arterial pressure, one can integrate the pressure waveform as a function of time and then normalize this value by the time duration of the pressure pulse. Eq. 6.41 assumes that the diastolic pressure acts for two-thirds of the pressure cycle and the systolic pressure acts for one-third of the pressure cycle. This is a reasonable approximation of the pressure waveform but is clearly an oversimplification of the fluid dynamics that are observed during the cardiac cycle.

In the arterioles, a temporally varying pressure waveform can be observed; however, the waveform looks slightly different from the left ventricular pressure waveform and the pulsatility begins to damp significantly. In the capillaries and the venous circulation, the

pressure pulse is negligible and the flow is largely nonpulsatile. Thus, the question remains whether the pulsatility in large vessels affects the calculations that we have been carrying out in previous sections.

One can argue that the steady flow assumption does or does not affect the calculations that we have done thus far. The flow is pulsatile; therefore, the change in velocity with regard to time cannot be zero (see any Navier–Stokes example in which we ignored the temporal variation in velocity; $\frac{\partial v}{\partial t}$). Thus, from one stance, the calculations of the fluid properties that we have conducted never describe the actual condition within the body. However, by restricting ourselves to describing the flow conditions at one instant in time, the calculations can be carried out by ignoring these temporal derivatives. However, if we were interested in a reasonably small time scale with a reasonable small time step, we could carry out the computations a few times, using the output of one time step as the input to the subsequent time step. The effect of this is that one loses the complete transmittance of the fluid throughout the vessel (e.g., if one was interested in how a blood cell moves with time or where particular fluid elements go, the information may be lost), but the solution of the problems can be carried out (i.e., you lose some information but gain some other information). By restricting the calculation to one instant in time, the assumption is made that the speed of blood everywhere throughout the blood vessel length is the same at that time. However, we have already discussed that because of the fluid flow and the elastic properties of the blood vessel, there is wave propagation within the walls of the blood vessel and within the fluid itself. Thus this may not be the best simplifying assumption. Additionally, the conservation laws that we have used tell us that the fluid velocity cannot be the same along the entire blood vessel length, when there is a change in cross-sectional area of the blood vessel. Additionally, we typically assume that the fluid has a viscosity, such that the velocity is not uniform within one cross-section. Therefore, when looking at one section of a blood vessel, the velocity profile will not be constant in magnitude and direction (at least in larger vessels) both within one cross-section and throughout the vessel. By considering the pulsatile nature of blood velocity, it more than likely requires the use of numerical methods to calculate flow properties (see Chapter 15 for more details) unless the inflow velocity waveform is overly simplified. The way to work around this and gain the ability to solve temporally varying problems by hand is to define the inlet velocity as a function of time and then solve for the flow conditions at discrete time points. Using this approach one can solve for the flow properties at those discrete time points, using the output of one solution as the input for the subsequent iteration over the length of interest.

Another factor that we have largely ignored is that blood flow can become turbulent, especially during the deceleration phase immediately after peak systole, when the blood velocity is the greatest and is rapidly reducing in velocity. Note that although the generation of turbulence is possible during this time, it is likely to occur only in the ascending aorta and/or the aortic arch, because of the combination of rapidly decelerating blood flow and the complex geometry that includes twists, tapers, and various branches. Additionally, the turbulence that may generate at this time is not a truly turbulent flow (as defined in [Section 2.12](#)) because the turbulent flows that generate are not self-sustaining and would almost instantaneously dissipate back toward laminar flow. Even with these two special conditions in the ascending aorta, it is unlikely for any significant mixing to occur, and thus we typically consider biological flows within the vascular system to be laminar at all locations and

over the entire flow duration. Recall that when flow becomes turbulent, there are random fluctuations within the fluid velocity and pressure. By nature of being random, they cannot be calculated or predicted, but they can be observed. For turbulent flows, we would discuss the velocity as a mean velocity plus some random velocity fluctuation term at each spatial point. It is unrealistic (and theoretically impossible) to be able to a priori define the entire flow field as a function of time and space under true turbulent conditions. Computational approximations of the turbulent flow field within computer simulations are needed to “accurately” represent turbulent flows. For hand calculations of turbulent flows to be carried out, one must be willing to make significant assumptions about the flow properties. Normally, there are two methods that are employed to approximate turbulent flows. The first would be the use of theoretical statistical methods, which aims to correlate the observed fluctuations in particular ways. Typically, one would look at frequency correlations or space–time correlations of fluctuating variables. The second approach used to approximate turbulent flows is the semiempirical modeling of the turbulent mean quantities. Empirical modeling relies solely on observations and/or experiments to reach a conclusion about the observations, whereas semiempirical modeling must rely on some observation/experiments and some theory. With this approach, many of the fluid dynamics principles that were developed in the earlier sections are extended to include various turbulence properties. Using this approach, the mean velocity in the x -direction and the fluctuation in the x -component of velocity, at one spatial location, would be defined as

$$\bar{u} = \frac{1}{T} \int_{t_0}^{t_0+T} u dt \quad (6.42)$$

$$u = \bar{u} + u'$$

where any fluid quantity with a prime ($'$) superscript denotes that we are talking about the fluctuating (random) component of that variable (as in [Section 2.12](#), we are using velocity as the example, but this analysis would hold for any fluid variable). For completeness, we will include some of the salient fluid mechanics equations that can be used in turbulent flow modeling. As discussed previously, the continuity equation for incompressible fluid flows can be defined as

$$\left. \frac{dm}{dt} \right|_{\text{system}} = \int_{\text{area}} \vec{v} \cdot d\vec{A} = 0 \quad (6.43)$$

if we can assume that the volume of interest does not change with time. Making these assumptions, we can substitute the turbulent velocity components (from [Eq. \(6.42\)](#)) into [Eq. \(6.43\)](#) to get

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = \frac{\partial(\bar{u} + u')}{\partial x} + \frac{\partial(\bar{v} + v')}{\partial y} + \frac{\partial(\bar{w} + w')}{\partial z} = 0 \quad (6.44)$$

or

$$\frac{\partial \bar{u}}{\partial x} + \frac{\partial \bar{v}}{\partial y} + \frac{\partial \bar{w}}{\partial z} = 0 \quad (6.45)$$

if Eq. (6.44) is time averaged. If Eq. (6.45) is subtracted from Eq. (6.44), but we do not time average the final result, we obtain

$$\frac{\partial u'}{\partial x} + \frac{\partial v'}{\partial y} + \frac{\partial w'}{\partial z} = 0 \quad (6.46)$$

The importance of Eqs. (6.45) and (6.46) is that both the mean velocity component and the fluctuating velocity component must each separately satisfy the continuity equations. If the fluid was compressible, these equations would be coupled by the mean density fluctuation term, which would be a function of both the mean velocity components and the fluctuating velocity components. Extending this analysis to the time-averaged turbulent Navier–Stokes equation, we obtain

$$\rho \frac{D\vec{v}}{Dt} + \rho \frac{\partial}{\partial x_j} \left(\overline{u'_i u'_j} \right) = \rho \vec{g} - \nabla \overline{p} + \mu \nabla^2 \vec{v} \quad (6.47)$$

which is used extensively in computational fluid dynamics (the derivation for Eq. (6.47) can be found in classic fluid mechanics textbooks). The term, $\overline{u'_i u'_j}$, is the turbulent inertial tensor, exists in all turbulent flows, and is one of the major reasons why calculations of turbulent flows becomes so difficult. Since this component is a tensor component, it iterates through nine variables in the standard Cartesian coordinate system (one must choose a value i and j for each x -, y -, and z -direction). Unfortunately, these nine components can be defined only by unattainable knowledge regarding the turbulent flow properties and knowledge about how these properties relate to local conditions (e.g., geometrical and surface roughness). If the turbulent flow can be simplified to a 2D problem, then, luckily, the turbulent inertial tensor is composed of only one complicated value; $\overline{u'v'}$ (assuming an x/y coordinate system). Even with this simplification, there are no physical or empirical observations that can help us solve for this value. Thus most of the simulations and work associated with turbulent flows are semiempirical at best.

Eq. (6.47) can be rearranged so that the turbulent inertial tensor is included within the stress terms on the right side of the equation (unfortunately, the turbulent inertial tensor components are not stresses, but some insights into the formula can be obtained from this manipulation). Rearranging Eq. (6.47), we get

$$\rho \frac{D\vec{v}}{Dt} = \rho \vec{g} - \nabla \overline{p} + \nabla \cdot \tau_{ij} \quad (6.48)$$

where

$$\tau_{ij} = \underbrace{\mu \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right)}_{\text{Laminar}} - \underbrace{\rho \overline{u'_i u'_j}}_{\text{Turbulent}} \quad (6.49)$$

Eq. (6.49) suggests that the turbulent inertial tensor consists of two components: a laminar Newtonian viscous stress plus an apparent turbulent stress. The particular components are

labeled “Laminar” and “Turbulent” in Eq. (6.49) for ease of visualization/identification. Unfortunately, even with these arrangements, the turbulent stress term is still unknown, and some observations are needed to analyze these equations. These fluctuating quantities can be resolved only after the flow has occurred and the fluctuations can be measured with respect to the mean velocity.

To continue our brief discussion of turbulence, we would like to define the energy equation for incompressible turbulent flows with constant properties. Using mathematical manipulations similar to those discussed earlier, we can time average the energy equation to obtain the following

$$\rho c_p \frac{D\bar{T}}{dt} = -\frac{\partial}{\partial x_i} (q_i) + \bar{\Phi} \quad (6.50)$$

where

$$\bar{\Phi} = \frac{\mu}{2} \overline{\left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial u'_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} + \frac{\partial u'_j}{\partial x_i} \right)^2} \quad (6.51)$$

and

$$q_i = \underbrace{-k \frac{\partial \bar{T}}{\partial x_i}}_{\text{Laminar}} + \underbrace{\rho c_p \overline{u'_i T'}}_{\text{Turbulent}} \quad (6.52)$$

Similarly to the previous discussion with the effective turbulent stress terms, this rearrangement of the energy equation generated a number of new terms that must be considered within the energy equation. The new dissipation term ($\bar{\Phi}$) is quite complex, even when we can simplify the flow to a 2D case, as illustrated here. Additionally, the conduction and turbulent convection terms were combined into a pseudoheat flux vector (q_i). This new term contains both the molecular flux resulting from laminar flow plus a new turbulent flux component. Again, at the onset of the flow we have no knowledge about these fluctuating terms; they only can be observed or semiempirically formulated. For complete derivation of these formula, please refer to classic fluid mechanics texts.

There are two more elegant formulas that have been derived in the case of turbulent flows. These relationships are quite important when designing devices that may introduce turbulence into the flow fields (e.g., some cardiovascular implantable devices may need to consider the following quantities in their designs). The turbulent kinetic energy can be defined as

$$\begin{aligned} \frac{D(KE)}{Dt} = & -\frac{\partial}{\partial x_i} \left[u'_i \left(\frac{1}{2} u'_i u'_j + \frac{p'}{\rho} \right) \right] - \overline{u'_i u'_j} \frac{\partial \bar{u}_j}{\partial x_i} \\ & + \frac{\partial}{\partial x_i} \left[\nu u'_j \left(\frac{\partial u'_i}{\partial x_j} + \frac{\partial u'_j}{\partial x_i} \right) \right] - \nu \frac{\partial u'_j}{\partial x_i} \left(\frac{\partial u'_i}{\partial x_j} + \frac{\partial u'_j}{\partial x_i} \right) \end{aligned} \quad (6.53)$$

where the term on the left side of the equation is the time rate of change of the turbulent kinetic energy, the first term on the right side represents the kinetic energy convective diffusion, the second term on the right side represents the kinetic energy production, the third term on the right side represents the work done by turbulent viscous stresses, and, finally, the fourth term on the right side represents the turbulent viscous dissipation. Similarly, the Reynolds stresses can be represented as

$$\begin{aligned} \frac{D\overline{u'_i u'_j}}{Dt} = & - \left(\overline{u'_j u'_k} \frac{\partial \overline{u_i}}{\partial x_k} \right) - 2\nu \frac{\partial u'_i}{\partial x_k} \frac{\partial u'_j}{\partial x_k} + \frac{p'}{p} \left(\frac{\partial u'_i}{\partial x_j} + \frac{\partial u'_j}{\partial x_i} \right) \\ & - \frac{\partial}{\partial x_k} \left[\overline{u'_i u'_j u'_k} - \nu \frac{\partial \overline{u'_i u'_j}}{\partial x_k} + \frac{p'}{p} \left(\delta_{jk} u'_i + \delta_{ik} u'_j \right) \right] \end{aligned} \quad (6.54)$$

where the left term is the time rate of change of the Reynolds stress, the first term on the right side represents the generation of stresses, the second term on the right side represents the dissipation of stresses, the third term on the right side represents the effects of pressure and strain on stresses, and the fourth term on the right side represents the diffusion of the Reynolds stresses. Again, it is unfortunate that when one analyzes flows with Eqs. (6.53) and (6.54), the majority of these terms are unknown before the flow. Some empirical correlations have been made for these equations, but for the most part they must be observed to be able to characterize the changes in turbulent biofluid mechanics properties. More research and approaches to these types of problems will be discussed in Chapter 15.

Because one cannot discretely define the properties of turbulent flows, most biofluid mechanics engineers discuss the common characteristics of turbulence, which were described in Section 2.12, if turbulence appears in the particular case that is being studied. Briefly recall that turbulent flows are characterized by being random, mixing flows, in which mass and heat transfer occurs between fluid laminae. Turbulent flows also are characterized by very large inertial forces compared with the internal viscous forces (e.g., the Reynolds number is normally in the range of 10,000). Turbulent flows also require a large amount of energy to maintain the turbulence, because a true fully developed turbulent flow is self-sustaining. The energy is needed to overcome the increased frictional forces that are found as a result of lamina mixing.

6.12 Womersley flow and solution*

In previous sections, we described the pulsatile nature of blood flow because of the time-varying nature of the heart contraction combined with the elastic recoil and dissipation of energy throughout the arterial circulation. In general fluid dynamics, flows that experience pulsatile changes in their flow parameters are termed *Womersley flows* (or pulsatile flows). The derivation of the principles that govern these flows was primarily derived and

*This section is considered advanced and can be skipped without a loss of continuity.

developed by J. Womersley in the 1950s, when he studied blood flow through arteries. In working toward a solution to describe these types of flows, a number of assumptions will need to be made to somewhat simplify the continuity and Navier–Stokes equations. We will assume that the fluid is flowing through a horizontal, circular vessel of constant cross-sectional area and the fluid itself is homogeneous, incompressible, and Newtonian. As we know, many of these fluid and geometrical properties do not hold for biological systems; however, these assumptions can help us arrive at mathematical solutions that can provide insight into the flow conditions. More robust solutions can be developed when these assumptions are relaxed. The wall of the constraining vessel has known elastic properties (note that we will derive solutions for a rigid wall chamber first, but the elasticity of the vessel wall should be considered) and the fluid flow is laminar, axisymmetric, and parallel to the tube wall only (e.g., $v_r = v_\theta = 0$). We will also assume that the pressure variation is a known periodic function and is the only driving force for fluid flow under these conditions. Under these simplifying assumptions (including a rigid wall analysis at this point), the continuity equation will reduce to

$$\frac{\partial v_z}{\partial z} = 0 \quad (6.56)$$

and the Navier–Stokes equations can reduce to

$$\rho \frac{\partial v_z}{\partial t} = -\frac{\partial p}{\partial z} + \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) \right] \quad (6.56)$$

Conventionally, for pulsatile flow solutions, the second term on the right side of Eq. (6.56) is written as

$$\mu \left[\frac{\partial^2 v_z}{\partial r^2} + \frac{1}{r} \frac{\partial v_z}{\partial r} \right]$$

by combining the derivative term by making use of the product rule. For the first situation that we will analyze, we will assume a pressure gradient that takes a sinusoidal form so that the pressure gradient can be represented as

$$\frac{\partial p}{\partial z} = P_0 e^{i\omega t}$$

where P_0 is a constant representing the steady-state pressure gradient across the channel and ω is the angular frequency associated with the pressure waveform. Note that for some solutions, it may be advantageous to decompose the pressure gradient into a Fourier series representation as

$$\frac{\partial p}{\partial z} = \sum_{n=0}^N P_n e^{in\omega t}$$

where P_0 (e.g. when $n = 0$) would represent the steady-state pressure gradient. The Fourier series representation is sometimes easier to understand and formulate computations with because it can be easily decomposed to significant values for n . For instance, in many cases, when n is large, the value of the exponential term is very small and may not play a significant role in the changes associated with the pressure gradient. If one assumes that the pressure takes a sinusoidal waveform, it would follow that the velocity profile would have a similar form as

$$v_z = v(r)e^{i\omega t}$$

or with the Fourier representation

$$v_z = \sum_{n=0}^N v_n e^{in\omega t}$$

In the velocity formulation, the velocity function is divided into a spatially varying component and a time-varying component. One can substitute both the pressure relationship and the velocity relationship into the Navier–Stokes equations to develop a governing relationship for this particular type of flow conditions. With some minor mathematical manipulations we get (for the first harmonic $n = 1$)

$$\begin{aligned} \rho \frac{\partial}{\partial t} (v(r)e^{i\omega t}) &= -P_0 e^{i\omega t} + \mu \left[\frac{\partial^2}{\partial r^2} (v(r)e^{i\omega t}) + \frac{1}{r} \frac{\partial}{\partial r} (v(r)e^{i\omega t}) \right] \\ i\omega \rho v(r) &= -P_0 + \mu \left[\frac{\partial^2 (v(r))}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} (v(r)) \right] \end{aligned} \quad (6.57)$$

To obtain this solution, we use the product rule for the partial derivatives and remember that $v(r)$ is not time varying and $e^{i\omega t}$ is not spatially varying. Eq. (6.57) can be rewritten and if the value of radius can be normalized as $r' = \frac{r}{R}$, where R is the radius of the circular channel, we get a more concise version of the differential equation as

$$\frac{d^2(v(r))}{dr'^2} + \frac{1}{r'} \frac{d(v(r))}{dr'} - i\alpha^2(v(r)) = \frac{P_0 R^2}{\mu} \quad (6.58)$$

Note that we changed from partial derivative to the full derivative based on our assumptions discussed previously. For those who are more familiar with mathematics, we can see that Eq. (6.58) can be conventionally solved with Bessel functions. With our solution approach, we also illustrated how the Womersley parameter (α) is defined (note that we will discuss this parameter in more details in Chapter 15).

$$\alpha = d \sqrt{\frac{\rho\omega}{\mu}} = d \sqrt{\frac{\omega}{\nu}}$$

Although we will not complete an exhaustive derivation at this point, it is important to note some of the important solutions that can be obtained from Eq. (6.58). For readers who are more interested in the derivation of these formulas, we recommend referencing

conventional fluid mechanics textbooks. For example, the instantaneous flow rate at a given cross section can be formulated as

$$Q = \frac{\pi R^2 P_0 e^{i\omega t}}{i\omega\rho} \left[1 - \frac{2J_1(i^{\frac{3}{2}}\alpha)}{i^{\frac{3}{2}}\alpha J_0(i^{\frac{3}{2}}\alpha)} \right]$$

Note that the appropriate trigonometric functions can be incorporated into this equation as needed to use this formulation in your various applications.

To extend this formulation to include the elastic properties of the blood vessel, a significant mathematical undertaking will be required. These formulations will require us to assume that the circular tube is homogeneous and responds isotropically with Hookean elastic properties. We will also assume that the tube is thin-walled, so that bending is negligible. Note that these derivations will build on the wave propagation dynamics discussed in [Section 6.8](#).

We will start our analysis by developing a relationship for the strains and stresses within the wall of the circular channel. These values will be ignored in the r -direction, because we assume that the wall is sufficiently thin so that no differences in these values can develop over the small spatial gradient. Thus, the strains in the θ and z -directions can be represented as

$$\varepsilon_\theta = \frac{2\pi(r + \phi) - 2\pi r}{2\pi r} = \frac{\phi}{r}$$

$$\varepsilon_z = \frac{\partial \zeta}{\partial z}$$

where ϕ and ζ represent the displacements in the θ and z -directions, respectively. Hookean materials follow the following generalized stress-strain relationship, which can help derive the equations for the stress experienced in the vessel walls, which become

$$\sigma_\theta = E \frac{\varepsilon_\theta + \nu \varepsilon_z}{1 - \nu^2} = E \frac{\phi/r + \nu (\partial \zeta / \partial z)}{1 - \nu^2}$$

$$\sigma_z = E \frac{\varepsilon_z + \nu \varepsilon_\theta}{1 - \nu^2} = E \frac{\partial \zeta / \partial z + \nu (\phi/r)}{1 - \nu^2}$$

where E is the elastic modulus and ν is Poisson's ratio. To continue to solve for the fluid profile, one must make a relationship for the fluid stresses along the wall of the channel and relate this to the motion of the wall. The wall fluid stresses were derived earlier in this text and will just be repeated here

$$\begin{aligned} \sigma_{rr-f} &= -p + 2\mu \frac{\partial v_r}{\partial r} & \sigma_{r\theta-f} &= \mu \left[\frac{1}{r} \frac{\partial v_r}{\partial \theta} + \frac{\partial v_\theta}{\partial r} - \frac{v_\theta}{2r} \right] \\ \sigma_{\theta\theta-f} &= -p + 2\mu \left[\frac{1}{r} \frac{\partial v_\theta}{\partial \theta} + \frac{v_r}{r} \right] & \sigma_{\theta z-f} &= \mu \left[\frac{\partial v_\theta}{\partial z} + \frac{1}{r} \frac{\partial v_z}{\partial \theta} \right] \\ \sigma_{zz-f} &= -p + 2\mu \frac{\partial v_z}{\partial z} & \sigma_{zr-f} &= \mu \left[\frac{\partial v_r}{\partial z} + \frac{\partial v_z}{\partial r} \right] \end{aligned}$$

Furthermore, the equations of motion for the circular channel can be represented as

$$\begin{aligned}\rho_{channel}h\frac{\partial^2\phi}{\partial t^2} &= \sigma_{rr-f} - \sigma_\theta\left(\frac{h}{r}\right) \\ \rho_{channel}h\frac{\partial^2\zeta}{\partial t^2} &= -\sigma_{zr-f} + \frac{\partial\sigma_z}{\partial z}\end{aligned}$$

in the r - and θ -direction, respectively. In the previous equation set, $\rho_{channel}$ is the density of the channel wall and h is the thickness of the wall. Combining the equations for the motion of the circular channel with the wall fluid shear stress formulations, we can obtain (if evaluated at the wall of the channel)

$$\begin{aligned}\rho_{channel}h\frac{\partial^2\phi}{\partial t^2} &= -p + 2\mu\left[\frac{\partial v_r}{\partial r}\right] - \frac{hE}{1-\nu^2}\left[\frac{\phi}{r^2} + \frac{v}{r}\frac{\partial\zeta}{\partial z}\right] \\ \rho_{channel}h\frac{\partial^2\zeta}{\partial t^2} &= -\mu\left[\frac{\partial v_r}{\partial z} + \frac{\partial v_z}{\partial r}\right] + \frac{hE}{1-\nu^2}\left[\frac{\partial^2\zeta}{\partial z^2} + \frac{v}{r}\frac{\partial\phi}{\partial z}\right]\end{aligned}\tag{6.59}$$

The complexity of Womersley flow analysis is that the governing fluid equations must be solved simultaneously with the stress–strain relationships in the vessel wall. Although we have discussed these general solution methods previously, an additional complication here is that we must consider the temporal variations in pressure, velocity, wall motion, stresses, etc. in the calculations in addition to the coupling of wall motion and fluid motion. Furthermore, if the vessel geometry is not uniform (e.g., there is a taper in the vessel or the vessel does not have a circular cross-section), and if gravity must be considered in the analysis, the solutions can become significantly more complicated. We have also assumed that the fluid is Newtonian and presented solutions only for the first harmonic; relaxing these assumptions will also complicate the solutions. Many numerical models have used these more complex formulations to solve their particular biofluid mechanics problems. For the majority of these cases the following boundary conditions are typically applied. The first boundary condition relates the fluid velocity at the wall to the motion of the wall in the r -direction as

$$v_r|_{r=R} = \frac{\partial\phi}{\partial t}$$

Additionally, motion of the wall in the z -direction can be related to the fluid velocity in the z -direction as

$$v_z|_{r=R} = \frac{\partial\zeta}{\partial t}$$

With these boundary conditions and the knowledge of inflow velocity and/or pressure waveforms, solutions to the previous set of differential equations can be obtained numerically.

6.13 Oscillatory blood flow and oscillatory shear index*

To extend the discussion of time-varying flow conditions, many important fluid parameters can be calculated from the known oscillatory flow solutions. Many of the parameters focus on different calculations of the wall shear stress gradient, because investigators have shown that it is not necessarily the absolute magnitude of wall shear stress that influences cell behavior but it is the variation of shear stress experienced by cells as a function of time that may be more important. In calculating these shear stress gradients it has become common to either consider the time-varying gradient at distinct and discrete regions of interest along the vascular wall or the spatially varying gradient along longer sections of the vascular wall. In particular, variations in these shear stress gradient values have been attempted to be correlated to vascular disease progression. Perhaps the simplest shear index to calculate is the temporal wall shear stress gradient (TWSSG), which is quantified as the time rate of change in wall shear stress over the time of interest. Mathematically it can be represented as

$$TWSSG = \frac{\partial \tau_w}{\partial t} \quad (6.60)$$

Analogous to Eq. (6.60), we can calculate the wall shear stress spatial gradient (WSSSG), which represents the magnitude of the spatially varying wall shear stress components in the directions of flow that are important for our particular flow conditions. In a general form, the WSSSG can be calculated as

$$WSSSG = \sqrt{\left(\frac{\partial \tau_w}{\partial x}\right)^2 + \left(\frac{\partial \tau_w}{\partial y}\right)^2 + \left(\frac{\partial \tau_w}{\partial z}\right)^2} \quad (6.61)$$

The two indices represented in Eqs. 6.60 and 6.61 can be normalized to a time-averaged version, which represents the average magnitude of the particular wall shear stress gradient experienced by the cells over the time of interest. Thus, the mean value of the TWSSG and the WSSSG, can be represented as

$$|TWSSG| = \frac{1}{T} \int_0^T TWSSG dt \quad (6.62)$$

$$|WSSSG| = \frac{1}{T} \int_0^T WSSSG dt \quad (6.63)$$

respectively. Oscillatory shear index (OSI) has also become a popular value to calculate. OSI is a unitless index that provides information about the directional changes in shear stress during the fluid cycle. In the case in which there is no net forward flow (e.g., perfect oscillation, where the reverse flow cancels the forward flow perfectly), OSI would have a

maximum value of 0.5. As you can imagine, the OSI values can vary from this depending on whether there is net forward flow or net reverse flow. OSI has been defined as

$$OSI = 0.5 \left(1 - \frac{\left| \int_0^T \tau_w dt \right|}{\int_0^T |\tau_w| dt} \right) \quad (6.64)$$

Finally, the transverse wall shear stress gradient (TaWSSG) is an index that calculates the time-averaged component of the wall shear stress that aligns perpendicularly with the mean flow direction. This value is useful in relating possible stretch-induced changes with the flow characteristics and can be evaluated with

$$TaWSSG = \frac{1}{T} \int_0^T \tau_w \cdot \left(\vec{n} \times \frac{\int_0^T \tau_w dt}{\left| \int_0^T \tau_w dt \right|} \right) dt \quad (6.65)$$

where $\vec{n}$ is representative of the surface normal to the flow field. Interestingly, many of these parameters have been shown to correlate with various pathological conditions related to atherosclerotic lesion growth and formation. Other groups have investigated other time-averaging or spatially averaging parameters to characterize the flow properties (e.g., the cross-flow index), and there are many excellent resources that the reader can refer to for a more complete discussion of these values.

6.14 Disease conditions

6.14.1 Arteriosclerosis, stroke, and high blood pressure

In [Section 5.7](#), we began a discussion of coronary artery disease and myocardial infarction as instigated through the formation of a plaque. Here we will more fully discuss the disease of arteriosclerosis and how it is manifested within the arterial system. In general, arteriosclerosis can be characterized by thickening and stiffening of the arterial wall. As we have discussed in this chapter, a decrease in the cross-sectional area of blood vessels can have multiple effects in the body. Flow can accelerate around the constriction, causing enhanced shear stresses or pressure gradients within the fluid. Flow also can be stagnated around the constriction if the pressure gradient is not large enough to overcome the enhanced resistance to flow. Flow can separate from the wall, which also decreases the mean fluid velocity and may enhance recirculation zone formation. When a mean flow velocity decreases, there is the potential for a reduction in the tissue oxygenation along with a decrease in the glucose delivered to cells. Also, stiffening of the arterial wall decreases the compliance of the vessel, and the vessel may not be able to withstand the high-pressure forces that act on the wall of the vessel. Arteriosclerosis is manifested in two main forms:

calcification of the arterial wall or atherosclerosis. Calcification is associated with the deposition of calcium salts between the tunica intima and the tunica media and a breakdown of smooth muscle cells. As discussed in Chapter 5, atherosclerosis is the deposition of lipids within the arterial wall. Monocytes that enter the vessel wall engulf the lipids, transform into foam cells, and attach themselves to the vessel wall. Foam cells can release cytokines and growth factors that aid in plaque formation.

Risk factors for arteriosclerosis include a diet high in cholesterol, high blood pressure, cigarette smoking, diabetes, obesity, being elderly, and being male (possibly from increased iron levels or decreased estrogen levels). Most of these risk factors can be addressed by having the patient make a lifestyle change. However, if the disease progresses too far, it is common for medical doctors to perform a balloon angioplasty to flatten the plaque and to use stenting to prevent restenosis or bypass surgery to redirect flow. A major focus of biofluids research efforts is on the initiation and development of cardiovascular diseases, for a number of reasons. First, cardiovascular diseases account for approximately half of all of the deaths in the United States. Many of the disease interventions are palliative, stressing lifestyle changes without addressing the root cause of the disease. Interventions focused on lifestyle changes can be largely ineffective because it is a requirement for the patient to adhere to the lifestyle change guidelines. Additionally, deficiencies of the cardiovascular system can affect many other organ systems and, thus, have wide-ranging systemic effects. It is critical to identify true mechanisms of disease initiation.

Arteriosclerosis is an inflammatory disease that arises as a result of altered fluid dynamic forces, which cause an injury to the vascular wall, and/or oxidation of lipoproteins (which transport lipids through water-based solutions, such as blood). When one of these processes occurs, it is common to see lipid deposition in the subendothelial space and proliferation of vascular smooth muscle cells, which combine to increase the thickness of the intima. Once lipoproteins become oxidized, it is common to observe enhanced expression of endothelial cell receptors that are associated with white blood cell and/or platelet adhesion (to either the endothelial cell layer or to other nonadherent cells). This helps localize inflammatory cells to the inflamed region, but in the case of arteriosclerosis, results in further damage to the underlying tissue.

Localization of white blood cells, in particular monocytes, is one of the primary determinants of whether arteriosclerosis will progress. In the early stages of lesion formation, monocytes extravasate from the blood into the tissue space and then differentiate into tissue macrophages. These macrophages engulf and retain the oxidized low-density lipoprotein cholesterol, eventually forming foam cells. These foam cells can release paracrine molecules, which attract additional macrophages to the region of plaque formation and cause the proliferation of vascular smooth muscle cells. If these functions occur for a significant amount of time without intervention, the intima begins to thicken and becomes hyperplastic. Intimal hyperplasia can have severe effects on flow around the lesion and may eventually occlude the flow, downstream of the forming lesion. These occlusions have varied effects, depending on their location and, thus, what vessels are downstream of the occlusion. For reference, there are typically four common sites for atherosclerotic lesion formation to occur within the systemic cardiovascular system. These sites include the coronary arteries (which provide blood to the heart), the branch points of the carotid arteries from the aortic arch (which provide blood to the brain), the branch points for the renal arteries from the aorta

(which provide blood to the kidney), and the branch points for the common iliac arteries where the aorta terminates (this provides blood to the lower limbs). Note that these locations are characterized by complex geometries.

When a blood vessel that supplies the brain with blood becomes atherosclerotic, there is a large possibility for stroke to develop. A stroke occurs when the blood supply to the brain is interrupted. This should be differentiated from brain hypoxia, which occurs when there is a reduction of oxygen delivery to the brain (this may occur when the atmospheric pressure reduces or during chronic pulmonary disease) even though the blood flow through the brain vasculature remains relatively stable. Cerebral ischemia, which can lead to stroke, occurs when there is an interruption in the blood supply to the brain. If this occurs over a relatively short time (5 to 10 minutes), after which the normal blood flow returns to the brain, it is atypical to see tissue death. However, if blood flow to the brain is interrupted for a longer time, it is common to see tissue death and stroke development.

To prevent an interruption in brain blood supply, the brain vascular system has a unique structure called the *circle of Willis*. The circle of Willis receives blood supply from the carotid arteries and the vertebral arteries and then supplies blood to all of the major brain blood vessels with blood. Therefore, a major blockage before or within the circle of Willis will more than likely not affect the overall blood supply to the brain because of this redundant system. However, a severe block downstream to the circle of Willis can cause a decrease in blood flow to particular sections of the brain. A brain that does not receive any blood for 5 to 10 seconds will instigate unconsciousness. It is also possible for a stroke to be generated by emboli within the vascular system. Emboli can form in a number of ways (some of these will be discussed later) but can be considered large particulate matter that flows within the vasculature. If this particulate matter becomes lodged within a significant feeding vessel to the brain, it is common to observe stroke formation.

High blood pressure (or hypertension) is a risk factor for many cardiovascular diseases. Patients with hypertension tend to have a mean arterial pressure that is greater than 110 mmHg (the normal mean arterial pressure during one cardiac cycle is approximately 90 mmHg). Typically, this relates to a diastolic pressure greater than 90 mmHg and a systolic pressure greater than 140 mmHg. In severe cases, the systolic pressure can approach 200 mmHg, with the diastolic pressure approaching 150 mmHg. Interestingly, mean systolic pressure has been shown to increase with age (from approximately 120 mmHg at age 20 to approximately 160 mmHg by age 80). This is found in both males and females; however, females tend to have a mean systolic pressure a few millimeters of mercury below the age-matched males. Additionally, the spread of mean blood pressure values found around the mean blood pressure increases with age; at 20 years old, 90% of the population is found to have a mean blood pressure between approximately 100 and 150 mmHg, whereas at 80 years old, 90% of the population is found to have a mean blood pressure between about 125 and 220 mmHg. These ranges may be considered normal depending on body mass, size, activity level, etc., so the definitions of when hypertension develops are somewhat difficult to make. Issues associated with hypertension are not necessarily related to the condition itself, but instead to conditions that it might invoke on other regions of the vascular system.

Any increases in blood pressure can lead to a higher chance of death predominantly from (1) increased work conducted by the heart, (2) hemorrhaging, or (3) vessel rupture.

Increased heart work can easily lead to heart failure because the cardiac muscle will use an excessive amount of energy to maintain the work and require a larger percentage of the blood supply. At some time, when the cardiac tissue exhausts all of the energy, the heart will not be able to contract anymore. Hemorrhaging associated with high blood pressure is common in the kidneys. This will lead to kidney failure because of the blood that is being pooled within the kidney. Kidney failure will always lead to death. Blood vessel rupture is also a serious problem if it occurs in the brain or in the cardiac tissue. As we have previously discussed, this can lead to stroke or cardiac ischemia.

A common cause for high blood pressure is excessive salt in the diet. With excess salt in the body, the osmotic balance of the blood and the extracellular fluid is shifted. To counter this, a person will typically increase the volume of fluids he or she drinks and produce more antidiuretic hormone (see Chapter 13), which both act to increase the volume of fluid within the extracellular space. With an increase in extracellular fluid, the external pressure acting on the blood vessels increases; that is, there is a preference for the blood vessels to collapse. Therefore, to maintain the same flow throughout the body, the mean arterial pressure must be increased.

Interestingly, atherosclerosis has been found in mummified remains, suggesting that the presence of atherosclerotic regions is not a new disease, solely based on changes in the lifestyles and diets of the modern world. The term *atherosclerosis* was first used in the early 1900s and was contrasted from *arteriosclerosis* by focusing more on the lipid-rich diseases, whereas arteriosclerosis is a more general disease that only requires that blood vessels thicken and stiffen. A second way to differentiate between atherosclerosis and arteriosclerosis is that arteriosclerosis tends to occur in concentric and diffuse patterns, whereas atherosclerosis tends to occur asymmetrically at particular points.

6.14.2 Platelet activation and thromboembolism

Another condition that typically occurs in parallel with cardiovascular diseases is enhanced platelet activation. Platelets can become activated after exposure to a short-duration high-intensity shear stress or other altered shear stresses (such as low-magnitude oscillatory shear stress). Activated platelets express negative phospholipids on the exterior leaflet of their cell membrane and release vasoactive compounds, release cytokines, and release growth factors. The products that platelets release on activation have the effect of activating more platelets, inducing a chain reaction that activates many additional platelets. As a result of all of these processes, it is possible for platelets to begin to aggregate onto the endothelial cell wall and to other platelets, if the activated platelets are not removed from the circulation.

Platelet aggregates can be considered small blood clots that are termed a *thrombus*. A thrombus can act like a plaque because it has the potential to block the blood flow and reduce the cross-sectional area of the blood vessel. At this point, it is possible for fibrinogen to be cleaved into fibrin and adhere to activated platelets within the aggregate. This increases the intercellular strength of the thrombus, making it harder to remove it from the circulation. As fibrin adheres to the thrombus, red blood cells and platelets can be caught within the growing thrombus. When the thrombus becomes larger, the shear forces that act on it also increase (because of the acceleration of blood around the thrombus). If the shear forces exceed

the strength of the intercellular and/or intermolecular bonds, a portion of the thrombus can break off and enter the circulation. A portion of the thrombus that breaks off of the main thrombus is termed a *thromboembolus* or *embolus* (plural emboli; in general, emboli can be any abnormal solid mass flowing within the cardiovascular system, see previous discussion).

Emboli that enter the circulation can have many devastating effects on the patient. Emboli have a definite size and mass associated with them. As they pass through the circulatory system, it is possible that emboli with different sizes become lodged in different sections of the cardiovascular system. This will cease the blood flow to that particular region, and depending on the region, it can cause death (a discussion similar to the downstream effects of lesion growth applies here; therefore, depending on the location of the blockage, various effects can be observed). If the emboli become stuck in the cerebral circulation, a stroke can occur. If they become stuck in the cardiac circulation, a heart attack or myocardial infarction can occur. In other instances, free-flowing emboli can recruit more platelets to them and potentially adhere back to a damaged endothelial cell wall. Whatever the outcome of the embolus is, it can have devastating effects within the body.

6.14.3 Aneurysm

An aneurysm (Fig. 6.28) is a bulge in the wall of an artery that is typically caused by a weakening of the muscles within the vascular wall. Because arteries carry blood under high pressure, they are more susceptible to aneurysm formation than veins. This typically occurs when a patient has high blood pressure that exceeds the viscoelastic mechanical properties of the blood vessel wall. The bulge in the blood vessel looks like a bubble within

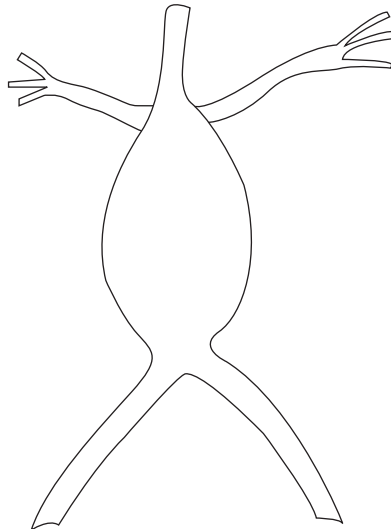


FIG. 6.28 Schematic of a saccular aortic aneurysm, which is a bulging of the blood vessel wall. Normally, the wall bulges because there is a deterioration of the muscular mass in the wall and the constant pressure loading the wall begins to bulge. In severe cases, the wall can deteriorate to such an extent that the vessel breaks and blood begins to pool in the extravascular space.

the vascular system. If the vessel wall has weakened to such a significant extent that it cannot maintain the blood pressure any longer, the aneurysm ruptures. This typically occurs in all aneurysms when they have continued to develop over a long period. Rupturing occurs because as the wall begins to weaken, it cannot withstand the pressure forces and weakens further. As the blood vessel wall continues to weaken, the bulge in the blood vessel becomes larger and the likelihood for rupture to occur increases. A blood vessel that ruptures can cause a severe hemorrhage, which may eventually lead to death, depending on the severity and the location.

Depending on the blood vessel that has experienced an aneurysm, the effect varies. Unfortunately, the arteries within the brain and the abdominal aorta are very susceptible to aneurysm formation because of their constant high-pressure loading (and unloading). A ruptured aneurysm in the brain can cause stroke or increased pressure on the brain; those in the aorta will cause excessive bleeding into the chest cavity. Blood in the chest increases the pressure on all of the organs present within the chest cavity and prevents them from functioning properly. In either case, because the blood vessel is supplying either the brain or some of the chest cavity organs with nutrients (depending on the location of the aneurysm, although approximately 95% of abdominal aneurysms occur distal to the renal arteries), the effect will be devastating.

A true aneurysm is one in which the intima of the blood vessel has bulged outside past the medial and the adventitial layers of the blood vessel wall. A false aneurysm is caused by blood leaking and clotting in a small space next to the blood vessel. The morphology of aneurysms varies, and the most common have been termed *saccular* (resembling a sphere in 3D space) or *fusiform* (resembling a cylinder in 3D space). Typical risk factors for aneurysm formation include high blood pressure, diabetes, tobacco smoke, and alcohol consumption.

It is interesting to apply some of the fundamental biofluid mechanics equations to the study of both arteriosclerosis lesion formation and the development of an aneurysm. In both cases, a simplified conservation of mass and Bernoulli principle can be used to aid in our discussion. Under these conditions, these rules can simplify to

$$A_1 v_1 = A_2 v_2$$

$$\frac{p_1}{\rho} + \frac{v_1^2}{2} = \frac{p_2}{\rho} + \frac{v_2^2}{2}$$

if we assume that the density is constant, gravitational and viscous effects are negligible, and that the flow is steady. Rearranging these equations, we can obtain

$$P_2 = P_1 + \left(\frac{\rho}{2}\right) \left[v_1^2 - \left(\frac{A_1}{A_2} v_1\right)^2 \right] \quad (6.66)$$

which shows that as the area ratio $\left(\frac{A_1}{A_2}\right)$ increases (e.g., A_2 decreases, as during a stenosis) the local pressure within the vessel decreases. This helps to accelerate the fluid through the constriction. Additionally, as the area ratio $\left(\frac{A_1}{A_2}\right)$ decreases (e.g., A_2 increases, as during

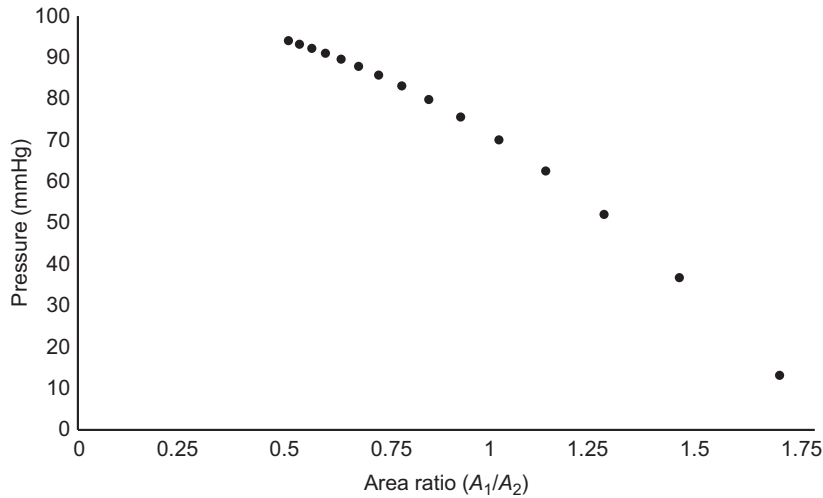


FIG. 6.29 Relationship between the ratio of the inlet area (A_1) to the outlet area (A_2) and the pressure recorded at the outlet area. This assumes that there is no variation within height between the inflow and outflow, that viscous dissipation can be ignored, and that there are no temporally varying components to this flow. As the area ratio increases (as would be seen during a stenosis), the pressure decreases and as the area ratio decreases (as would be seen during an aneurysm), the pressure increases.

an aneurysm) the local pressure within the vessel will increase. Therefore, during an aneurysm, the pressure within the aneurysm increases, which can help rupture the already weakened arterial wall. A curve of this relationship is shown in Fig. 6.29.

Summary

- 6.1. Arteries are blood vessels that transport blood away from the heart. The arterial wall is composed of three distinct layers: the tunica intima, the tunica media, and the tunica adventitia. The tunica intima is the inner layer of the vessel wall and is composed of endothelial cells. The tunica media is composed of smooth muscle cells and is typically the thickest layer within an artery. The tunica adventitia is composed mostly of connective tissue. The arterial side of the vascular system is under high pressure. The arteries have a mean pressure in the range of 90 to 100 mmHg, whereas the arterioles have a mean pressure that ranges from 40 to 80 mmHg. Arterioles are the major resistance vessels in the circulatory system.
- 6.2. Veins are blood vessels that transport blood toward the heart, and the venous wall is also composed of three layers. The major difference between the arterial wall and the venous wall is the thickness of the tunica media; the arterial wall is typically thicker than the venous wall. Another major difference between the arterial anatomy and the venous anatomy is that veins contain valves to prevent the backflow of blood toward the capillary beds. Flow through the veins is carried out under low pressure and is facilitated through the contraction of skeletal muscles neighboring the veins termed the *venous pump*.

- 6.3. Blood is composed of two major components, the cellular component and the plasma component. Under normal conditions, the cellular component accounts for approximately 40% of blood. The cellular component is divided into the red blood cells (greater than 99% of all cells), the white blood cells (approximately 0.2%), and the platelets (approximately 0.1%). Red blood cells are primarily responsible for the delivery of oxygen and carbon dioxide. White blood cells are primarily responsible for protection against foreign particles (e.g., inflammatory responses). Platelets are responsible for hemostasis. The plasma component consists of water, proteins, and other solutes such as sugars and ions, among others.
- 6.4. Rheology is the study of a flowing material combined with the study of the physical properties of that material. Plasma behaves as a Newtonian fluid and has a viscosity of approximately 1.2 cP. Whole blood, however, does not have a constant viscosity. The viscosity of whole blood varies with shear rate, hematocrit, temperature, and disease conditions, and this is predominantly due to the presence of cells and other compounds within the fluid. The Casson model for blood states

$$\sqrt{\tau} = \sqrt{\tau_y} + \sqrt{\eta\dot{\gamma}}$$

as a relationship between shear stress and shear rate, where τ_y is a constant yield stress (which varies based on hematocrit), and η is an experimentally fit constant, which approximates the fluids viscosity. Under most physiological conditions, the yield stress of blood can be approximated as 0.05 dyne/cm^2 . The velocity profile of a fluid modeled with the Casson flow can be described by

$$u(r) = \begin{cases} -\frac{1}{4\eta} \frac{dp}{dx} \left(R^2 - r^2 - \frac{8}{3} r_y^{0.5} (R^{1.5} - r^{1.5}) + 2r_y(R - r) \right) & r_y \leq r \leq R \\ -\frac{1}{4\eta} \frac{dp}{dx} (\sqrt{R} - \sqrt{r_y})^3 \left(\sqrt{R} + \frac{1}{3} \sqrt{r_y} \right) & r \leq r_y \end{cases}$$

Red blood cells can form aggregates termed *rouleaux*. Interestingly, the presence of rouleaux in the blood is dependent on the shear rate, at which the fluid is flowing. At lower shear rates, rouleaux are more prevalent, likely because of the greater time that cells can come into contact with each other and/or proteins in the blood.

- 6.5 The pressure, flow, and resistance in the arterial system are related by

$$Q = \frac{\Delta P}{R}$$

The volumetric flow rate also can be approximated using the Hagen–Poiseuille solution

$$Q = \frac{\pi \Delta P r^4}{8\mu L}$$

which is valid for laminar flow within a cylindrical tube.

- 6.6. The formulas derived for the relationship among pressure, flow, and resistance in the arterial system also can be used in the venous system. However, it is unlikely for the veins to be perfectly cylindrical. In this case the Navier–Stokes solution would need to be solved for the noncircular-shaped venous conduit, which can find a relationship between pressure, flow, and resistance. The general Navier–Stokes for cylindrical components under these conditions would be

$$v_z(r) = \frac{r^2}{4\mu} \frac{\partial p}{\partial z} + c_1 \ln(r) + c_2$$

where the integration constants would need to be obtained for the particular conditions. It is possible to do a weighted average of laminae of fluid with known average velocities.

- 6.7. The Windkessel model is a powerful representation of flow throughout the arterial circulation. It makes the assumption that the inflow properties can be defined with a time-varying component, the outflow properties are steady, and the difference in these two terms relates to the dissipation/accumulation of blood and energy within the arterial circulation.
- 6.8. Wave propagation within the arterial circulation can occur in two ways. The first is the pressure pulse that displaces the arterial wall, where a differential area would need to be considered within the properties. The mechanical properties of vessel wall would also need to be considered in these formulations. Making assumptions about the homogeneity of the arterial wall mechanical properties, the wave speed can be computed from

$$c = \sqrt{\frac{Eh}{4pr_i}}$$

The second wave that can be propagated throughout the arterial system is the fluid pressure (or velocity) at bifurcations. The geometry of the bifurcation would determine the relative division of the pressure between the branches. However, one must consider that some of the energy is reflected back along the main feed branch. In this case the relative pressure within the daughter branches and the main branch can be solved by

$$\frac{p_r}{p_p} = -\frac{Z_p^{-1} - (Z_{d1}^{-1} + Z_{d2}^{-1})}{Z_p^{-1} + (Z_{d1}^{-1} + Z_{d2}^{-1})}$$

$$\frac{p_{d1}}{p_p} = \frac{p_{d2}}{p_p} = \frac{2Z_p^{-1}}{Z_p^{-1} + (Z_{d1}^{-1} + Z_{d2}^{-1})}$$

- 6.9. At bifurcations, the flow also will be separated based on the geometry of the bifurcation. By minimizing the work that the branches conduct, a set of formulas have been developed to describe the most ideal branch angles. These formulas are

$$r_1^3 = r_2^3 + r_3^3$$

$$\cos\theta = \frac{r_1^4 + r_2^4 - r_3^4}{2r_1^2 r_2^2}$$

$$\cos\phi = \frac{r_1^4 - r_2^4 + r_3^4}{2r_1^2 r_3^2}$$

$$\cos(\theta + \phi) = \frac{r_1^4 - r_2^4 - r_3^4}{2r_2^2 r_3^2}$$

Flow separation occurs at bifurcations because the wall pressure gradient becomes positive, and therefore, the flow would tend to move upstream along the wall. Another occurrence at bifurcations is that the flow tends to skew toward the inner walls of the bifurcation. This means that the maximal velocity is no longer along the centerline of the blood vessel.

- 6.10. Most blood vessels experience a significant taper along their length. This can be modeled with the exact formulation for the wall geometry or can be simplified with steps at specified distances along the vessel length. Regardless of the choice, one would need to consider these assumptions within the formulations.
- 6.11. Within the majority of the arterial circulation, the velocity and pressure waveforms vary with time. This is directly related to the contraction (and hence the pressure pulse) of the left ventricle as well as the elastic properties of the blood vessels themselves. Because of the pulsatile nature of the blood velocity, temporal changes in the fluid parameters must be considered in biofluid mechanics problems. However, there are ways to work around the temporal changes in blood velocity and blood pressure if one considers the discrete steps in time and numerically couples the time steps. It is also possible for turbulence to develop within the arterial system at very specific locations and very specific times. However, true turbulence rarely forms because any turbulent flows would dissipate nearly instantaneously and are thus not typically self-sustaining in biological flows. In special cases one may want to analyze the flow conditions using turbulent properties. In these instances, turbulent flows are typically modeled with statistical methods, in which the time-averaged fluctuations in fluid properties must be considered, or with semiempirical modeling, which looks at a combinations of observations and theory. For a general fluid property, the formulation would be

$$\bar{u} = \frac{1}{T} \int_{t_0}^{t_0+T} u dt$$

$$u' = u - \bar{u}$$

Some of the formulations for turbulence were described within the text for completeness.

- 6.12.** Flows that experience pulsatile changes in their flow parameters are termed *Womersley flows* (or pulsatile flows). If we assume that the fluid flowing through a horizontal, circular tube of constant cross-sectional area is homogeneous, incompressible, and Newtonian, we can work toward the Womersley solutions. In many cases it has become convenient to describe the pressure gradient variation with a sinusoidal waveform as

$$\frac{\partial p}{\partial z} = P_0 e^{i\omega t}$$

Refer back to the text, but the instantaneous flow rate at a given cross-sectional area can be calculated from

$$Q = \frac{\pi R^2 P_0 e^{i\omega t}}{i\omega \rho} \left[1 - \frac{2J_1(i^{3/2}\alpha)}{i^{3/2}\alpha J_0(i^{3/2}\alpha)} \right]$$

These formulations also can be extended to include the elastic properties of the blood vessel wall allowing us to develop relationships for the changes in the vessel motion as a function of the changes in the fluid properties. One such instant of this can be formulated from

$$\begin{aligned} \rho_{channel} h \frac{\partial^2 \phi}{\partial t^2} &= -p + 2\mu \left[\frac{\partial v_r}{\partial r} \right] - \frac{hE}{1-\nu^2} \left[\frac{\phi}{r^2} + \frac{v}{r} \frac{\partial \zeta}{\partial z} \right] \\ \rho_{channel} h \frac{\partial^2 \zeta}{\partial t^2} &= -\mu \left[\frac{\partial v_r}{\partial z} + \frac{\partial v_z}{\partial r} \right] + \frac{hE}{1-\nu^2} \left[\frac{\partial^2 \zeta}{\partial z^2} + \frac{v}{r} \frac{\partial \phi}{\partial z} \right] \end{aligned}$$

- 6.13.** Recently many parameters have been developed to calculate the time-varying or spatially varying properties of the wall shear stress. Some of these are repeated below, and many of these properties have been correlated to vascular disease progression under various disease conditions.

$$TWSSG = \frac{\partial \tau_w}{\partial t}$$

$$WSSSG = \sqrt{\left(\frac{\partial \tau_w}{\partial x} \right)^2 + \left(\frac{\partial \tau_w}{\partial y} \right)^2 + \left(\frac{\partial \tau_w}{\partial z} \right)^2}$$

$$OSI = 0.5 \left(1 - \frac{\left| \int_0^T \tau_w dt \right|}{\int_0^T |\tau_w| dt} \right)$$

- 6.14. Arteriosclerosis, stroke, and high blood pressure are common diseases that affect the vascular tree. Arteriosclerosis is characterized by a decrease in the cross-sectional area of arterial blood vessels. If a blood vessel that supplies the brain becomes arteriosclerotic, it is possible for stroke to develop. High blood pressure is linked to arteriosclerosis because the heart would need to develop a high-pressure head to force blood through the vascular tree. Platelets can activate in the presence of high shear stress, which can be generated when the cross-sectional area of the blood vessels decreases. If platelets begin to aggregate, there is the potential for emboli to form, which can occlude other regions of the vascular system. An aneurysm occurs when there is a thinning of the vascular wall that eventually leads to distention of the blood vessel because it cannot maintain the high pressure within the arterial circulation.

Homework problems

- 6.1. Blood is primarily transported through the venous system by
 - a. increasing the intravascular blood pressure.
 - b. muscle contractions.
 - c. venous valve system.
 - d. b and c.
- 6.2. Which of the following changes would have the most significant effect on increasing the vascular resistance?
 - a. Doubling the blood vessel diameter
 - b. Halving the blood vessel length
 - c. Doubling the blood viscosity
 - d. Halving the blood vessel diameter
 - e. Doubling the blood vessel length
- 6.3. Discuss the salient anatomical differences between arteries and veins, and detail how this relates to the function of each blood vessel.
- 6.4. Why is the blood flow to some organs (such as the stomach, intestines) discontinuous and the blood flow to other organs (such as the brain, heart) continuous?
- 6.5. The plasma component of blood contributes approximately ____ percent to the total blood volume, of which water accounts for ____ percent of the total plasma volume.
- 6.6. Discuss the important proteins that are found in plasma. Why are the concentrations of these proteins so tightly regulated?
- 6.7. Discuss coagulation and the role of platelets in the coagulation process.
- 6.8. When you are dehydrated, it would cause an (increase or decrease) in the hematocrit. What effect would this have on blood flow, viscosity, blood pressure, etc.?
- 6.9. The three cellular components of blood have different anatomical structures that relate to their functions. Briefly discuss the important structures for each cellular component.
- 6.10. Calculate the difference in blood flow rate for a 5-cm section of a blood vessel with a pressure difference of 25 mmHg that experiences an increase in blood vessel diameter from 100 to 200 μm . Also calculate the blood flow rate for a constriction that reduces

Homework problems (cont'd)

- the diameter to 50 μm . For each of these three cases, what is the vascular resistance? Assume that blood viscosity is 3.5 cP.
- 6.11. When a patient experiences high blood pressure, discuss what happens to the vascular flow rate. What changes must occur to allow the vascular flow rate return to normal conditions? Assume that the peak systolic blood pressure for the hypertensive patient is 190 mmHg and that the diastolic pressure is 130 mmHg. Compare this flow with the normotensive case (120/80 mmHg).
 - 6.12. Calculate the wave propagation speed for a 100- μm -thick blood vessel with a radius of 10 mm. This blood vessel has a pressure of 85 mmHg and a Young's modulus of 12.5 kPa. Under disease conditions, the vascular wall can stiffen so that the Young's modulus approaches 30 kPa. Calculate the change in the wave speed under these conditions. What blood vessel property is likely to change in response to the increase in stiffness and why?
 - 6.13. Model the pressure wave propagation at a branching junction where one parent vessel branches into two daughter vessels (e.g., Fig. 6.16). Assume that the diameter of the parent branch is 100 μm , the diameter of one daughter branch is 60 μm , and the diameter of the other daughter branch is 45 μm . Assume that the thickness of each vessel is the same and is 10 μm , that the incident pressure within each branch is 50 mmHg (for wave propagation), and that the Young's modulus of each vessel is 15 kPa. Calculate the reflected pressure and the pressure within each daughter branch.
 - 6.14. Calculate the radius of the parent branch knowing that the radii of the two daughter branches are 400 and 435 μm . Determine the bifurcation angles and draw an accurate figure of this branch.
 - 6.15. Calculate the radius of the daughter branches and the angles of bifurcation if the parent branch has a radius of 500 μm .
 - 6.16. Can Murray's law be extended to a more complicated branching pattern (i.e., two daughter branches that branch in three dimensions or three daughter branches)? If so, derive the applicable relationships.
 - 6.17. The velocity through a tapering channel can be estimated as $\vec{v} = v_i \left(1 - e^{\frac{2x}{L}}\right) \hat{i}$. Calculate the acceleration of any particle along the centerline and the position of a particle that is located at $x = 0$ at time 0, where L is the vessel length and v_i is the inflow centerline velocity.
 - 6.18. The radius of a continuously tapering blood vessel can be modeled as $r(x) = r_i \left(e^{-\frac{x}{L}}\right)$. Determine the velocity and the acceleration of the fluid within this blood vessel.
 - 6.19. Under atherosclerotic conditions, the aorta can reduce in cross-sectional area. Is it more likely for the blood flow to remain laminar or become turbulent? What would happen to the blood flow if there is an aneurysm present within the aorta?
 - 6.20. Show that the volumetric flow rate for a Casson model of blood flow is

$$Q = \frac{\pi R^4}{8\eta} \left[-\frac{dp}{dx} - \frac{16}{7} \left(\frac{2\tau_y}{R}\right)^{0.5} \left(-\frac{dp}{dx}\right)^{0.5} + \frac{4}{3} \left(\frac{2\tau_y}{R}\right)^4 \left(-\frac{dp}{dx}\right)^{-3} \right]$$

Continued

Homework problems (cont'd)

- 6.21. If the elastic deformation of the blood vessel wall is relatively small, what happens to the pressure flow relationship? Show the approximate function and describe the physiology behind this.
- 6.22. If the diameter of a person's aorta is abnormally large, would the flow through the aorta more likely be laminar or turbulent? What if the heart rate is increased but flow rate is maintained the same?
- 6.23. In a Casson model of flow, the yield shear stress varies with hematocrit as $\tau_y = (0.325 * Hct)^3$, where Hct is the hematocrit (e.g., 0.4). Plot and describe this relationship for various cardiovascular diseases.
- 6.24. We defined various shear stress parameters that can be used to characterize flow through biological vessels (including TWSSG, WSSSG, OSI, and TaWSSG). Because the calculations of these values typically takes into account time or spatially varying shear stress parameters, write a simple numerical code that can extract the shear stress gradient from numerical simulations and calculate these parameters. Also, discuss the relevance of these parameters in the context of pathological disease development.

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Microvascular beds

LEARNING OUTCOMES

- Contrast capillary physiology versus arterial and venous physiology
- Describe the important structures within a capillary bed
- Examine mass transfer across the capillary wall
- Discuss endothelial cell physiology
- Discuss smooth muscle cell physiology
- Identify the mechanisms for information transfer between endothelial cells and smooth muscle cells
- Assess the theories for local control of blood flow
- Model the pressure distribution throughout microvascular beds
- Model the velocity distribution throughout microvascular beds
- Develop the Stokes equations to describe flow through microvascular beds
- Analyze the drag force on particles immersed within a fluid
- Discuss the relevant physiology of the interstitial space
- Formulate a relationship between flow through the capillary wall and the pressure within the capillary and the interstitial space
- Compare the hematocrit in capillaries to larger blood vessels
- Describe the Fahraeus–Lindquist effect
- Distinguish between the Fahraeus and the Fahraeus–Lindquist effect
- Illustrate the plug flow principle in capillaries
- Model the accumulation of species within the microcirculation
- Analyze blood flow within capillaries as a two-phase fluid
- Describe the interactions of blood cells with the endothelial cell wall
- Explain disease conditions that affect microvascular beds

7.1 Microcirculation physiology

Throughout the first two sections of this textbook, we have restricted our discussion of fluid mechanics to flows that remain within their particular container (e.g., large blood vessel). This means that mass continuity includes only inflows, outflows, changes in the container volume, and changes in the fluid density. However, for flows within the microcirculation, there is an additional transport, that is, the transport of fluid and molecules into or out of the blood vessel into the interstitial space across the wall of the containing blood vessel. One may consider that we should just add an additional lumped sum inflow and/or outflow parameter to include the flow across the vessel wall. Although this approach may lead to a reasonable approximation of the flow, solution methods do not typically use this approach because of the possible changes in the transport, which cannot be easily modeled with singular inflow/outflow parameters. Instead, to model this phenomenon, we typically make use of permeability concepts that will need to be included in the mass balance formulations. The benefit of this type of approach is that permeability as a function of time and/or space (along the capillary wall) can be easily included into the analysis, in lieu of a single permeability value. Furthermore, permeability for different species can be included if the functions for each of those species are known. We will see in later sections of this chapter that the permeability through the vascular wall is not constant and not uniform for all of the different molecular species. This transport across the vascular wall is arguably the most crucial function that the entire cardiovascular system performs. Without this function, few cells within the human body would be able to obtain oxygen or glucose, and these same cells would not be able to remove cellular wastes from their local environment.

Microvascular beds are primarily composed of capillaries, which are small, thin blood vessels. In fact, the vascular wall of capillaries is composed of a single layer of endothelial cells without any substantial connective tissue or smooth muscle cell layer. These cells are highly permeable and partially regulate the transport of molecules across the vascular wall. It has been estimated that there are on the order of 35 billion capillaries within the systemic circulation, with a total surface area of approximately 2000 m^2 , all of which are available for molecular transport/exchange. Nearly all cells are within $50 \text{ }\mu\text{m}$ of a capillary, which is within the free diffusion distance for all essential nutrient transportation (this will be discussed in detail in Chapter 8). Cells outside of this range would require some form of facilitated (and possibly active) transport to obtain nutrients and remove wastes. Clearly, the net efficiency of transport would decrease significantly if the majority of cells were outside of the approximately $50\text{-}\mu\text{m}$ distance from capillaries. Furthermore, if this were the case, a significant percentage of metabolic energy would be expended on these transport functions, because it would be likely that an active process would be required to transport nutrients over the significant distances.

At the point at which the arterial circulation has branched into arterioles that are on the order of 10 to $15 \text{ }\mu\text{m}$ in diameter, the regulation of the blood flow through these vessels becomes critically important to the capillary beds. Vessels within this diameter range are typically called *metarterioles* (or terminal arterioles). These are the last blood vessels that have a smooth muscle cell layer before blood enters the capillary bed (most capillaries have an internal diameter ranging between 5 and $8 \text{ }\mu\text{m}$). At the point where a metarteriole diverges

into a capillary, there is one last smooth muscle cell that encircles the blood vessel. This smooth muscle cell is termed the *precapillary sphincter*. Like all sphincters, it closes the lumen of the particular vessel (or channel) when it constricts and opens the lumen when it dilates. Therefore, in the case of precapillary sphincter constriction, the resistance to flow through the particular downstream capillary network increases significantly and the pressure gradient typically cannot overcome this resistance to flow. Therefore, in the microcirculation when a precapillary sphincter constricts, blood is shunted from the capillary bed downstream of that sphincter to a different microvascular bed because the resistance to flow through the constricted sphincter is too large to permit blood flow. Once blood has passed through a capillary, blood vessels begin to converge into venules; eventually the blood vessels continue to converge and return blood to the heart by the inferior and superior vena cava. This leads to an important definition. A true capillary is defined by divergent flow at its inlet and convergent flow at its outlet (Fig. 7.1).

It is important to note here (although we will discuss this more fully in Section 7.3) that the metarterioles (and hence the precapillary sphincters) are in a close proximity to the capillaries themselves. This allows for the local changes in nutrient concentrations (e.g., oxygen, glucose) or waste concentrations (carbon dioxide, metabolites) within the downstream capillary bed to partially regulate the dilation and constriction of the precapillary sphincter. Because of the relatively close proximity between the capillaries and the precapillary sphincters, the overall “needs” of the neighboring tissue can rapidly, within a few seconds, be addressed. Thus, there is not a significant demand for an overarching “central command center” for every capillary bed within the cardiovascular system, and furthermore, the response time of such a centralized controller would potentially be too large to accommodate tissue needs, reducing the overall efficiency of blood transport, nutrient delivery, and waste removal through the microvasculature.

There are four common types of capillary bed organizations in the cardiovascular system, and they are classified by their ability to compensate for arterial or venous blockages. The supply to the tissue can be defined as either independent or overlapping (Fig. 7.2).

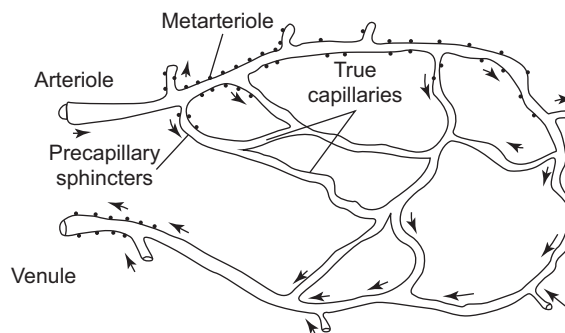


FIG. 7.1 Typical structure of a capillary bed, which is fed by an arteriole. Metarterioles are the last vessels on the arterial side that have a smooth muscle layer. These vessels highly regulate the flow through the microvascular beds. The last endothelial cell associated with a smooth muscle cell is termed the *precapillary sphincter*, and it is this cell that determines blood flow through capillaries. True capillaries are defined with divergent flow at their inlet and convergent flow at their outlet. Capillaries feed blood into the venous circulation. (Modified from *Textbook of Medical Physiology*, 10th edition, Saunders.)

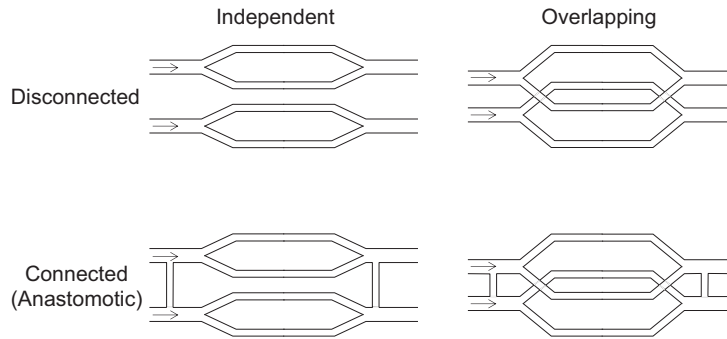


FIG. 7.2 Schematic of different arrangements of capillary networks. Capillary networks can be independent of neighboring networks or they can overlap neighboring networks. Additionally, neighboring networks can be disconnected or connected (termed anastomotic). Each of these organizations has advantages and disadvantages, which include redundancy (for anastomotic and overlapping networks, but for different reasons) or ease of downstream control for independent and disconnected networks. Most tissues have a combination of these different types of networks. Note that the collateral circulation typically has little to no flow and is only used under pathological conditions.

Independent arrangements of capillary beds suggest that one and only one capillary bed supplies one tissue region with blood, whereas an overlapping arrangement would have multiple capillary beds supplying one tissue region with blood. In either of these arrangements, the terminal arterioles and/or postcapillary venules may be disconnected or connected with each other. Disconnected systems do not allow mixing or shunting of blood between the microcirculation regions, whereas connected systems, also termed *redundant systems*, allow for mixing of blood between microcirculation regions. In the redundant system, the connected vessels are said to be anastomotic, and this special redundant circulation is sometime referred to as the *collateral circulation*. Each of these types of organizations are viable options to perfuse the tissue but there are some very important implications regarding the different designs of these systems. Comparing the extreme cases, we can see that a disconnected independent network is very susceptible to any damage upstream of the capillary network. For instance, an occlusion upstream would prevent any blood from reaching the downstream tissue. However, the specific and precise control of flow to any downstream tissue region is very easy with these types of arrangements. Compared to the other extreme case, it would be relatively difficult to control the tissue perfusion within an anastomotic overlapping system. However, these systems are not as susceptible to upstream blockages. Each of these types of systems, which are depicted in Fig. 7.2, can be found throughout the body.

Flow through capillary beds is typically not continuous. Depending on the tissue that the capillary bed is feeding, the flow can alternate between on and off every few seconds or up to every minute, in a process termed *vasomotion*. As stated earlier, the changes in flow are controlled by the dilation and constriction of the precapillary sphincters. Tissue oxygenation is the most critical factor that affects local vasomotion. A tissue that is under hypoxic conditions for a few seconds will rapidly induce the precapillary sphincters to dilate. An interesting point about changes in vasomotion is that it is independent of the organization of the

capillary arrangements shown in Fig. 7.2; changes in capillary perfusion can alter the precapillary sphincter of any feeding arteriole. The most common cause for decrease in oxygen concentration is an increase in oxygen use through a cellular respiration process. Under these conditions, when there is a large oxygen demand, the flow through that particular vascular network will be turned on for a larger percentage of time and turned off only for very short periods. This helps prevent other neighboring tissue locations from becoming hypoxic. This condition would persist until the tissue oxygen concentration returns to normal levels. Once the oxygen levels within the capillary bed return to the specific tissues' normal level, the flow throughout the network returns to its regular on/off pattern.

As stated earlier, flow through the capillary is not the only flow that occurs. There is also a flow of molecules across the endothelial cell wall; nutrients typically have a net movement out of the blood vessel, whereas metabolic wastes typically have a net movement into the blood vessel. The capillary wall is composed of a single endothelial cell and has a thickness on the order of $0.5\ \mu\text{m}$. The extravascular side of the endothelial cell is directly connected to the extracellular matrix of the surrounding tissue. In most capillary beds, there are two major methods for molecular transport across the endothelial cell barrier: the intercellular cleft and plasmalemmal vesicles (Fig. 7.3). Both of these methods will be discussed in more detail throughout the remainder of this section. There are some exceptions to these transport mechanisms, in specialized capillary beds, such as the fenestrated capillaries of the glomerulus or the continuous capillaries within the brain microvasculature.

The intercellular cleft is the location where two neighboring endothelial cells associate with each other. Note that we used the term *associate* because endothelial cells do not come directly into contact with each other. Between neighboring endothelial cells there is a gap of approximately 10 to 15 nm in thickness (see Fig. 7.3, termed *intercellular cleft*). The endothelial cell–endothelial cell association that maintains the intercellular cleft is primarily carried out by gap junctions, cadherins, and other cell membrane adhesion proteins.

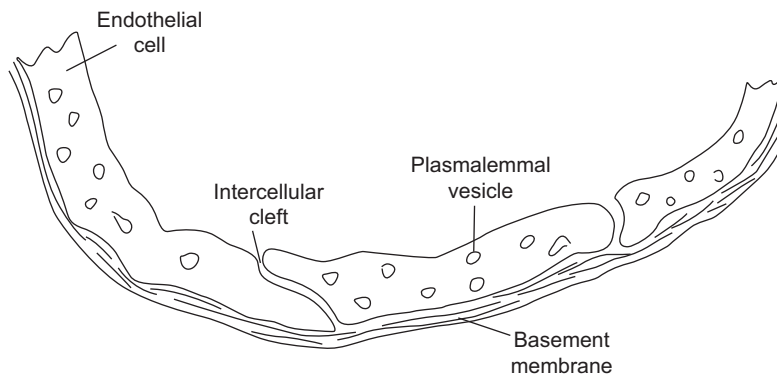


FIG. 7.3 Cross-section of a capillary, showing possible transport mechanisms across the capillary wall. Recall that the capillary is composed of a single endothelial cell (in thickness) surrounded by a small basement membrane. There are typically two to three endothelial cells that form a capillary in circumference, but these cells do not overlap with each other in thickness. In between endothelial cells, there is an intercellular cleft that is responsible for the majority of transport between the blood and the extravascular space. Plasmalemmal vesicles are responsible for the transport of larger molecules; however, this is a slow transport mechanism. (Modified from *Textbook of Medical Physiology*, 10th edition, Saunders.)

These clefts represent a very small proportion of the total capillary surface area (about 1/1000 of the total available surface area). However, because the permeability of nutrients across this barrier is so large, some of the most important molecules that need to be transported, can diffuse very rapidly through the intercellular cleft. Furthermore, flow through the intercellular cleft is approximately 80 times faster than blood flow through the capillary itself, and, therefore, this allows for a rapid equilibrium to be reached between the blood and the interstitial fluid. This type of intercellular cleft is present in most tissues. Two exceptions are the brain and the liver, where the intercellular cleft is much smaller and much larger, respectively, compared with the cleft discussed. In the brain capillaries the cleft is so small that only small molecules are allowed to pass (such as oxygen, glucose), preventing the entrance of potential dangerous and unwanted compounds into the brain tissue. In the liver, the cleft is so large that even plasma proteins can pass through this space. Because the liver partially acts to detoxify blood, it requires access to all of the blood components. In general tissue, only metabolically important compounds are transported through the intercellular cleft, except for within the liver capillaries and other fenestrated capillary beds (refer to Chapter 14), where many other large compounds can pass through the cleft space.

The second method of transport across the endothelial cell is by plasmalemmal vesicles. These vesicles form on both the vascular side and the interstitial side of the endothelial cell by a cellular invagination process. Through this process, fluid and molecules are trapped within the vesicle and then are slowly transported to the opposing endothelial cell surface, through the endothelial cell itself. Once the plasmalemmal vesicles reach the opposing endothelial cell surface, they fuse with the cell membrane and release the contents into the vascular space or the interstitial space. This is clearly not an effective method to transport nutrients/wastes to every cell within the body because it is slow and requires a significant amount of energy to form vesicles and transport them across the cell. However, larger molecules that cannot fit through the intercellular cleft are transported with this mechanism. Additionally, the efficiency of this system is relatively low compared with transport through the intercellular cleft.

7.2 Endothelial cell and smooth muscle cell physiology

As already discussed, endothelial cells compose the interior lining of all blood vessels within the body. These cells can partially regulate the transport of nutrients across the blood vessel wall and play a very critical role in coagulation and inflammation reactions. Endothelial cells join to form a sheet with one of three different structures. Continuous endothelial cells are found in arteries, veins, and capillaries throughout the body. The transport of nutrients across these endothelial cell sheets is regulated by the type and quantity of junctions between neighboring cells. Primarily, cadherin junctions mediate cell–cell adhesion and gap junctions regulate the communication between cells. Endothelial cells are typically 10 μm in width, and, depending on their location within the circulatory system, their length can vary from 50 to 200 μm (note that the cell thickness is on the order of 1 to 2 μm and varies based on the location within the cell). Continuous endothelial cell capillary beds are by far the most commonly found in the body. A subset of continuous endothelial cells are endothelial cells that essentially prevent the free diffusion of molecules between the blood vessel and the

extravascular space. These types of capillaries are primarily found in the vasculature that surrounds the brain and helps restrict the movement of molecules into the central nervous system.

The second type of endothelial cell sheets is the discontinuous endothelial sheet. These are endothelial cells that are not as tightly connected to each other as some of the other structures. This allows for a free diffusion around the endothelial cells and is typically present in the liver and spleen. Most large molecules, including proteins, can pass through this type of endothelial cell sheet, and as the reader can imagine this is a very specialized type of endothelial cell organization that would not be viable in many tissues. The third type of endothelial cell sheet is the fenestrated endothelial sheet. These types of endothelial cell sheets are located within the kidney's glomerulus and have intercellular connections similar to those of continuous endothelial cells. However, there are channels that span throughout the entire cell that effectively expose the extracellular space to the blood vessel lumen. These channels facilitate the movement of large molecules across the endothelial cell wall. In the glomerular capillaries, it is the podocytes and the slit membrane that are primarily responsible for restricting the diffusion of molecules between the blood vessels and the nephron tubules and not the endothelial cells that restrict diffusion.

Vascular endothelial cadherin (VE-cadherin) is the primary cadherin located on the endothelial cell membrane. This protein is expressed as a dimer of two cadherin proteins. Each protein passes through the cell membrane and has an intracellular portion that is connected to the cytoskeleton. This strong cytoskeletal connection allows for force transmittance through the endothelial cell. The association of these proteins depends on the local calcium concentration. With calcium concentrations lower than approximately 0.5 mM, each cadherin dimer dissociates and then the individual cadherin monomers cannot make connections to other cells or the cytoskeleton. When the calcium concentration increases above the approximately 0.5 mM threshold, cadherin monomers associate into dimers and can then adhere to a cadherin dimer from a neighboring cell. The role of cadherin is to connect cells together and mechanically couple the endothelial cell sheet with the intracellular load-bearing components.

Vascular smooth muscle cells perform mechanical work in a manner similar to the way that skeletal muscles perform mechanical work, except that the loads they transmit are typically orders of magnitude lower than the loads transmitted by skeletal muscle. Smooth muscle cells contract when actin and myosin form a cross-bridge. Similar to skeletal muscle, calcium regulates cross-bridge formation in vascular smooth muscle cells. However, the internal arrangement of proteins within the smooth muscle cells is vastly different from the ubiquitous sarcomere structural unit seen in skeletal muscle cells. The size of vascular smooth muscle cells is also smaller than that of skeletal muscles. They typically range from 1 to 5 μm in diameter and approximately 100 μm in length.

Neighboring vascular smooth cells form one structural unit that contract or dilate as one large muscle "fiber." The cell membranes of these cells are connected to each other by cadherin junctions (similar to endothelial cells) and gap junctions. This allows for the uniform force generation across smooth muscle cell sheets. Gap junctions are also present within the sheet of smooth muscle cells to electrically couple neighboring cells. Gap junctions allow for the free movement of ions between cells. Similar to the cardiac muscle cells, this allows for the rapid transmittance of the ions that can lead to an action potential between cells.

Interestingly, there is a second group of specialized gap junctions that allow for the free communication between endothelial cells and smooth muscle cells.

Briefly, there are many similarities between smooth muscle and skeletal muscle contraction. However, within smooth muscle cells, actin and myosin filaments are able to interact without the troponin/tropomyosin complex, which regulates skeletal muscle contraction. Smooth muscle cell contraction is regulated by calcium and adenosine triphosphate (ATP) concentration in a slightly different way than that of skeletal muscle. In addition, instead of a sarcomere subunit, smooth muscle cells have a more disorganized structure. Actin filaments are directly connected to dense bodies, which are typically located within the cell membrane of the smooth muscle cell (note that some dense bodies are located sporadically throughout the cytoplasm). Myosin filaments are randomly dispersed throughout the cytoplasm, potentially coming in contact with the actin filaments (Fig. 7.4). Cell membrane-associated dense bodies of one smooth muscle cell can adhere to cell membrane-associated dense bodies of a neighboring smooth muscle cell, which allows for force transmittance throughout the vascular smooth muscle sheet. Because of this seemingly random arrangement of dense bodies, there is no “net” organized contraction direction within the smooth muscle cell; however, the extent of connections between smooth muscle cells and how those connections are organized can dictate the contraction direction.

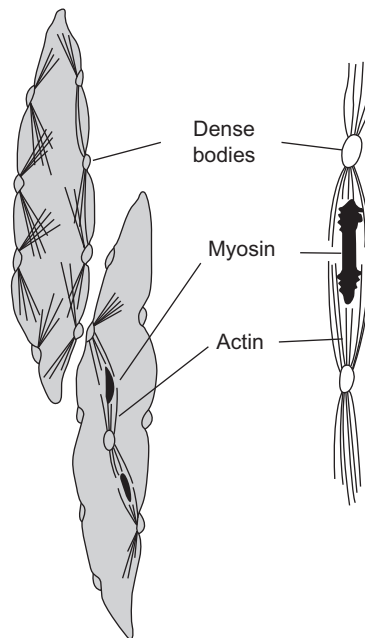


FIG. 7.4 Structure of a smooth muscle cell, with an *inset* showing the relationships among actin, myosin, and the dense bodies. Adjacent smooth muscle cells can be physically connected at the dense body locations, which are also interspersed throughout the cell's cytoplasm. These connections allow for force transmittance between cells. The actin and myosin in smooth muscle have a much more random organization and orientation than skeletal or cardiac muscle cells, allowing for contraction in multiple directions. (Modified from *Textbook of Medical Physiology*, 10th edition, Saunders.)

To initiate smooth muscle cell contraction, intracellular calcium ion concentration increases in response to nervous input, humoral signals, hormonal signals, and mechanical stretch. Once there is a sufficiently high calcium ion concentration within smooth muscle cells, calmodulin activates through the binding/association of calmodulin with four calcium ions. Calmodulin, instead of troponin, initiates myosin–actin cross-bridge formation by activating a separate protein, myosin kinase (calmodulin associates with myosin kinase, forming a protein–protein complex). One of the myosin protein chains becomes phosphorylated, through the action of myosin kinase, which is always active when calmodulin associates with four calcium ions. This allows myosin to constantly form cross-bridges with actin if sufficient ATP is present. To stop this process, a second enzyme, myosin phosphatase, removes the phosphate group from myosin and thus myosin can no longer form cross-bridges with actin. As long as there is a high enough concentration of calcium within the vascular smooth muscle cell, calmodulin and myosin kinase remain active, and therefore myosin is always in a phosphorylated state. However, once the calcium concentration drops below a critical value, calmodulin dissociates from calcium and myosin kinase, thus causing myosin kinase to become inactive. Therefore, under these conditions, actin cannot form cross-bridges with myosin because myosin phosphatase is the dominate enzyme. A quite complex signaling pathway transmits an extracellular signal to increase intracellular calcium concentration. The following section deals with the control of intracellular calcium in response to various external signals.

7.3 Local control of blood flow

The basis for the local control of blood flow rests with the needs of the tissue that the capillary network supplies. This means that every tissue in the body can have a slightly different requirement at one instant in time and also that this requirement can change over time based on the tissue's energy usage. For instance, how much blood does the gastrointestinal system tissues/organs need immediately before eating Thanksgiving dinner (assuming you have not smelled the food cooking yet) compared with immediately after eating Thanksgiving dinner? Would this be different? In general, the answer is that yes, the needs of the gastrointestinal system are different immediately before a meal compared with after the meal. Continuing the example of the gastrointestinal tract, any nutrients that have been broken down in the system and need to be absorbed into the cardiovascular system will be absorbed after eating a meal and generally not before eating a meal. In the stomach, the motion of the stomach and the secretion of gastric juice accelerates after eating a meal, and thus the blood flow would need to accommodate and account for these changes. This is one of the reasons why it is easier to get skeletal muscle cramps during a workout immediately after consuming a meal. Under these conditions, a certain percentage of the blood is directed to the digestive system, and therefore, there is potentially not enough blood to supply the skeletal muscular system with sufficient nutrients (and the reduced blood supply cannot remove the increased metabolic wastes of the skeletal tissue) it needs to function. Blood flow to any particular tissue is normally maintained at a level just above the minimum requirements for that tissue. The most critical nutrient for most tissues is oxygen, and therefore, this minimum requirement would be based on the level of oxygen needed to maintain the normal tissue

oxygenation level for that tissue (note that the required oxygenation level can be very different for different tissue types) but not to significantly exceed the normal tissue oxygenation level (this would be hyperoxic conditions). If all tissues in the body were constantly supplied with blood to significantly exceed its particular tissue oxygenation level, the amount of blood needed would exceed the work capacity of the heart, and nutrient delivery would not be effective. In addition, because tissues do not store oxygen, most of the excess delivered oxygen would go to “waste” and would be expelled out through the lungs or potentially diffuse out of the skin. Therefore, under normal conditions, the blood supply to all tissues meets the minimum requirements of the tissue and does not surpass this value.

In general, there are two mechanisms to control blood flow to tissues. The first mechanism is an acute local control, which accounts for rapid constriction or dilation of the blood vessels. The second control system is a long-term control, which leads to changes in the number of blood vessels and/or the resting size (diameter/length) of the blood vessel. We will restrict our discussion to the rapid acute control mechanism at this point, because the mechanism(s) involved in the long-term control are fairly complex and there are a significant number of control systems involved with this process.

As mentioned earlier, the first major regulator of blood flow is the tissue oxygenation level. When the quantity of oxygen in the blood or the quantity of oxygen within the tissue reduces, there is an appreciable increase in the blood flow to that tissue. The rate of blood flow increase is almost inversely proportional to the percentage of oxygen within the arterial blood. At a level of 50% of the normal oxygen concentration, the blood flow increases by approximately 2 times. At a level of 25% of the normal oxygen concentration, the blood flow increases by slightly more than three times. However, be cautioned that these changes are not described by a linear relationship. The first possible mechanism that regulates increased blood flow under decreased arterial oxygen concentration is an increased vascular adenosine concentration to act as a vasodilator (other vasodilators [e.g., carbon dioxide, nitric oxide, and hydrogen ions] can follow a similar mechanism, but currently it is unknown which of these vasodilators plays the most significant role in physiological changes). As a result of a decreased availability of oxygen, the surrounding tissues release adenosine (or other dilators) into the bloodstream. These dilators cause the local vascular smooth muscle cells to relax and effectively increase blood flow to that tissue by increasing flow through the capillary network. One problem with this theory is that the vasodilator that is released into the blood capillaries would have to diffuse against the blood flow (i.e., upstream) to the arterioles/precapillary sphincters to have a substantial effect on blood flow changes. Therefore, this mechanism cannot account for all of the vascular changes seen in response to low tissue oxygenation.

A second common thought is that low oxygen concentration itself can directly induce changes in the diameter of blood vessels. There is some evidence for this mechanism as well, but the same problem about downstream sensing receptors and the communication to the upstream vascular smooth muscle cells is associated with this theory. However, a better theory would include some combination of these mechanisms. Some microcirculatory research groups have experimental results that suggest that there is a rapid communication between the endothelial cells that form the capillaries and those that line the metarterioles. This communication exists through the presence of gap junctions between cells and can progress in an upstream direction. In a manner similar to that in the previously discussed theory, when oxygen (or other nutrients) concentration decreases in the tissue supplied by the

capillary beds, by-products of cellular respiration or other vasoactive compounds or signaling molecules can be formed that alter endothelial cell functions. These compounds can then be transported up through the vascular network to the endothelial cells that form the lining of the metarterioles, by intercellular channels such as gap junctions. With this communication mechanism, there would be no problem associated with movement against the blood flow direction. Once these compounds have made it to the metarteriole location, they can communicate with the precapillary sphincters to induce constriction or dilation depending on the need of the tissue. It is known that there are communicating junctions between endothelial cells and vascular smooth muscle cells that help regulate changes in the diameter of the blood vessel. However, we also know that vasoactive compounds are released into the bloodstream. Therefore neither theory represents the physiology completely, but as stated earlier, it is likely that some combination of these theories would be responsible for changes to the caliber of the blood vessel diameter.

There are two other theories related to the local blood flow regulation that are based on the pressure changes that can occur within the blood vessel. Imagine an increase in arterial blood pressure. This would be accompanied with an increase in blood flow to the tissue, causing an increased oxygen/nutrient delivery to the tissue. It has been experimentally shown that within a minute, this increase in blood flow returns back to normal levels in a process termed *autoregulation of blood flow*. The first theory, the metabolic theory, proposes that an increased oxygen/nutrient delivery causes constriction of the blood vessels in much the same way that was discussed previously. Increased oxygen (or nutrients) causes an increase in cellular by-products to be released within the vascular network (or within endothelial cells), which directly communicates with precapillary sphincters, causing a constriction. The second theory, the myogenic theory, suggests that it is not cellular compounds that regulate blood flow. Instead, the constriction of blood vessels is caused by the pressure-induced stretch of the blood vessels. It has been observed that after blood vessels experience a small sudden stretch, the vascular smooth muscle cells begin to constrict to counter the stretch and as a response to the increased stresses that are imposed on the cells. When the pressure reduces in the blood vessels, the diameter suddenly reduces, causing a relaxation of the vascular smooth muscle cells to counter the decreased pressure forces. This relaxation may be the result of mechanical factors to counter the reduced blood vessel diameter and/or changes in the release of local metabolically active compounds. Either of these changes has the net effect of bringing the vessel back to its normal resting state, thus maintaining a normal/regular pressure within the particular vessel. Again, it is likely that some combination of all of these mechanisms is responsible for the local control of blood vessel diameter.

We will now briefly discuss the humoral regulation of blood vessel diameter. Three of the most potent vasoconstrictors are vasopressin, angiotensin, and norepinephrine. Vasopressin works in conjunction with the kidneys to increase water absorption by decreasing the flow through the circulatory system. Angiotensin acts to increase the vascular resistance of all of the arterioles within a specific tissue upon release. This effectively decreases blood flow through the tissue. During stress situations, norepinephrine is released and can partially regulate blood flow to areas of need by shunting blood away from areas with a lower need. Two of the most potent vasodilators are the superfamily of kinins and histamine. These compounds have direct roles in the inflammatory response by increasing vascular flow to an inflamed region. Additionally, these compounds increase the permeability of the capillaries to allow for the rapid extravasation of white blood cells.

7.4 Pressure distribution throughout the microvascular beds

The pressure gradient across microvascular beds has been shown to be one of the most critical fluid parameters in regulating the flow throughout these vessels (the fluid velocity is so slow in these vessels that small changes in the pressure can induce large changes in the flow conditions, including velocity, shear stress, and shear rate). The pressure gradient across microvascular beds has been experimentally measured using two flow probes inserted into various branches along the network. By knowing the distance between these probes and the pressure readings obtained from the probes, an estimate of the pressure gradient can be calculated. This estimate may assume that the pressure gradient varies linearly with distance and that time-varying changes and wave propagation are minimal in the microcirculation, among other simplifying assumptions. As the diameter of the blood vessel decreases through the vascular network (e.g., arterioles to capillaries), the pressure gradient significantly increases. In contrast, as the diameter of the blood vessel increases (capillaries to venules), the pressure gradient reduces again. This can be explained by the rapid changes in hydrostatic pressure within the precapillary arterioles, caused by constriction or dilation of the precapillary sphincter.

In contrast, the hydrostatic pressure within the arteriolar side of the circulation is relatively constant until the blood vessels approach a diameter of approximately 40 μm . Therefore, the pressure gradient throughout these vessels is relatively low (refer to Fig. 6.27, which shows that the mean arterial pressure is relatively stable and constant in vessels larger than capillaries on both the arterial and venous side of the circulation). Vessels with a diameter in the range of 40 μm would typically be found one or two bifurcations upstream of the metarteriole/precapillary sphincters. For arterioles in the range of 15 to 40 μm in diameter, there is a rapid decrease in pressure to approximately 30 mmHg, which is associated with a rapid increase in the pressure gradient throughout the vessel. This rapid decrease in nominal pressure occurs so that the blood velocity is slow enough for nutrient and waste exchange to occur within the capillaries at the same time that blood is rapidly directed into the capillaries themselves. Observe that the gauge mean arterial pressure variation in capillaries and venules is much lower than that seen in the precapillary arterioles (see Fig. 6.27). Within capillaries (diameter ranging from 5 to 10 μm) the pressure decreases from approximately 25 mmHg to at most 20 mmHg, under normal conditions. However, the pressure gradient driving blood into the capillaries is relatively large so that blood movement toward and through these vessels is efficient. Within the venous circulation, the pressure continually drops (to approximately 0 mmHg in the right atrium), but it is important to remember that this decrease is much more gradual compared with the pressure drops observed within the arterial system. Over the entire length of the venous system, the hydrostatic pressure reduces by approximately 20 mmHg, whereas the pressure drop over the arterial system is in the range of 100 mmHg. Therefore, the pressure gradient is much lower within the venules/venous system. In postcapillary venules (diameter as large as 50 μm), the pressure is no more than 15 mmHg under normal conditions.

To continue the discussion of the pressure gradient throughout microvascular beds, there is approximately an eight-fold increase in the pressure gradient within small capillary

segments (100- to 300- μm length) compared with arterioles and venules (approximately 2000- μm length, approximately 40- μm diameter). For metarterioles and postcapillary venules (approximately 15- μm diameter), the pressure gradient is 50% of the pressure gradient throughout the capillaries. This suggests that the flow is directed into the capillaries and then it slows to allow sufficient time for nutrient exchange. Recall that the gradient may be large, but flow will be diverted into many small capillaries to perfuse the entire vascular bed.

The pressure variation in microvascular beds under hypertensive and hypotensive conditions also has been investigated. Interestingly, under both conditions, the mean hydrostatic pressure within the capillaries and the pressure gradient across the capillaries were equivalent to that observed under normal physiological conditions. In addition, the pressure (hydrostatic and pressure gradient) within the postcapillary venules was nearly identical under these pathological conditions compared with the pressure values observed during normal physiological conditions. The most significant change in pressure during pathological conditions was observed within the arteriolar vasculature where the pressure gradient was significantly greater under hypertensive conditions or significantly lower under hypotensive conditions (compared with the appropriate physiological conditions). This suggests that metarterioles (and the precapillary sphincters) regulate capillary blood flow to maintain it at its normal physiological levels, regardless of possible pressure changes upstream of the capillary. Importantly, this suggests that the functions accomplished at the capillary level are critical to maintain at normal levels. In the simplest case, we would consider that one of these functions, nutrient exchange, is maintained at the optimal level. This also suggests that the circulatory system is designed to maintain a constant flow through the microcirculation, independent of changes within the mean arterial pressure. This is fairly significant and can be considered as a mechanism to damp any pressure variations before the site of exchange within the vasculature. Imagine the significant negative implications that would occur if the exchange of nutrients was disrupted during altered vascular pressure conditions.

The last major variation in pressure throughout the microvascular beds that may be observed is based on the temporal changes from the cardiac pressure pulse and the wave propagation throughout the vasculature. The pressure values discussed so far have been averaged across the cardiac cycle, by taking multiple readings during the entire cardiac cycle, and can be considered the mean values observed within the microcirculation. However, during the cardiac cycle, the hydrostatic pressure changes within the microvascular beds oscillating on the order of 2 mmHg. We previously stated that the hydrostatic pressure within the capillaries is approximately 25 mmHg. This means that the pressure would vary between approximately 24 and 26 mmHg during the cardiac cycle. These temporal changes are not that significant compared with the relatively stable pressure gradient across the blood vessels. Furthermore, these changes in pressure would not alter the exchange of nutrients significantly and are typically disregarded when approximating the flow conditions within the microcirculation. Most of the data discussed in this section were collected by B. Zweifach and his research group during the 1970s.

7.5 Velocity distribution throughout the microvascular beds

In large blood vessels, in which the vessel diameter exceeds the diameter of cells within the blood by at least three times, the mean blood velocity is approximately equal to the mean velocity of the cells flowing through/within the fluid. This is because the cells tend to spread evenly throughout the cross-section of the blood vessel (imagine the cell distribution across a section of the aorta). However, as the blood vessel diameter approaches the diameter of the suspended cells, it is no longer true that the mean cell velocity is equal to the mean blood velocity. The mean blood cell velocity within blood vessels that have a diameter in the range of 15 to 25 μm is larger than the mean blood velocity. This is caused by a phenomenon in which the blood cells are pushed to the centerline of the blood vessel because of the large imbalance of forces on opposing sides of the cell. As discussed previously, under single-phase flow, the fully developed parabolic flow will have a centerline velocity that is greater than the mean blood velocity. However, in the small blood vessels the flow profile will be blunted (similar to the Casson model velocity profile) because the blood cells account for a significant portion of the cross-sectional area (this will be discussed further in [Section 7.7](#)). As the blood vessel diameter reduces to less than 15 μm , the mean blood cell velocity and the mean blood velocity approach the same value again. The blood vessels that have different mean cell velocities and mean plasma velocities are found within the microvascular beds.

The change in the relationship between the velocity of blood cells and the velocity of the blood occurs because the blood cells account for the majority of the cross-sectional area of the blood vessel. In other words, the blood vessel diameter reduces to a value that is similar to the cellular diameter in the smallest of capillaries. When this occurs, the blood cells tend to plug the vessels and dominate the entire velocity profile, especially toward the centerline, where the velocity would be the greatest. What typically occurs is that red cells group together in packets termed *rouleaux* and pass through the capillary as one unit. This is then followed by a packet of plasma, which passes through the capillary at approximately the same velocity as the cells. This again would be followed by a red cell packet (which would more than likely be of a different size than the first packet of red blood cells). However, independent of red blood cell group size, the velocity of the individual cell/fluid packets would be the same. In slightly larger vessels, when the blood vessel diameter is approximately 15 μm , the red blood cells tend to move toward the centerline, as will be discussed in [Section 7.7](#). In these 15- μm vessels, plasma flows along the walls of the blood vessel with a slow velocity, at the same time that the red blood cells flow along the centerline of the vessel with a higher mean velocity. Therefore, the red blood cell velocity would have an overall greater value than the mean blood velocity and the plasma velocity. As the blood cells enter the smallest capillaries from these slightly larger 15- μm vessels, the plasma is further squeezed against the blood vessel wall, and eventually it leaks back through the narrow gap between the cells and the vessel wall. This leak-back plasma collects at one location, and once it forms a significant mass, it can disrupt the flow of red blood cells and induce a break in the *rouleaux*. It is interesting that this thin leak-back layer also acts a lubricating layer between the cells and the vessel wall. The splitting of red blood cells into

discrete packets depends on many factors, and it is very difficult to predict the exact formation of rouleaux and the size of individual rouleaux. Red blood cells that are following this first packet of cells (whether or not they are in their own packet) also push the plasma toward the wall and then backward between the wall and cells, which again causes red cells to congregate into a single-file packet followed by a plasma packet. One should note that even though rouleaux are mostly cells, there will be some plasma mixing in between the cells that make up the individual rouleaux, but this is a relatively minimal percent of the total plasma mass. One can also remember this concept of red blood cells having a large mean velocity compared with some of the other observable velocities in the microcirculation by recalling the no-slip boundary condition. Because the red blood cells stream toward the centerline of the blood vessel, effectively pushing the plasma toward the walls, the plasma will have a velocity that is close to zero (e.g., the velocity of the blood vessel wall). From the cellular point of view, this looks like the plasma is flowing backward, but in reality the plasma is just holding relatively steady along the wall. Eventually enough of this plasma builds up mass, and it has the potential to break off the wall and cause a break in the stream of red cells. If and when the plasma breaks free from the wall, a plasma packet would form, splitting the red blood cells into discrete packets.

The spatial difference in velocity in the radial direction is relatively negligible in capillaries because, on average, the entire cell will travel with the same velocity. When a plasma portion moves through the capillary, it does not have sufficient time/length to fully develop and it has the ability to move as a plug in between two red blood cell packets. To model the flow of blood through these small vessels, it is typical to use the assumption that the fluid is inviscid and is composed of elastic particles. However, this will not accurately account for the portion of blood that consists solely of plasma, and the red blood cells do exhibit some viscous properties themselves (e.g., the red blood cell membrane is a viscoelastic material). To develop a more accurate model, we will discuss fluid flow at low Reynolds numbers (the Reynolds number will be discussed in more detail in Chapter 15, with numerical methods, but it was developed earlier in the text; see [Section 1.6](#)). Without going into the complete details of the Reynolds number here, using typical blood flow properties found in the microcirculation, the Reynolds number is within the range of 0.001 and 0.01. At a Reynolds number in this range, the viscous effects of the blood flow dominate over the inertial effects (i.e., velocity). In this situation, the Navier–Stokes equations simplify to

$$\begin{aligned}\frac{\partial p}{\partial x} &= \rho g_x + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\ \frac{\partial p}{\partial y} &= \rho g_y + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\ \frac{\partial p}{\partial z} &= \rho g_z + \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right)\end{aligned}\tag{7.1}$$

If gravitational effects can be ignored (which is probably a good assumption within the microvasculature because the length scales tend to be relatively small), then Eq. (7.1) can be further simplified to

$$\begin{aligned}\frac{\partial p}{\partial x} &= \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) = \mu \nabla^2 u \\ \frac{\partial p}{\partial y} &= \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) = \mu \nabla^2 v \\ \frac{\partial p}{\partial z} &= \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right) = \mu \nabla^2 w\end{aligned}\tag{7.2}$$

Eq. (7.2) shows the famous Stokes equations, which hold for relatively slow, viscous flows that are only pressure driven. It is important to emphasize that the validity of these equations is only for flows in which the viscous terms dominate the inertial terms by at least 1 order of magnitude or that the length scales are so small that the fluid inertial effects do not have time to overcome the viscous effects and that gravitational effects can be neglected. However, we will see in Chapter 10 that many gas flows (e.g., airflow in the lungs) and blood flow within the microcirculation can be characterized as a Stokes flow, because they obey the simplified Navier–Stokes equations shown in Eq. (7.2). The Stokes equations in cylindrical coordinates are

$$\begin{aligned}\frac{\partial p}{\partial r} &= \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (rv_r) \right) + \frac{1}{r^2} \frac{\partial^2 v_r}{\partial \theta^2} - \frac{2}{r^2} \frac{\partial v_\theta}{\partial \theta} + \frac{\partial^2 v_r}{\partial z^2} \right] \\ \frac{\partial p}{\partial z} &= \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_z}{\partial \theta^2} + \frac{\partial^2 v_z}{\partial z^2} \right] \\ \frac{\partial p}{\partial \theta} &= r\mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (rv_\theta) \right) + \frac{1}{r^2} \frac{\partial^2 v_\theta}{\partial \theta^2} + \frac{2}{r^2} \frac{\partial v_r}{\partial \theta} + \frac{\partial^2 v_\theta}{\partial z^2} \right]\end{aligned}\tag{7.3}$$

Example 7.1

Consider the flow of a blood cell within the microcirculation (Fig. 7.5). Determine the velocity profile within a 16- μm -diameter blood vessel with an 8- μm -diameter cell (assume that it is cylindrical, see Fig. 7.5) flowing through the blood vessel and centered with the blood vessel. Assume that the cell is flowing with a uniform velocity of $v_{z-\text{max}}$. Also assume that the viscosity of the blood can be represented by μ and that the pressure gradient only acts within the z -direction and is $\frac{\partial p}{\partial z}$. Solve for the velocity profile at the blood cells centerline.

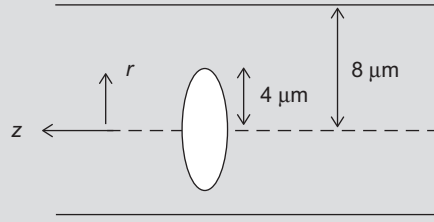
Example 7.1 (cont'd)

FIG. 7.5 Schematic of a red blood cell flowing through a centerline. This figure is associated with the in-text example.

Solution

$$\frac{\partial p}{\partial z} = \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_z}{\partial \theta^2} + \frac{\partial^2 v_z}{\partial z^2} \right]$$

$$\frac{\partial p}{\partial z} = \frac{\mu}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right)$$

$$\int \frac{r}{\mu} \frac{\partial p}{\partial z} = \int \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right)$$

$$\frac{r^2}{2\mu} \frac{\partial p}{\partial z} + c_1 = r \frac{\partial v_z}{\partial r}$$

$$\int \frac{r}{2\mu} \frac{\partial p}{\partial z} + \frac{c_1}{r} = \int \frac{\partial v_z}{\partial r}$$

$$v_z(r) = \frac{r^2}{4\mu} \frac{\partial p}{\partial z} + c_1 \ln(r) + c_2$$

$$v_z(4 \mu m) = v_{z-\max}$$

$$v_z(8 \mu m) = 0$$

$$v_{z-\max} = \frac{(4 \mu m)^2}{4\mu} \frac{\partial p}{\partial z} + c_1 \ln(4) + c_2$$

$$v_{z-\max} = \frac{4 \mu m^2}{\mu} \frac{\partial p}{\partial z} + c_1 \ln(4) + c_2 \quad (1)$$

$$0 = \frac{(8 \mu m)^2}{4\mu} \frac{\partial p}{\partial z} + c_1 \ln(8) + c_2$$

$$0 = \frac{16 \mu m^2}{\mu} \frac{\partial p}{\partial z} + c_1 \ln(8) + c_2 \quad (2)$$

Equation (1)–(2)

$$v_{z-\max} = \frac{-12 \mu m^2}{\mu} \frac{\partial p}{\partial z} - 0.693c_1$$

$$c_1 = -1.44v_{z-\max} - \frac{17.31 \mu m^2}{\mu} \frac{\partial p}{\partial z}$$

$$0 = \frac{16 \mu m^2}{\mu} \frac{\partial p}{\partial z} + \left(-1.44v_{z-\max} - \frac{17.31 \mu m^2}{\mu} \frac{\partial p}{\partial z} \right) \ln(8) + c_2$$

Continued

Example 7.1 (cont'd)

$$\begin{aligned}
c_2 &= -\frac{16 \mu m^2}{\mu} \frac{\partial p}{\partial z} + 3v_{z-\max} + \frac{36 \mu m^2}{\mu} \frac{\partial p}{\partial z} = 3v_{z-\max} + \frac{20 \mu m^2}{\mu} \frac{\partial p}{\partial z} \\
v_z(r) &= \frac{r^2}{4\mu} \frac{\partial p}{\partial z} + \left(-1.44v_{z-\max} - \frac{17.31 \mu m^2}{\mu} \frac{\partial p}{\partial z} \right) \ln(r) + 3v_{z-\max} + \frac{20 \mu m^2}{\mu} \frac{\partial p}{\partial z} \\
v_z(r) &= \begin{cases} v_{z-\max} & r < 4 \mu m \\ \frac{r^2}{4\mu} \frac{\partial p}{\partial z} + \left(-1.44v_{z-\max} - \frac{17.31 \mu m^2}{\mu} \frac{\partial p}{\partial z} \right) \ln(r) + 3v_{z-\max} + \frac{20 \mu m^2}{\mu} \frac{\partial p}{\partial z} & 4 \mu m \leq r \leq 8 \mu m \end{cases}
\end{aligned}$$

The previous problem (Example 7.1) is simplified to a form similar to that of many of the Navier–Stokes examples that we solved previously. It is important to note that we made the assumption that the entire red blood cell will travel with the same velocity and that the flow is axisymmetric and steady. The validity of the red blood cells as a rigid body would need to be verified in the particular flow scenario, but using this assumption may still provide a somewhat accurate reflection of the real flow conditions. In Chapter 6 we presented a number of analytic formulas for the flow through noncircular channels. One of the sets of equations we provided was for flow through a concentric annulus. An extension of this formula can be developed under the conditions described in Example 7.1, in which the inner portion of the concentric annulus is moving with a constant velocity of $v_{z-\max}$. Under these conditions the velocity profile can be found to be equal to

$$v_z(r) = \begin{cases} v_{z-\max} & 0 \leq r \leq b \\ \frac{1}{4\mu} \left(-\frac{d\vec{p}}{dx} \right) \left[a^2 - r^2 + (a^2 - b^2) \ln \left[\frac{\left(\frac{a}{r} \right)}{\left(\frac{b}{a} \right)} \right] \right] + v_{z-\max} \ln \left[\frac{\left(\frac{r}{a} \right)}{\left(\frac{b}{a} \right)} \right] & b \leq r \leq a \end{cases}$$

In Stokes flow situations the viscous forces dominate the flow profile. As a consequence, there is a significant amount of drag on a particle that is within the fluid. To quantify this, we will introduce the drag coefficient (C_D), which relates the viscous stresses on the surface of a particle to some fluid properties. In a general form, the drag coefficient is defined as

$$C_D = \frac{F}{\frac{1}{2} \rho v^2 A} \quad (7.4)$$

where F is the applied force on the particle from the viscous fluid stresses, ρ is the fluids density, v is the mean fluid velocity, and A is the cross-sectional area of the particle. For a sphere with radius of r , the viscous forces are equal to

$$F = 6\pi\mu r v \quad (7.5)$$

which has been empirically quantified for smooth spherical objects. Substituting Eq. (7.5) into Eq. (7.4), the drag coefficient for a sphere is equal to

$$C_D = \frac{6\pi\mu rv}{\frac{1}{2}\rho v^2 \pi r^2} = \frac{12\mu}{\rho v r} \quad (7.6)$$

We will see in a later chapter that the drag coefficient is strongly dependent on the Reynolds number (Re). Incorporating the Re into Eq. (7.6),

$$C_D = \frac{24}{\text{Re}} \quad (7.7)$$

Example 7.2

Using the formulation from the previous in-text example, Example 7.1, calculate the viscous forces on a red blood cell in the microcirculation and the drag coefficient. Assume that the velocity of the red blood cell is 15 mm/s, the viscosity of blood is 5 cP, and the density of the blood is 1100 kg/m³.

Solution

The average blood velocity is approximately equal to half of the maximum blood velocity of 15 mm/s (if we assume laminar Newtonian steady flow around the red blood cell):

$$F = 6\pi(5\text{cP})(4\text{ }\mu\text{m})\left(7.5\frac{\text{mm}}{\text{s}}\right) = 2.83\text{ nN}$$

$$C_D = \frac{12(5\text{cP})}{(1100\text{ kg/m}^3)(7.5\text{ mm/s})(4\text{ }\mu\text{m})} \cong 1820$$

In the microcirculation, it is common for the Reynolds number to range between 0.001 and 0.01. This is associated with a very large drag coefficient for any particle within the fluid. As illustrated in Example 7.2, the actual forces on each red blood cell are not necessarily large (e.g., the force is in the nano-Newton range; however, the actual force/stress experienced by individual cells is relatively large and it may be able to elicit biological responses). However, because of the high viscous forces compared with the small particle size (as related to the inertial forces), there is a large drag on the individual cells. As one can imagine, the forces on a nonaccelerating particle (linear and rotational acceleration) would be equal to zero and in general, uniform particles that are flowing along the centerline of a channel will experience no net force. However, these assumptions, where cellular matter is generally not uniform in shape and size, cannot typically be applied to biological scenarios.

Similar to the pressure distribution within the microcirculation, there is a temporal variation in the velocity distribution based on the cardiac cycle and the propagation of the velocity throughout the cardiovascular system. The velocity can change on the order of a few millimeters per second within the capillaries. For most calculations, however, this is a relatively small change and is typically neglected. This allows for a fairly valid assumption of steady flow within the microcirculation. As with the pressure distribution, the relative changes based on vessel diameter are more important to consider than the temporal changes.

7.6 Interstitial space pressure and velocity

The interstitial space is the area between cells, which is typically composed of fluid and proteins (such as collagen and/or proteoglycans). Note that some cells, such as inflammatory cells, can reside within the interstitial space, but typically these types of cells account for a very small portion of the total volume of the interstitial space. The proteins that are present within the interstitial space function to “connect” cells together into a uniform tissue that can withstand mechanical loads as one entity. The fluid within the interstitial space has a composition similar to that of plasma, except for a much lower concentration of plasma proteins. Plasma proteins are unable to diffuse through the blood capillary wall (e.g., through the endothelial cells) under normal conditions and therefore do not enter the interstitial space and should account for a very small percentage of the composition of the interstitial space proteins. The fluid component of the interstitial space also helps maintain the structural integrity of tissue under certain types of mechanical loading.

In Chapter 8 we will see that the pressure within the interstitial space is critical in determining the transport of fluid and nutrients between the blood vessels and the extravascular space. The flow rate of water across the blood vessel wall is directly proportional to the pressure (osmotic and hydrostatic) within the blood vessel and the interstitial space (Fig. 7.6). This is summarized by Starling’s theory

$$\dot{m} = K_p(P_B - P_I - \Pi_B + \Pi_I) \quad (7.8)$$

where $\dot{m}$ is the volumetric flow rate of water across the blood vessel wall. K_p is a permeability constant, which will be discussed later, but is typically empirically found. P_B is the

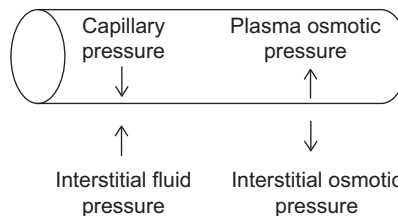


FIG. 7.6 The capillary and interstitial fluid hydrostatic pressure and the colloidal osmotic pressure (for plasma and interstitial space) affect the movement of fluid within microvascular beds. The capillary hydrostatic pressure and the interstitial osmotic pressure generally aid in water movement out of the capillary. The interstitial hydrostatic pressure and the interstitial plasma pressure generally aid in water movement into the capillary.

hydrostatic pressure within the capillary, and this force tends to aid in water movement out of the blood vessel. P_I is the hydrostatic pressure within the interstitial space. This force tends to inhibit the movement of water out of the blood vessel (if it is positive) but can aid in fluid movement out of the blood vessel (if it is negative). Π_B is the osmotic pressure within the capillary, and this force tends to promote the movement of water into the blood vessel from the interstitial space. Π_I is the osmotic pressure within the interstitial space, and this tends to promote the movement of water out of the blood vessel into the interstitial space. Note that the Starling theory sometimes includes a reflection coefficient, which relates to the ability of the capillary wall to restrain the movement of particular species. When this coefficient is included, each of the osmotic pressure terms would be multiplied by the reflection coefficient and these values would relate to the transport across the capillary wall in the appropriate direction. As previously discussed, the capillary hydrostatic pressure is within the range of 25 mmHg on the arterial side and within the range of 12 mmHg on the venous side. The interstitial pressure is approximately negative 3 mmHg (this is a gauge pressure) but can increase to positive 4 to 5 mmHg when the space between the cells constricts or under edema conditions. Cell constriction occurs as a result of different tissue loading conditions, such as an increased external pressure (e.g., pushing on a region of your body with your hands will locally increase the external pressure. Additionally, leaning on a solid surface can locally increase the pressure at that region.). This increase would inhibit water movement out of the capillary.

The osmotic pressure within capillaries averages to approximately 28 mmHg. This pressure is developed from all of the compounds within the capillary that cannot diffuse across the endothelial cell barrier. The major contributor to this is albumin, which solely develops an osmotic pressure of approximately 22 mmHg within the capillary. The globulins in the capillary are the major contributors to the remaining portion of the osmotic pressure. We would like to remind the readers that the total protein concentration within the interstitial space is greater than the protein concentration within the capillaries. This typically suggests that the osmotic pressure of the interstitial space should be larger than the plasma osmotic pressure. However, because the volume of the interstitial space is significantly larger than that of the capillary, the total osmotic pressure of the interstitial fluid is approximately 7 mmHg. The osmotic pressure does not change significantly between the arterial and venous side of the capillary because proteins do not leave the blood vessel and the blood volume remains relatively constant, even though some transport occurs.

The total driving force for water movement across the capillary wall is simply the summation of all of these pressure values, according to Starling's theory, if we assume that the reflection coefficient has a numerical value of 1 for the transport of nutrients across the capillary wall in both directions. On the arterial side of the capillary, the summation of the forces that tend to aid in fluid movement out of the capillary is composed of

$$P_B - P_I + \Pi_I = 25 \text{ mmHg} - (3 \text{ mmHg}) + 7 \text{ mmHg} = 35 \text{ mmHg}$$

The only force that tends to prevent fluid movement out of the capillary is the plasma osmotic pressure

$$\Pi_B = 28 \text{ mmHg}$$

Therefore, the total driving force of fluid out of capillaries on the arterial side is approximately 7 mmHg. By using this same analysis for the venous side of the capillary, the balance of the forces shifts to aid in water movement back into the capillary

$$P_B - P_I - \Pi_B + \Pi_I = 15 \text{ mmHg} - (-3 \text{ mmHg}) - 28 \text{ mmHg} + 7 \text{ mmHg} = -3 \text{ mmHg}$$

Therefore, along the venous side of the capillary there is a net reabsorption of water that was lost along the arterial side. This change from water loss within the capillary to water gain within the capillary is primarily governed by the change in the capillary hydrostatic pressure. The other pressures that make up the Starling equation (osmotic and interstitial hydrostatic) are relatively constant along the capillary length. We would like to point out that we made the assumption that there is little change in the plasma osmotic pressure, but one can observe that there is not a balance between water lost on the arterial side and water gained on the venous side. Therefore, there must be some (although it might be minor) change in the capillary osmotic pressure along the capillary length. In addition, these hydrostatic and osmotic pressure values (and the permeability) are tightly controlled by the body, because slight changes in any of them can cause either edema (increased water within the interstitial space, swelling) or dehydration, by having a significant effect on the movement of water across the capillary wall. These controlling factors are primarily represented in the reflection coefficient and the permeability of the vascular tissue to specific species.

The velocity of fluid within the interstitial space is relatively slow compared with the flow within the cardiovascular system, and most of the fluid does not have the ability to move freely through the interstitial space. Because of the high concentration of charged proteins (collagens/proteoglycans) within the interstitial space, water becomes associated with the proteins through hydrogen bonding events. The interstitial space is primarily composed of these charged proteins, and thus, water does not have the ability to flow through the interstitial space, but instead it diffuses by hydrogen bonding to different proteins. For instance, a water molecule must disrupt at least one hydrogen bond to move through the interstitial space, and while the molecule is moving, it will make a new hydrogen bond(s) with charged molecules in its vicinity. The energetics of these reactions are fairly significant when the scale of the body is considered. Although the vast majority of fluid in the interstitial space is associated with proteins, there are small vesicles of fluid that can flow freely between the proteins. Under normal conditions, less than 1% of the water in the interstitial space can flow freely in this manner and the remaining 99% is loosely bound to proteins through hydrogen bonding events. However, under disease conditions such as edema, the amount of free fluid can increase to approximately 50% of the total fluid in the interstitial space. This is caused by an increase in water volume and not a decrease in protein concentration.

Diffusion of water through the interstitial space occurs at a rate on the order of 50 to 100 $\mu\text{m/s}$. This is slightly slower than the free movement of water through the interstitial space. However, because the distance that water (and dissolved solutes) must move in the interstitial space is small, the transport of nutrients is very rapid and can be accounted for by the water motion associated with charged molecules. Therefore, almost as soon as the water/nutrients enter the interstitial space they are absorbed by cells that are close to the blood vessel. Thus, this is a very effective way to transport nutrients throughout the interstitial space that surrounds the capillary bed.

7.7 Hematocrit/Fahraeus—Lindquist effect/Fahraeus effect*

We have already discussed how the blood within the capillary is nonhomogeneous because there are packets of red blood cells followed by packets of plasma. These individual packets do not fully mix until they reach the venous circulation. This has an effect on the hematocrit (the percentage of red blood cells in whole blood), which the reader should recall is typically in the range of 40% under normal conditions. There are a few reasons why the hematocrit value appears to change within the microcirculation and that these changes can significantly alter the flow conditions, until the blood remixes and pools in the venous circulation. Imagine a bifurcation in which the fluid velocity is not the same within the two daughter branches. Since red blood cells tend to move toward the blood vessel centerline (i.e., high-velocity location) before the bifurcation, they will have a tendency to follow the higher velocity pathway through the bifurcation. This means that the daughter branch with a higher velocity will tend to have more red blood cells entering it and thus a higher hematocrit compared with the daughter branch with the slower velocity. Additionally, the daughter branch with the higher velocity obtains more blood from the feeding vessels centerline compared with the daughter branch with a slower flow. Our discussion has ignored branch geometrical considerations, which can cause cell skimming into one of the branches more favorably than the others independent of some of the other factors discussed. Thus, the combination of all of these factors that influences blood distribution into the daughter can be quite complex.

Mathematical and experimental studies have been conducted to determine the relationship between the hematocrit observed within the daughter branches and the velocity of blood within the same branches. In the laboratory experiments that address these questions, it is typical to use the same diameter tubing for the inflow and the two daughter branches, but this is not a necessary condition to answer these questions. Regardless of the tube size, this type of approach allows for a relationship to be formed between the volume flow rate within each of the three tubes as follows

$$Q_{\text{inflow}} = Q_{\text{branch 1}} + Q_{\text{branch 2}} \quad (7.9)$$

Eq. (7.9) is developed from the continuity equation assuming that the fluid density within each tube is the same. Again, this equation will hold for any experiment regardless of tube cross-sectional area. To determine how the hematocrit is related to the tube velocities, multiple groups have conducted experiments in which a known hematocrit is fed through a tube of known diameter. The feeding tube branches into two daughter tubes with known diameters. The fluid that is discharged from each of the daughter branches is collected, and the hematocrit in each collection tube is measured. The velocity of red blood cells and the average tube velocity can be quantified by optical means in these experiments (if the tubes are transparent). A relationship has been developed for the quantity of red blood cells within a particular cross-section at an instant in time (tube hematocrit). The quantity of red blood cells was found to be equal to the mean tube speed multiplied by the cross-sectional area of the feed tube multiplied by the discharge hematocrit. This was also found to be equal to the mean red

*This section is considered advanced and can be skipped without a loss of continuity.

blood cell speed multiplied by the cross-sectional area of the daughter tube multiplied by the daughter tube hematocrit. Mathematically this can be represented as

$$Quantity_{RBC} = v_{\text{feed-tube}} A_{\text{feed}} Hct_{\text{discharge}} = v_{RBC} A_{\text{daughter}} Hct_{\text{daughter}} \quad (7.10)$$

If the cross-sectional areas are the same, the discharge hematocrit is equal to

$$\begin{aligned} \text{Discharge hematocrit} &= \text{Tube hematocrit} \left(\frac{\text{Mean red blood cell speed}}{\text{Mean tube flow ppeed}} \right) \\ Hct_{\text{discharge}} &= Hct_{\text{daughter}} \left(\frac{v_{RBC}}{v_{\text{tube-feed}}} \right) \end{aligned} \quad (7.11)$$

Different cross-sectional areas can be incorporated into Eq. (7.11) as needed to represent the particular flow conditions. Substituting Eq. (7.11) into Eq. (7.9)

$$Hct_{\text{inflow}} v_{\text{inflow}} = Hct_{\text{branch 1}} v_{\text{branch 1}} + Hct_{\text{branch 2}} v_{\text{branch 2}} \quad (7.12)$$

Again, assuming that the cross-sectional areas are the same, Eq. (7.9) can be simplified to a relationship between the mean velocities within each tube. Using this to simplify Eq. (7.12), we obtain

$$Hct_{\text{inflow}} = \frac{Hct_{\text{branch 1}} v_{\text{branch 1}} + Hct_{\text{branch 2}} v_{\text{branch 2}}}{v_{\text{branch 1}} + v_{\text{branch 2}}} \quad (7.13)$$

because

$$v_{\text{inflow}} = v_{\text{branch 1}} + v_{\text{branch 2}}$$

As a word of caution, this formulation is highly dependent on the relationship between the cell diameter and the tube diameter. Under conditions in which the ratio of the cell diameter to the tube diameter is close to 1, Eqs. (7.10) through (7.13) are valid. As the ratio decreases, as occurs within the macrocirculation, these equations are no longer valid because the cell velocity has little to no effect on the tube velocity. It is interesting to note that the ratio of the hematocrit in the two daughter branches has been empirically found to be accurately represented by the following linear relationship

$$\frac{Hct_1}{Hct_2} - 1 = a \left(\frac{v_1}{v_2} - 1 \right) \quad (7.14)$$

In Eq. (7.14), a is a phenomenological parameter, which depends on the ratio of the cell diameter to tube diameter, the shape of the cell, the rigidity of the cell, and the feeding tube hematocrit. This number can obviously vary significantly based on the physiological, pathological, or engineered conditions used.

The hematocrit in capillaries is lower than in the arterial hematocrit as shown in the previous mathematical formulations. This is because the red blood cells are fairly restricted to the centerline (higher velocity flow) in the capillaries, and thus, within a particular time frame,

there will be a lower chance of “catching” a red blood cell compared with “catching” the slower plasma along the blood vessel wall (e.g., using still photography). With an inflow hematocrit in the range of 40% to 50%, it has been shown that the capillary hematocrit can be as low as 10% but averages to approximately 20%. This reduction in hematocrit begins to be seen in arterioles with a diameter in the range of 100 μm (where the cell diameter/tube diameter $\cong 0.1$). The hematocrit decreases steadily until the capillaries, in which the hematocrit is around 10% to 20%. The hematocrit in the venules rapidly increases to the inflow hematocrit level within vessels that have a diameter in the range of 50 μm (hematocrit is typically 30% to 35%). This is caused by the overall slow velocity in these blood vessels, the ability for the cells and plasma to mix and the increase in the cell-to-tube ratio. It has been suggested that the endothelial cell glycocalyx (a region of glycosylated membrane-bound proteins that extends into the lumen) also plays a role in the decreased hematocrit. This region may partially help force the flow of red blood cells to the centerline in blood vessels with a smaller diameter, but has little to no effect in blood vessels with larger diameters. A typical glycocalyx extends for approximately 100 nm into the lumen of the blood vessel. On removal of the endothelial cell glycocalyx, it has been seen that the capillary hematocrit increases, but the value does not return back to the inflow hematocrit levels.

Taken together, blood vessels with a relatively high ratio of blood cell diameter to tube diameter have a lower than normal hematocrit. This is partially caused by the fluid dynamics (velocities, no-slip boundary condition, and diameter relationship), but also may be partially regulated by biological factors (such as the glycocalyx).

In the early 1930s, a number of studies were conducted by Fahraeus and Lindquist to determine the effects of vessel radius on viscosity and hematocrit. For these experiments, the diameter of the tube was restricted to be less than 250 μm and the shear rate was relatively high compared with the normal microcirculation, approximately 100 s^{-1} . The shear rate was this large so that the flow in the feeding tube would be Newtonian. The pressure difference across the tube and the volumetric flow rate were quantified and fit to the Hagen–Poiseuille equation. Interestingly, the normal flow rate relationship was not dependent on the bulk viscosity of the fluid, but instead it was dependent on an effective fluid viscosity. It has been experimentally shown that the new Hagen–Poiseuille relationship that is valid for flows within the microcirculation is represented as

$$Q = \frac{\pi \Delta P r^4}{8 \mu_{\text{eff}} L} \quad (7.15)$$

where μ_{eff} is the effective viscosity of the fluid within the microcirculation. The effective viscosity is highly dependent on the diameter of the blood vessel and the pressure drop across the blood vessel.

In general, the effective viscosity reduces with a decreasing tube radius. For a hematocrit of 40%, the normal blood viscosity is in the range of 3.5 cP. As the diameter of the blood vessels reduces to 1 mm, and the effective viscosity will reduce by approximately 5%. However, for blood vessels that are smaller than 500 μm , the reduction in viscosity is much more pronounced and approaches 2 cP in blood vessels with a diameter less than 50 μm . This drop also can be accounted for by the overall restriction of red blood cells toward the centerline of the blood vessel as discussed previously. Within blood vessels with a diameter in the

range of the red blood cell diameter, the viscosity increases rapidly again because of plug flow principles (see [Section 7.8](#)). These results were explained by the presence of a plasma layer along the blood vessel wall. This layer is void of red blood cells, consisting solely of plasma, which has a viscosity of approximately 1 cP (i.e., water). Because this low-viscosity solution is next to the wall, where the shear stresses would be the highest, the overall viscosity appears to reduce because the force needed to overcome this “low”-viscosity solution is far less than would be needed if cells were present.

To more accurately describe the presence of a plasma layer, one must consider the hemodynamic forces that act on a red blood cell. Because a red blood cell has a size associated with it (i.e., it is not assumed to be a particle), the forces that act on the cell must satisfy Newton’s law of motion under translational and rotational motions. If the red blood cell is not located directly within the flow centerline (assuming that the flow is fully developed and parabolic and that the red blood cell is symmetrical), the forces induced by the fluid velocity will be different on opposing sides of the red blood cell. As a result of this imbalance of forces, the red blood cell will tend to rotate toward the region with lower stresses. Recall that the location where the fluid experiences a higher velocity has a lower shear stress under normal conditions (because the spatial change in velocity is lower here). The corollary to this is that the higher shear stress would be located closer to the vessel wall. Thus, the lower stresses would be located along the centerline. This rotation of the red blood cell and imbalance of forces would continue until the forces acting on the red cell are balanced and do not cause cell rotation. Therefore, red blood cells move to the lower stress regions that have high velocities to balance forces and to minimize the overall force loading on the cell. This will occur only when the red cell is centered within the blood vessel (again, if the flow is fully developed and the red blood cell is uniform). This is another factor that affects the location of red blood cells within the blood vessel.

A final factor that promotes the formation of a plasma skimming layer is that red blood cells cannot be located within a specific near-wall region. Most red blood cells traverse through the cardiovascular system face-on and not end-on. This means that a red blood cell cannot be located within one cell radius (approximately 4 μm) of the blood vessel wall. If red blood cells entered this region, part of the cell would have to be “outside” of the blood vessel or that portion of the cell would need to deform and “scrape” along the vessel wall. Red blood cell deformation is not favorable from an energy standpoint, because this would likely induce a higher energy state and would at least require energy input to cause the deformation. Therefore, from a probability standpoint, it is more likely for a red blood cell to be located close to the centerline and far from the vessel wall. This will effectively promote a plasma layer reducing the blood viscosity.

7.8 Plug flow in capillaries*

As previously discussed, red blood cells flowing through capillaries tend to plug the capillary, preventing the plasma flowing freely as it does in larger blood vessels. Although the red blood cells flow fairly steadily, the plasma surrounding the cells experiences non-self-

*This section is considered advanced and can be skipped without a loss of continuity.

sustaining turbulent eddies and recirculation zones that dissipate quickly. These eddies help move material from the centerline of the plasma toward the vessel wall, potentially helping in the transfer of materials toward and across the capillary wall. These eddies tend to move compounds to the endothelial cell wall, so that the compounds can solely diffuse across the wall, instead of convect through the blood first and then diffuse across the wall (note that this second pathway to move compounds would significantly increase the time associated with nutrient transfer and would thus decrease the efficiency of transfer). In addition, these eddies would act to maintain a high concentration gradient of diffusing species near the wall. Additionally, there is a very small layer of plasma along the blood vessel wall that experiences very high shear stresses, because that plasma is squeezed between a red blood cell and an endothelial cell. This can be considered the proverbial rock and a hard place for plasma. Because the shear stress increases significantly, thus effectively slowing the flow of blood, it can be quantified through an increase in the apparent viscosity. The slowing of material near the endothelial cell wall also increases the residence time of materials near the wall, increasing the overall ability for the material to diffuse into the extravascular space.

To model plug flow, the velocity of the fluid is assumed to be constant across any cross-sectional area of the blood vessel. Normally, to solve a plug flow problem, it is assumed that there is no mixing across the individual plugs, so that there is no transfer of material from upstream to downstream around the plug of red cells. It is also assumed that each fluid plug and each cellular plug are homogeneous, but individual plugs may have different compositions. For instance, the first red blood cell plug may consist of 10 red cells whereas the second plug may consist of 20 red cells. Within that one plug, however, the density, viscosity, velocity, and all other parameters do not change. The fluid plugs can have different volumes with different compositions, but we will assume that the fluid properties are uniform across the volume (i.e., perfectly mixed within one plug) to simplify the calculations. Furthermore, it is easiest to assume that the flow is steady and that there is no wave propagation throughout the fluid, which when incorporated could significantly increase the complexity of the calculations. As discussed earlier, this is a relatively good assumption within the microcirculation, in which the temporal variation in the pressure and velocity waveform is relatively small.

The first governing equation for this type of problem is the conservation of mass throughout the individual plugs. For red blood cells, this is simply that the number of red blood cells that enter the region of interest must exit the region of interest. Under normal conditions, red blood cells cannot pass through the endothelial cell wall and are not produced within the capillary; this becomes the exact solution. This solution assumes that a red blood cell cannot leave one plug and join another, which can be found to occur under physiological conditions, but it is somewhat rare because the amount of inertia that would need to be overcome to move between plugs is very significant. Unlike cellular matter, which cannot be generated or consumed within the capillaries, the plasma portion of the fluid and any compound dissolved within the plasma, would obey the conservation of mass in its full form. For this example, we will make use of oxygen as our species of interest (for simplicity), but we can use this same formulation to discuss any species of interest. Under these conditions, the conservation of mass becomes

$$(O_2)_{\text{accumulated}} = (O_2)_{\text{entering}} - (O_2)_{\text{exiting}} + (O_2)_{\text{generated}} - (O_2)_{\text{consumed}} \quad (7.16)$$

Clearly, the amount of oxygen (or any other species) generated and consumed would depend on the kinetics of particular molecular reactions within the plasma components. Summing all of these components together, this can be formulated as

$$\pi r^2 u (C_{O_2}(x) - C_{O_2}(x + dx)) + \pi r^2 R_{O_2} Z dx = 0 \quad (7.17)$$

where r is the radius of the blood vessel, C is the concentration of a particular species at location x (the inflow of the vessel, for our example we are referring to oxygen) or $x + dx$ (the outflow of the vessel), u is the fluid velocity, R is the kinetic reaction rate of the specific species (this would be positive if generating species or negative if consuming species; again, we are referring to oxygen), and Z is a stoichiometric coefficient. The first term on the left side of Eq. (7.17) represents the difference between the amount of species that enter the capillary versus what leaves the capillary as a function of the flow rate within the capillary. The second term on the left side of the equation represents the overall kinetics of the generation and consumption formulas, within the area of interest. For instance, if there is a net generation, this term would be positive whereas a net consumption would appear as a negative rate. To develop this equation, we have made the assumption that no oxygen (or any general species) accumulates within the capillary (e.g., Eq. (7.17) is set equal to zero, and thus any imbalance between the inflow and the outflow is accounted for in the kinetics term). This assumption is reasonable, because there is little to no store for oxygen within the tissue or within the blood. When developing equations for other species, one must account for whether that particular species can accumulate or not within the capillary. Simplifying Eq. (7.17) into a differential form we obtain

$$u \frac{dC_{O_2}}{dx} = Z R_{O_2} \quad (7.18)$$

Note that $\frac{dC_{O_2}}{dx} = \frac{C_{O_2}(x+dx) - C_{O_2}(x)}{dx}$ and that the cross-sectional area is assumed to be constant along the blood vessel length. In typical kinetic reactions, the kinetic reaction rate depends on the concentration of the particular species present. As an example, if the kinetic reaction rate can be modeled with a first-order kinetic reaction, then

$$R_{O_2} = k C_{O_2}$$

Using the first-order kinetic reactions within Eq. (7.18), we can derive the following equation to represent the change in concentration as a function of distance. Note that k is the rate constant for the particular reaction and typically depends on temperature and the medium within which the reaction is occurring.

$$\frac{dC_{O_2}}{dx} = \frac{k Z C_{O_2}}{u} \quad (7.19)$$

$$\frac{dC_{O_2}}{C_{O_2}} = \frac{k Z}{u} dx$$

$$\ln(C_{O_2}) = \frac{kZx}{u} + C$$

$$C_{O_2}(x) = C_{\text{inlet}} e^{\frac{kZx}{u}}$$

Clearly, depending on the particular conditions and the kinetics of the reaction, this formulation can differ significantly. The assumption of first-order kinetics is a reasonably accurate representation for many of the reactions that occur within capillary blood flow, but if the kinetics change, then Eq. (7.19) is no longer valid. Using the few fairly accurate assumptions made about the species concentration within the fluid phase of the plug flow, the conservation of mass simplifies for species within the microcirculation to an exponential decay or rise relationship depending on the kinetics of the reaction.

Example 7.3

Consider the change in oxygen concentration and carbon dioxide concentration along a 500 μm blood vessel. Assume that the kinetics for each of these two molecules are described by first-order reactions. The blood velocity within this particular capillary is 10 mm/s. The kinetic rate constant for each reaction is -17 mol/s (for oxygen consumption) and 1.17 mol/s (for carbon dioxide formation). For these particular reactions, one oxygen molecule is consumed or two carbon dioxide molecules are formed. The inlet blood concentrations of oxygen and carbon dioxide are 400 and 120 mL, respectively (dissolved gas concentration). Plot the change in concentration as a function of distance along the capillary. What is the outlet concentration of oxygen and carbon dioxide?

Solution

Oxygen concentration at the outlet would be

$$C_{O_2}(0.5 \text{ mm}) = 400 \text{ mL} O_2 e^{(0.5 \text{ mm} * 1 * -17 \text{ mol/s}) / (10 \text{ mm/s})} = 171 \text{ mL} O_2$$

Carbon dioxide concentration at the outlet would be

$$C_{CO_2}(0.5 \text{ mm}) = 120 \text{ mL} CO_2 e^{(0.5 \text{ mm} * 2 * 1.17 \text{ mol/s}) / (10 \text{ mm/s})} = 135 \text{ mL} CO_2$$

The change in concentration over the distance of the blood vessel is shown in Fig. 7.7. Because these reactions can be described by first-order kinetics, Eq. (7.19) was directly applicable. In addition, note that the generation rate constant is positive and the consumption rate constant is negative and the stoichiometric constant of the carbon dioxide reaction is 2, because two carbon dioxide molecules will be generated during each reaction.

Continued

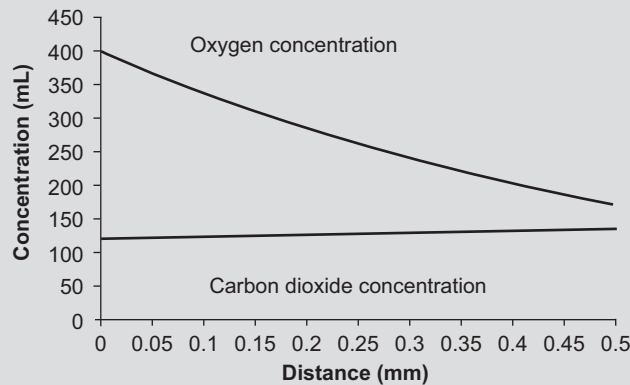
Example 7.3 (cont'd)

FIG. 7.7 Change in oxygen and carbon dioxide concentration within a capillary, as modeled with first-order kinetic reactions. This figure is associated with the in-text example.

7.9 Characteristics of two-phase flow*

In Chapter 2, we briefly described the nature of two-phase flows. Here we will develop some of the foundational concepts, but we will leave a complete discussion of two-phase flow concepts for more traditional fluid dynamics textbooks. In typical engineering applications, the two phases are either different fluids or the same fluid that exists in two phases (i.e., gas and liquid). Blood is a two-phase flow because the plasma component has different physical properties compared with the cellular components, and these two components interact with each other during the flow conditions. Under most conditions, it is not necessary to use two-phase flow principles within the macrocirculation. This is because the cellular component has little to no effect on the overall flow conditions. However, as discussed in this chapter, the cellular component can significantly alter the flow conditions within the microcirculation. For the remainder of this section, we will discuss some of the approaches available to solve two-phase flow problems. For this type of analysis, it is important to know the exact location of each particle within the fluid. Therefore, the Lagrangian approach would be used to solve the two-phase flow problem. However, if average values are more important, the Eulerian approach should be used.

Using the Lagrangian approach, our goal would be to solve Newton's second law of motion for each particle within the flow field. In this instant, Newton's law takes the form of

*This section is considered advanced and can be skipped without a loss of continuity.

$$\vec{F}_p(t) = m_p \frac{d\vec{v}_p}{dt} \quad (7.20)$$

where $\vec{F}_p(t)$ is the summation of all forces acting on one particular particle. To solve this equation, information regarding the exact instantaneous velocity and the position of each particle would be required. If at time t , the velocity and the position of a particle are known, the particle will move to a new position at time δt , according to

$$x(t + \delta t) = x(t) + v_p \delta t \quad (7.21)$$

The velocity of the particle is developed using a known mean velocity component and a fluctuating component, which arises from turbulence, variations in the particles, or variations in the flow field. This is conceptually similar to the concepts for turbulence modeling discussed briefly in [Section 6.11](#). To predict the variation, a number of approaches have been developed that are all related to a Lagrangian correlation function. Most of these approaches use statistical distributions to predict the fluctuations in velocity. The general Lagrangian correlation function is defined as the time average of the velocity fluctuations (u') as

$$R(t) = \frac{\overline{u'(t) * u'(t + \tau)}}{\sqrt{\overline{u'^2(t)}} \sqrt{\overline{u'^2(t + \tau)}}}$$

In most two-phase flow approaches, this correlation function is linearized based on some fluid parameters (such as the time of fluctuations or the length scale of fluctuations). One of the most common and simplest approaches to linearize the correlation function is to use the eddy decay lifetime in the form of

$$R(t) = 1 - \frac{t}{2t_D} \quad (7.22)$$

where t_D is the average eddy decomposition time and t is the time of interest for the fluid within the flow field.

Under the Eulerian approach, the average fluid properties for each phase would be used independently to define the motion of the total fluid. All of the equations that have been developed in previous chapters (e.g., for mass conservation, momentum conservation, and Navier–Stokes) can apply to each phase individually. However, there is an additional boundary condition such that the interface of the phases must have the same fluid properties (e.g., velocity, pressure, stress), thus allowing for a balance between the two phases. The difficulty with this approach would be defining where the interface between the two phases occurs within the fluid regime, because the cells are deformable and somewhat irregularly shaped and each cell may have different geometrical properties. In addition, for a problem in which blood is the fluid, there may be more than one interface, which makes the computations very time consuming by hand. For a 50 μm -diameter blood vessel, there can be a total of five red blood cells aligned within one particular cross-section (if they are flowing face-on, at one instant in time). To solve this particular problem using two-phase flow methods, the exact distance between each cell, at each location, would need to be known. Instead of using the Navier–Stokes equations to solve for the entire flow field within the 50 μm -diameter

vessel, each section of the vessel would need to be solved independently and the boundary conditions at each interface would need to be applied for the solution of a different section, which would develop a number of coupled differential equations. When this concept is extended into three-dimensional (3D) space, the boundaries can become very complicated.

7.10 Interactions between cells and the vessel wall

Within the microcirculation, cell–wall interactions need to be considered to accurately depict the flow field. As discussed previously, red blood cells squeeze through the capillaries, effectively shearing against the endothelial cell wall. In slightly larger vessels (25 to 50 μm in diameter), red blood cells can rebound off of the wall, changing the flow profile of the cell and the blood. It is common for white blood cells to stick to the vascular wall and roll along it. This changes the cross-sectional area and affects where the no-slip boundary condition would occur. In larger vessels, it is unlikely that any cell–wall interaction will disturb the flow profile and thus these concepts are typically not considered within simulations of the macrovasculature.

To model these interactions, we need to make a number of assumptions for the flow around the cells. First, we will assume that there is a no-slip condition at the vessel wall and along the membrane of the particle. This means that the fluid velocity should be matched along the entire length of the cell membrane; however, if the cell is within the free fluid, this leads to an imbalance along the cells that forces the cells to move toward the flow centerline. This imbalance also becomes important when one portion of the cell adheres to the vessel wall and a different portion of the cell and/or the wall is exposed to fluid flow. To model these interactions, we will make the assumption that the particles are neutrally buoyant, which means that the forces acting on the cell must summate to zero. This allows us to compute a solution by hand instead of using numerical methods (see Chapter 15).

To model these conditions, the mechanical properties of the cell and the cell membrane should be developed first. For red blood cells, it has been shown that the bending moment of the cell is very important to allow the cell to squeeze through a small capillary. For instance, if the red blood cell is too stiff to accommodate changes in the capillary cross-sectional area, the red blood cell seals off the blood flow preventing other red cells from entering that capillary. If the red blood cell is too pliant, the fluid flow stresses can easily shear the cell, preventing it from functioning properly. For flexible 2D axisymmetric spheres, the principal bending moments can be defined as

$$\begin{aligned} M_1 &= \frac{G(K_1 + \nu K_2)}{\lambda_2} \\ M_2 &= \frac{G(K_2 + \nu K_1)}{\lambda_1} \end{aligned} \tag{7.23}$$

where G is the bending stiffness, ν is Poisson's ratio, λ_n is the extension ratios, and K_n are the changes in curvatures of the membranes. The relationship between the stress and the extension ratios is also needed for these solutions. These are typically defined as

*This section is considered advanced and can be skipped without a loss of continuity.

$$\begin{aligned}
 T_1 &= \frac{E(\lambda_1^3 - \lambda_1)}{2\lambda_2} + T_0 \\
 T_2 &= \frac{E(\lambda_2^3 - \lambda_2)}{2\lambda_1} + T_0
 \end{aligned}
 \tag{7.24}$$

for the principal directions, where E is the elastic modulus and T_0 is an initial (or possible inherent) stress. Once the cell membrane mechanical properties are defined (there are many research papers that have investigated these mechanical properties), we need to classify the various mechanical and physical properties for the interior of the cell. Typically, the interior of the cell is assumed to be a uniform Newtonian fluid; that way, forces that act on the cell can be transmitted evenly throughout the cell interior. It is also typically assumed that the total surface area of each cell remains constant during any deformation (for short time durations, this may be true). The assumption that the interior portions of the cell behaves as a Newtonian fluid is somewhat valid, because the intracellular fluid is primarily composed of water; however, there are many other proteins (e.g., the cytoskeleton) that influence the mechanical properties of the cell. The second assumption, however, is not very accurate because white blood cells and platelets are known to add and/or remove sections of membrane in response to various stimuli. However, the modeling of these cell membrane functions is somewhat complex and not typically taken into account in many solutions for cell–wall interactions. Furthermore, for short time durations, the assumption that the membrane area remains similar may be appropriate.

Using the previously discussed assumptions, many groups have studied how red blood cells deform through the microvasculature at different viscosities, pressure differences, blood vessel diameters, and hematocrits. In general, they have all found similar results that suggest that the pressure within the blood vessel depends very strongly on the cell diameter. With greater cellular packing, the pressure gradient across the vessel increases as well, because the inertia of the cellular mass increases; thus, more force would be required to maintain the motion of this mass. Groups have also verified that the cells typically stream toward the centerline and that they have a higher mean flow than the fluid, as was experimentally determined and described earlier.

The second critical parameter to consider while modeling cell–wall interactions is the adhesion probability between the blood cell and the vessel wall. Adhesion between cells and the blood vessel wall is mediated through cell membrane–bound proteins, commonly selectins in the vasculature, but there are many types of adhesion proteins that can account for cell–cell or cell–wall adhesion. There is no simple way to quantify the amount of selectins (or other adhesion molecule) expressed on the cell membrane and the location of the specific protein on the cell membrane, because the quantity of proteins expressed is somewhat variable between discrete cells and the location of the protein along the membrane is dependent on the particular properties/experiences of the cell. To account for these modeling complications, most computational models use probability theory to help predict where and when the molecules will be expressed. Usually, the surface density of the receptor is an assumed parameter and it is assumed that the proteins are evenly distributed across the surface (again the validity of these assumptions would need to be verified). If the quantity of adhesion molecules is not held constant within the model, there will be some criterion for adhesion molecule expression; for instance, when the shear stress level exceeds 40 dynes/cm², x many adhesion molecules can be expressed. Once this defined criterion is met, the model

will have a probability statement that states that some percentage of cells will express the adhesion protein at a particular rate (note that simpler models can include the expression as an instantaneous event). If the criterion for expression persists, more cells will continually express more of the adhesion molecule. Additionally, it may be possible to increase the number of expressed receptors per cell. However, if the criterion is transient, the majority of cells will not express the adhesion molecule, and there are likely coding statements for the probability of an expressed protein to be recycled within the cell. After the adhesion molecules have been expressed, other probability statements may come into play and these statements are usually based on spatial variables. For instance, they will state if any portion of the cell that is expressing adhesion molecules comes within one cell diameter from the vessel wall, there is some probability for adhesion between the cell and the vessel wall to occur (clearly we are assuming that any protein on the cell membrane is active, although this may not be the case). Once adhesion occurs, the adhesion between the cell and the vessel wall is typically modeled as a spring, so that if the fluid forces exceed the spring's elastic capacity, the bond between the cell and the wall will break. However, once the cell is attached to the wall, there is also some probability that states how likely it will be for additional cell membrane adhesion molecules to adhere to additional wall adhesion proteins. As more connections are made, the capacity of the system increases. This is similar to a mechanical system in which

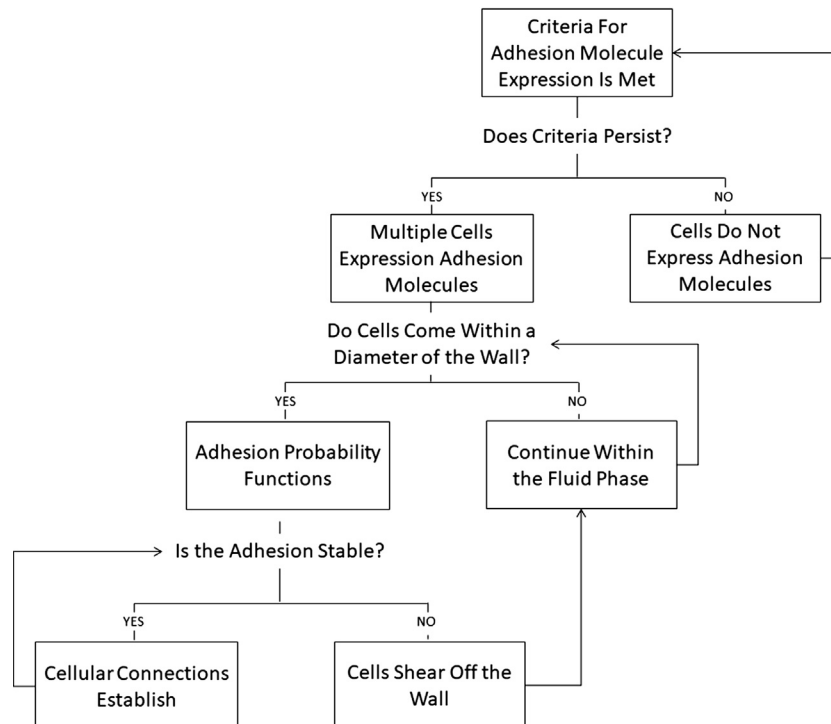


FIG. 7.8 Possible flow chart for cell–wall interaction modeling. There is a certain predetermined probability that is associated with each step in the flow chart, but these probabilities may be adaptive over the time course of interest. In addition, the first step in the flow chart can continually change and is reversible, making this flow chart not a direct path from beginning to end. Clearly, this is a somewhat simplified approach to cell wall adhesion, but is intended to provide a general idea for the flow of a probabilistic modeling event.

more springs are added to the connection. Once the adhesion between the membrane protein and the wall becomes stable (e.g., there are multiple connections), it is modeled with an on/off probability, which states how likely the cell will maintain the connection. These probabilities can be based on known kinetic constants or other criteria that are defined within the mode. This process is summarized in the following flow chart (Fig. 7.8), and some examples are discussed in Chapter 15.

7.11 Disease conditions

7.11.1 Shock and tissue necrosis

Shock is a condition that can occur after a significant loss of blood from a significant decrease in the blood pressure and the decrease in nutrient exchange (as a result of blood volume loss). In general, shock is defined as a failure of the cardiovascular system to deliver the chemical compounds necessary for cell survival and removal of metabolic waste products. This will eventually cause an abnormal membrane structure and irregular metabolism that will eventually lead to cell death. In response to pressure reductions, there are rapid responses that act to increase the blood pressure back to resting conditions. For example, along the carotid artery and the aortic wall, there are pressure sensors termed *baroreceptors*. When these receptors sense a significant decrease in blood pressure, they instigate a neuronal response that increases cardiac output by increasing the heart rate to over 150 beats per minute, and in parallel these signals can increase the vascular resistance by causing constriction of the blood vessels. Combined, these responses have the effect of increasing blood pressure and draw on the venous blood reserve. In the short term, hormones also can be released to aid in vasoconstriction and heart rate increase (e.g., epinephrine, antidiuretic hormone). This mechanism typically can work up to a 25% blood volume loss, without showing signs of a decrease in nutrient exchange within the microcirculation. With more significant blood loss, other mechanisms would need to be activated.

Medically, there are typically three stages of shock; if they are controlled early enough, the extent of cellular death can be controlled. Stage 1 is when the patient presents with low blood pressure (hypotension). There are a number of reasons why a patient may experience severe hypotension. The first is a significant loss of blood, as discussed earlier. In many cases, a significant decrease in cardiac output (maybe the result of heart failure) is the initiating factor for shock cases. In septic shock, there is a significant decrease in the peripheral vascular resistance (e.g., an increase in the blood vessel diameter), with little change to the cardiac output. Regardless of the cause of the decrease in blood pressure, the baroreceptor compensatory mechanism(s) initiates, which have the overall goal of restoring arterial pressure and blood flow to vital organs.

The second stage of shock is associated with a decreased tissue perfusion. After the patient experiences a massive decrease in blood pressure, the compensatory reactions initiate, but they may not be sufficient to maintain perfusion to vital organs. It is typical for a patient to present with cyanotic, cold, and clammy skin, especially at the extremities, if they have progressed into stage 2. At this point, the damage of shock can still be reversed if the patient's cardiac output can be restored by some means. If the cardiac output cannot be restored, the patient typically progresses to stage 3 of shock, which is associated with microcirculatory dysfunction. There is typically a significant alteration to cellular metabolism under these

conditions, because the cells cannot obtain nutrients or remove wastes at the rate needed to sustain function. Significant vasoconstriction has likely occurred by this point, and therefore, blood clots can be found within less vital organs, damage to the gastrointestinal tract mucosal layer occurs, the glomerular flow and permeability is typically altered, acidosis is found, and an overall decrease in cellular function or death of tissue is also observed. If shock continues to progress unchecked past this point, the flow through the coronary circulation is likely to be diminished, which perpetuates the shock effects.

If the shock progresses to a severe extent but is remedied, the long-term problem stemming from the potential shock-associated blood loss is the necessary increase of blood volume to make up the loss. A decrease in capillary pressure will increase the movement of water back into the capillary along the venous side. Antidiuretic hormone increases the overall retention of water from the kidneys. Red blood cell maturation rate will be increased to make up for the loss of the cellular component of blood. Typically, with a 25% loss of blood volume, the water portion can be returned to a normal volume within a few hours. However, the cellular portion will not return to normal levels for a few days, at best. With larger volumes of blood loss, it would take a longer time to make up the fluid and cellular compartment. In some scenarios, a transfusion may be the best approach to remedy the fluid loss issues once the cardiac output and the vascular tone (constriction/dilation) have been controlled.

The goal of the combined innate response mechanisms acts to return nutrient exchange to normal levels. However, if any of the mentioned mechanisms fail or there is a more significant loss of blood, it is likely for stage 3 shock to develop. If this condition persists for an extended period, there will be local tissue necrosis (tissue death similar to myocardial infarction) in regions where the microvascular beds have been shut down to divert the blood flow to more critical regions (such as the brain). Necrosis is irreversible death of tissue and should be avoided, as much as possible, to maintain the overall health of the patient. However, with the combination of blood volume loss and lowered arterial pressure, it is more difficult for the heart to pump blood throughout the cardiovascular system. Cells that die prematurely through necrotic pathways do not follow the typical planned cell death pathway, termed *apoptosis*. Cells that undergo necrosis typically release their contents in the surrounding extracellular space, which initiates an inflammatory reaction from cells that are not undergoing necrosis. For the most part, necrotic tissue must be surgically removed, once the shock symptoms have been controlled (or the other symptoms that have initiated the necrotic tissue). Necrosis typically follows one of two pathways, the first initiates through the osmotic swelling of the cells that have a disrupted cell membrane. Under these conditions, the nucleus shrinks and the DNA becomes fragmented and is degraded by various nucleases. The second pathway involves the fragmentation of the nucleus.

As hinted, there are many causes for necrosis, which include a decrease in blood flow to tissue (as described in the context of shock), damage to blood vessels, frostbite, abnormal innate immune functions (complement system), invading pathogens, and venoms.

7.11.2 Edema

Edema is a condition in which there is an excessive accumulation of interstitial fluid within the interstitial space. This fluid is not recollected by the capillary networks or the lymphatic system (see Chapter 9). There are many causes of edema, but they all stem from an imbalance between the hydrostatic pressures and the osmotic pressures within the microvascular beds, and thus, there is a net intake of water that is not met by the excretion of water by the

kidneys or by extrarenal mechanisms. The most common cause for edema is an increase in the arterial blood pressure associated with hypertension, which translates to the capillary pressure; this can be observed through changes within Starling's theory. As a result of an increase in the capillary hydrostatic pressure at the arterial side, there is a net increase in the movement of water out of the capillary. Additionally, a decrease in the capillary osmotic pressure could aid in net water movement out of the blood vessels. This could result from defects in plasma protein synthesis, increases in protein degradation, or possible transport of plasma proteins out of the vasculature. The inflow of water on the venous side typically cannot make up for the extra loss of water along the arterial side. Therefore, there is a net accumulation of water within the interstitial space.

In some edema cases, the capillary wall begins to break down, which allows for the movement of plasma proteins into the interstitial space. This causes an increase in the interstitial osmotic pressure, preventing the movement of water into capillaries along the venous side of the capillary. In the case of bruising, there is swelling because the capillary wall has become damaged. In other conditions, the plasma osmotic pressure can decrease because there is either not enough protein being formed or the proteins are being broken down within the cardiovascular system. In either case, because of the pressure changes that disrupt the delicate pressure balance in the capillaries, fluid has a preference to stay within the interstitial space.

Edema can also occur in specific organs in response to the inflammatory response such as pancreatitis. Particular organs can also develop edema based on certain biochemical and biophysical phenomena that occur within that organ. For instance, cerebral edema commonly occurs when there is an abnormal metabolic state. Corneal edema occurs in conjunction with glaucoma. Cutaneous edema is common with venomous/poisonous insect bites or plant contact such as poison ivy (but there are many other examples associated with cutaneous edema). Finally, the treatment of edema usually includes administering diuretics, but in general, one must be careful with this approach because diuretics tend to alter the blood pressure. This type of approach can exacerbate the problem or remedy the problem.

Summary

- 7.1. The microcirculation includes all of the capillaries and the smallest arterioles that dictate where blood flows in the vascular beds. Within the microcirculation, there is a transport of nutrients, dissolved species, and water across the vascular wall. Therefore, mass balance can no longer be accounted for by the inflow equaling the outflow. True capillaries have a diameter in the range of 8 μm . Flow through the capillaries is not continuous and is primarily dictated by the need of the surrounding tissue. An intercellular cleft is located between neighboring endothelial cells (typically 10 to 15 nm thick), and the vast majority of transport occurs by this channel. The flow through this channel is approximately 80 times faster than the blood flow through the capillary.
- 7.2. Endothelial cells are typically 10 μm in diameter and range in their lengths. This cell type lines all blood vessels and plays a role in hemostasis, inflammation, and nutrient transport. Vascular smooth muscle cells can perform work, similar to other muscle

cells. However, the regulation of contraction and the organization of the actin and myosin do not mimic those of other muscle cells. Endothelial cells can communicate with other endothelial cells or with smooth muscle cells via gap junctions.

- 7.3. There are two primary mechanisms for blood flow control. The first is the acute local control and the second is long-term control. Acute control is rapid constriction or dilation in response to stimuli. Long-term control is the formation of new blood vessels as a result of changes in the length/diameter of existing blood vessels. The regulation of these mechanisms is primarily through the need of the tissue, although there is some disagreement as to the actual mechanism that controls blood flow. There is no centralized “command center” that continuously controls blood flow through the capillaries.
- 7.4. The pressure gradient across capillaries is relatively low, not more than 5 mmHg. However, there is a large pressure gradient in the arterioles, which effectively forces the blood into the microvascular beds. However, if one looks at the pressure gradient in small segments of blood vessels, approximately 100 μm lengths, the pressure gradient across the capillaries is much larger than that of other blood vessels. Under disease conditions, the mean pressure within capillaries remains the same. The changes in pressure under these conditions are largely accounted for by the arterioles. A significantly reduced cardiac pressure pulse can be observed within the microvasculature, but this usually does not confound results or analysis techniques.
- 7.5. The mean blood velocity in capillaries is the slowest of all blood vessels and can be approximated by the blood cell velocity. Flow through the capillaries is dominated by the viscous fluid effects and not the inertial effects (i.e., there is a low Reynolds number). Under these conditions, the Navier–Stokes solution can be simplified to the Stokes equations, which are

$$\begin{aligned}\frac{\partial p}{\partial x} &= \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) = \mu \nabla^2 u \\ \frac{\partial p}{\partial y} &= \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) = \mu \nabla^2 v \\ \frac{\partial p}{\partial z} &= \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right) = \mu \nabla^2 w\end{aligned}$$

or

$$\begin{aligned}\frac{\partial p}{\partial r} &= \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r v_r) \right) + \frac{1}{r^2} \frac{\partial^2 v_r}{\partial \theta^2} - \frac{2}{r^2} \frac{\partial v_\theta}{\partial \theta} + \frac{\partial^2 v_r}{\partial z^2} \right] \\ \frac{\partial p}{\partial z} &= \mu \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_z}{\partial \theta^2} + \frac{\partial^2 v_z}{\partial z^2} \right] \\ \frac{\partial p}{\partial \theta} &= r \mu \left[\frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r v_\theta) \right) + \frac{1}{r^2} \frac{\partial^2 v_\theta}{\partial \theta^2} + \frac{2}{r^2} \frac{\partial v_r}{\partial \theta} + \frac{\partial^2 v_\theta}{\partial z^2} \right]\end{aligned}$$

The Stokes equations are relevant for many gas flows. Since the cellular matter takes a larger portion of the fluid cross-sectional area, the cellular elements may experience significant drag forces, which can be quantified using

$$C_D = \frac{6\pi\mu r v}{\frac{1}{2}\rho v^2 \pi r^2}$$

assuming that the cellular elements are spherical.

- 7.6. The hydrostatic pressure within the capillaries and the interstitial space, the colloidal osmotic pressure of the plasma, and the interstitial space dictate the net direction of water movement into or out of the capillary. This can be formulated as

$$\dot{m} = K_p(P_B - P_I - \Pi_B + \Pi_I)$$

Along the arterial side of the capillary, the net direction of water movement is generally out of the capillary, with a driving force of approximately 7 mmHg. Along the venous side, the forces tend to balance to aid in water movement back into the capillary with a driving force of approximately 3 mmHg. The fluid velocity within the interstitial space is relatively slow, and the majority of fluid does not have the ability to move freely. This is because there is a high concentration of charged proteins within the interstitial space that attract water molecules.

- 7.7. The hematocrit within capillaries tends to change based on the bifurcation angles and the splitting of fluid within the microcirculation. Two relationships that can be used to determine the branch hematocrit and branch velocities are

$$Hct_{\text{inflow}} v_{\text{inflow}} = Hct_{\text{branch 1}} v_{\text{branch 1}} + Hct_{\text{branch 2}} v_{\text{branch 2}}$$

$$Hct_{\text{inflow}} = \frac{Hct_{\text{branch 1}} v_{\text{branch 1}} + Hct_{\text{branch 2}} v_{\text{branch 2}}}{v_{\text{branch 1}} + v_{\text{branch 2}}}$$

Within the microcirculation, there is a general reduction in the hematocrit, which reduces the overall effective viscosity of blood. The effective velocity can be used in a modified Hagen–Poiseuille formulation to calculate the flow rate through a capillary as

$$Q = \frac{\pi \Delta P r^4}{8 \mu_{\text{eff}} L}$$

This reduction in viscosity is primarily caused by a streaming of the blood cellular elements streaming toward the centerline velocity. Under normal conditions, there is an

imbalance of forces on the cell, which would push the cell toward the lower shearing force. This would be balanced only when the cell is aligned with the highest fluid velocity.

- 7.8. In capillaries, red blood cells tend to form packets that act as plugs. Within these red blood cell packets there is very little plasma, and in fact the plasma normally collects in between different red blood cell plugs. Because of this plug formation, we can model the mass conservation of compounds within the fluid by

$$(O_2)_{\text{accumulated}} = (O_2)_{\text{entering}} - (O_2)_{\text{exiting}} + (O_2)_{\text{generated}} - (O_2)_{\text{consumed}}$$

which is shown for oxygen. The rate that a species is generated or consumed would depend on the particular kinetics of that reaction.

- 7.9. Two-phase flows are flows that have either two phases of matter (e.g., liquid and gas) or one phase of matter with different material properties (e.g., oil and water). In the microcirculation, the plasma phase and the cellular phase must be accounted for with different methods when analyzing flow conditions. This would be fairly difficult to do by hand because Newton's second law of motion would need to be solved independently for each particle within the fluid. In general, these types of flows are solved using numerical methods.
- 7.10. In the microcirculation, the effect of cell–wall interactions must also be accounted for because a cell adhered to the vessel wall may significantly alter the flow profile. In addition, it is likely that white blood cells migrate out of the blood vessels and into the extravascular space along the capillary wall. To model these interactions, the mechanical properties of the cells should be developed and included within the solution method. In general, the bending moments and the extension ratios of the cells can be defined as

$$M_1 = \frac{G(K_1 + \nu K_2)}{\lambda_2}$$

$$M_2 = \frac{G(K_2 + \nu K_1)}{\lambda_1}$$

$$T_1 = \frac{E(\lambda_1^3 - \lambda_1)}{2\lambda_2} + T_0$$

$$T_2 = \frac{E(\lambda_2^3 - \lambda_2)}{2\lambda_1} + T_0$$

respectively. To make the modeling of blood cell–wall interactions more complicated, probability functions that describe the expression of cell surface receptors need to be developed. In general, the surface density of these receptors depends on various stimuli within the fluid phase.

- 7.11. Disease conditions that are common within the microcirculation are shock and edema. Shock occurs after there is a massive loss of blood that can lead to a significant decrease in blood pressure and a decrease in nutrient exchange. Edema is a condition in which there is excessive fluid accumulation within the interstitial space, either because the lymphatic system is not collecting the excess fluid or because too much fluid is leaving the blood vessel.

Homework problems

- 7.1. The blood vessels that play the most important role in regulating the blood flow through microvascular networks are the
 - a. arteries.
 - b. arterioles.
 - c. true capillaries.
 - d. venules.
 - e. veins.
- 7.2. The exchange of gases, nutrients, and wastes occurs through only what type of blood vessels? Why?
- 7.3. There are four forces that affect the movement of water through the capillary wall. The net osmotic pressure forces water (into, out of) the capillary wall. What is the major constituent of the osmotic force?
- 7.4. Discuss the primary forces that cause water movement out of the capillary along the arterial end and into the capillary along the venous end.
- 7.5. There are two major mechanisms that control the blood flow through tissues. Which of these mechanisms is rapid, and which is more long term? Do both mechanisms have the same net effect?
- 7.6. The myogenic theory is not widely accepted as the only regulator for blood flow through microvascular networks. Prepare a short statement that supports the myogenic theory and one that is against the myogenic theory.
- 7.7. The endothelial cell nucleus protrudes into the bloodstream within the capillary beds. Does this affect blood flow and cellular transport through the microvascular network? Why is the capillary not “smooth”?
- 7.8. How does the intercellular cleft restrict the diffusion of small uncharged molecules through the capillary wall? How does the intercellular cleft restrict the diffusion of larger charged molecules? Why is there a difference between the diffusion of these two types of molecules?
- 7.9. List the major differences between vascular smooth muscle cells and skeletal muscle cells. Is mechanical work generated in a similar way between these two cell types?
- 7.10. Calculate the apparent viscosity for a capillary that has a pressure difference of 4 mmHg, a diameter of 10 μm , a mean velocity of 12 mm/s, and a length of 100 μm .

Homework problems (cont'd)

- 7.11. Calculate the apparent viscosity for the same conditions as in Homework Problem 7.10 if the mean velocity reduces to 0.2 mm/s because of precapillary sphincter constriction.
- 7.12. Determine the velocity profile within a 12 μm -diameter capillary, with a viscosity of 4 cP, and a pressure gradient of $-5 \text{ mmHg}/500 \mu\text{m}$. Assume that gravitational effects can be ignored and that the blood vessel is perfectly cylindrical.
- 7.13. Determine the velocity profile within a 12 μm -diameter capillary that has a red blood cell (8 μm diameter) flowing down the centerline of the blood vessel. Assume that the centerline velocity is 10 mm/s, that the pressure gradient is $-5 \text{ mmHg}/500 \mu\text{m}$, and that the viscosity is 4 cP. The capillary is vertical, so gravitational effects cannot be ignored. In addition, assume that the entire red blood cell flows with the same velocity and that the density of blood is 1050 kg/m^3 .
- 7.14. Calculate the drag coefficient and viscous forces on the surface of the red blood cell in Homework Problem 7.13, assuming that the only force that acts on the blood cell is shear stress as a result of the flowing blood. In addition, simplify the geometry of the red blood cell so that the area of interest can be considered a perfect sphere. What is the Reynolds number in this flow scenario?
- 7.15. Calculate the volumetric flow rate of water out of the capillary under normal conditions in which the permeability constant is $0.25 \text{ mL}/(\text{min} * \text{mmHg})$. How much fluid leaks out of the capillary within 1 day? Is this reasonable?
- 7.16. A patient is experiencing edema and the permeability constant increases to $1 \text{ mL}/(\text{min} * \text{mmHg})$. Assuming that the capillary hydrostatic pressure reduces to 23 mmHg, the interstitial pressure increases to -2 mmHg , and the osmotic pressures have not changed, how much fluid leaks out of the capillary within 1 day?
- 7.17. What is the hematocrit in each of the daughter branches for a simple network of one parent to two daughter branches, if the inflow velocity is 50 mm/s (in a tube with a diameter of 60 μm) and the velocity in the first branch is 75 mm/s (in a tube with a diameter of 40 μm)? The diameter of the second branch is 30 μm . The feed hematocrit is 40%, and the hematocrit in the second branch is 24%.
- 7.18. Calculate the concentration of carbon dioxide within a capillary assuming that all reactions can be modeled with first-order kinetics. In this scenario, the blood vessel is 300 μm in length, with a mean blood velocity of 15 mm/s. The kinetic rate constants for carbon dioxide formation and consumption are 1.17 mol/s and -0.2 mol/s , respectively. Assume that the initial concentration of carbon dioxide within the blood vessel is 100 mL.
- 7.19. Assume that the consumption of oxygen can more accurately be modeled with second-order kinetics ($R_{O_2} = k(C_{O_2})^2$), where the kinetic rate constant for oxygen consumption is 20 mol/s . Calculate the outflow concentration of oxygen if the inflow concentration of oxygen is 200 mL, within a blood vessel that is 50 μm in length and has a mean velocity of 35 mm/s.
- 7.20. *Modeling.* Compose a code that can accurately predict the flow through a capillary with consideration on the accumulation of carbon dioxide and depletion of oxygen (using the kinetics discussed) throughout the capillary.

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Mass transport and heat transfer in the microcirculation

LEARNING OUTCOMES

- Estimate the rate of gas diffusion between the respiratory system and the cardiovascular system
- Use Fick's laws of diffusion to quantify diffusion flux
- Determine the rate-limiting steps in gas diffusion into or out of red blood cells
- Learn important mass transport dimensionless parameters
- Relate kinetic reactions to diffusion reactions
- Analyze the tissue oxygenation area with the Krogh model
- Explain mechanisms for glucose (and other large molecules) transport into the extravascular space
- Model the vascular permeability for various compounds with different molecular weights, different sizes, and different net charges
- Consider the energy of adhesion during transport
- Analyze the strength of various molecular forces, including adhesion, cohesion, and electrostatic forces
- Calculate the strength of molecular forces
- Model the organization of water in the vicinity of a charged surface
- Learn methods to describe transport through porous media
- Analyze internal forced convection within the microcirculation
- Describe how white blood cells adhere to the endothelial cell surface and transfer to the extravascular space

8.1 Gas diffusion

In this section, we will consider the diffusion of oxygen and carbon dioxide from the alveolar space (which is discussed in more detail in Chapter 10) into the pulmonary capillaries and then from the systemic capillaries into the extravascular space/tissue. Chapter 10 also describes the transport of oxygen and carbon dioxide through the cardiovascular system (however, it differs by discussing this from the respiratory system standpoint), which is an integral component of gas diffusion, so some of the details may be presented in Chapter 10 instead of here. The pulmonary capillaries are designed as a very efficient and rapid gas exchanger. Under normal conditions, the partial pressure of oxygen within the blood entering the pulmonary capillaries is approximately 40 mmHg. The partial pressure of oxygen in blood leaving the pulmonary capillaries approaches 100 mmHg. Under resting conditions, the partial pressure of oxygen rises from 40 to 100 mmHg along the first one-third of the pulmonary capillary length. The remaining distance (approximately two-thirds of the pulmonary capillary length) is left as a safety reservoir system to allow for the blood oxygen level to increase to 100 mmHg under nonnormal or pathological conditions (e.g., disease or strenuous exercise). As we will discuss in detail in Chapter 10, this rapid increase in the partial pressure of blood oxygen is accounted for by at least five different diffusion events. Oxygen must first diffuse through the alveolar space to the respiratory boundary (Fig. 8.1). Oxygen must then diffuse across the respiratory boundary, which can be modeled with different components because of the different cells that compose the respiratory boundary (see Chapter 10) or the model can be simplified to a single barrier. Oxygen must diffuse through the blood and then diffuse across the red blood cell membrane (the red blood cell membrane is typically considered a single barrier). Finally, oxygen must diffuse through the cytoplasm of the red blood cell to come into contact with hemoglobin. Carbon dioxide follows a similar process, but in the reverse direction within the pulmonary capillaries. However, it must be noted that a very small portion of carbon dioxide is carried directly by hemoglobin; much of the carbon dioxide is transported indirectly in the blood. Therefore carbon dioxide movement can be modeled as a diffusion process across the red blood cell cytoplasm and/or blood with the addition of the kinetic reactions that describe the conversion of carbon dioxide and water into carbonic acid to fully describe the movement of carbon dioxide.

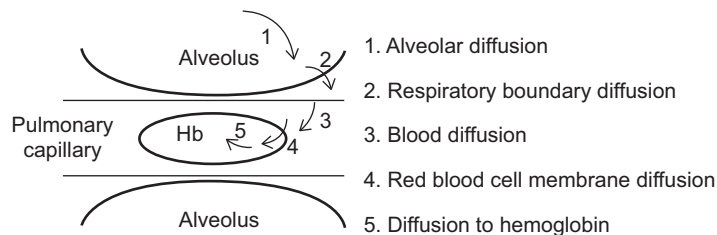


FIG. 8.1 The five salient diffusion events for red blood cells within the pulmonary capillaries to become oxygenated. By comparing the relative rates of diffusion of these five events, we can see that respiratory boundary diffusion, blood diffusion, and diffusion/association with hemoglobin are the rate-limiting steps of red blood cell oxygenation. Models of red blood cell oxygenation would assume a homogenous distribution of air within the alveolus and a rapid diffusion across the red blood cell membrane.

The difference in the partial pressure of carbon dioxide within the lung is approximately 40 mmHg in alveolar air and approximately 45 mmHg in the pulmonary capillary.

Diffusion can be characterized by Fick's first and second laws of diffusion. The first law of diffusion relates the flux of molecules across a barrier to the concentration gradient across the same barrier. Mathematically, this can be represented as

$$\vec{J} = -D\nabla\vec{C} \quad (8.1)$$

where J is the diffusive flux, D is the diffusion coefficient, and C is the concentration of species, which may depend on spatial and temporal variables. In one-dimensional (1D) diffusion cases, which is what we will typically assume for this textbook, the concentration gradient would be equal to $\frac{\partial\vec{C}}{\partial x}$, because there is no gas movement or volume in the y - and z -directions. Fick's second law of diffusion relates the change in concentration over time to the concentration gradient over the diffusion barrier. This can be represented as

$$\frac{\partial\vec{C}}{\partial t} = D\frac{\partial^2\vec{C}}{\partial x^2} \quad (8.2)$$

for 1D diffusion examples. Fick's second law of diffusion can be directly obtained from Fick's first law of diffusion as

$$\frac{\partial\vec{C}}{\partial t} = -\frac{\partial}{\partial x}(\vec{J}) = \frac{\partial}{\partial x}\left(D\frac{\partial\vec{C}}{\partial x}\right) = D\frac{\partial^2\vec{C}}{\partial x^2}$$

The general form for Fick's second law of diffusion would use the gradient operator for the concentration differences, shown as

$$\frac{\partial\vec{C}}{\partial t} = \nabla \cdot (D\nabla\vec{C})$$

or

$$\frac{\partial\vec{C}}{\partial t} = D\nabla^2\vec{C}$$

if the diffusion coefficient is constant in all directions. Solving the differential equation (Eq. 8.2) for a 1D diffusion example, the concentration of a species will vary with time and distance, as given by the function

$$C(x, t) = C(0) \left[\frac{x}{2\sqrt{Dt}} \right] \quad (8.3)$$

where $C(0)$ is the initial concentration at some point in space at time zero. Note that when we solve these types of scenarios, we typically assume that the feeding concentration (e.g., where oxygen is obtained from, but it can represent any other species) is uniform and homogeneous and that it cannot deplete with time. If we included the decrease in the source oxygen

concentration, we would need to couple multiple differential equations to solve the diffusion problem. Perhaps numerical solvers will be necessary for these more complicated problems.

The denominator of the expression in Eq. (8.3) is termed the *diffusion length* and is used to provide a relative measure of how far the molecules move within a given time. The diffusion length can be used to compare the diffusion of different molecules; molecules with a larger diffusion length will typically diffuse more freely than those with a smaller diffusion length (under the particular tissue conditions). For an alveolus, which is assumed to be circular with a radius of R_A , the diffusion length will be equal to

$$R_A = 2\sqrt{Dt}$$

$$t = \frac{R_A^2}{4D}$$

assuming that the reference point is the center of the circle (this is derived directly from Eq. (8.3)). Using measured values for the oxygen diffusion coefficient within air ($0.2 \text{ cm}^2/\text{s}$) and a typical alveolar radius of $100 \text{ }\mu\text{m}$, the average diffusion time for oxygen through the alveolus is 0.125 ms . This is a relatively accurate measurement for the time required for the oxygen concentration to equilibrate within the alveolus, assuming that oxygen enters from the center of a uniform alveolus. In addition, this diffusion time is generally very fast compared with the blood velocity within the pulmonary capillaries, and therefore, it can be assumed that the gas concentration within the alveoli is uniform (i.e., there is no effective concentration gradient within the alveolar space in regard to oxygen concentration). Therefore, we typically do not need to consider the oxygen diffusion time throughout the alveoli within the model of red blood cell oxygenation because it is not limiting the diffusion process.

The second diffusion event that we will consider for red blood cell oxygenation is the movement of oxygen across the respiratory boundary, which is primarily composed of the alveolar epithelial cells and the capillary endothelial cells (note that there is a basement membrane that exists between the two cells, but this does not play a significant role in controlling the permeability of the respiratory boundary to oxygen/carbon dioxide). In the simplest case, the diffusion of oxygen across this boundary can be modeled by permeability laws. Assuming that the permeability of oxygen is uniform throughout the entire respiratory boundary, the permeability can be defined in terms of the diffusion coefficient, the thickness of the boundary, and the partition coefficient for oxygen, as follows

$$P = \frac{p_c D}{x} \quad (8.4)$$

where p_c is the partition coefficient, D is the diffusion constant, and x is the thickness of the boundary. The partition coefficient is the ratio of the diffusing concentration across the diffusion boundary to the original concentration. In our example, it is the concentration of oxygen in the alveolar space versus the concentration of oxygen within the blood. The average thickness of the respiratory boundary is on the order of $2.2 \text{ }\mu\text{m}$, but can be as small as $0.3 \text{ }\mu\text{m}$. The diffusion coefficient for oxygen across the respiratory boundary is approximately $2.3 \times 10^{-5} \text{ cm}^2/\text{s}$, which has been experimentally determined. This simplified formula can be extended

to the actual respiratory boundary by a summation of the different permeabilities, which can be assumed to be in series (i.e., the thickness and diffusion coefficients for each cell type would be needed for this analysis). An average respiratory permeability also can be obtained through a thickness-weighted average for the individual permeabilities (e.g., the thickness of the cell membrane, the thickness of the cytoplasm). Under normal conditions, this process must be considered during red blood cell oxygenation, because the cells that make up the respiratory boundary can partially regulate the movement of species across the boundary.

The third diffusion event for oxygen is the diffusion of oxygen through the plasma to reach the red blood cell membrane. This diffusion is actually a combination of convection and diffusion since the blood velocity through the pulmonary capillaries will move (e.g., convect) the dissolved species along the capillary length in the absence of any diffusion. Thus, oxygen is propelled along the length of the capillary, while it is diffusing toward the red blood cells. Diffusion of oxygen typically occurs tangent to the blood flow direction, and diffusion is the only component that accounts for the movement of oxygen toward the red blood cell wall (this is an assumption that is relatively accurate because the red blood cells typically traverse a capillary in single file, and red blood cells do not have much freedom of movement in the radial direction). The permeability of oxygen through plasma is typically modeled through the use of a mass transfer coefficient, which is related to the Sherwood number (Sh), the diffusion coefficient, and a characteristic length. The Sherwood number is a dimensionless parameter that is the ratio of the convective mass transport to the diffusive mass transport

$$Sh = \frac{Kx}{D} \quad (8.5)$$

In Eq. (8.5), K is the mass transfer coefficient, x is the characteristic length, and D is the diffusion coefficient. In plasma, the diffusion coefficient for oxygen is on the order of $2 \times 10^{-5} \text{ cm}^2/\text{s}$. The plasma layer (characteristic length) ranges from 0.35 to 1.4 μm , depending on the exact red blood cell orientation and capillary size. The mass transfer coefficient is based on many physiological parameters, such as blood viscosity, blood speed, and dissolved species within the blood, and can be calculated only from the other parameters and not measured empirically. The Sherwood number has been found to depend on the blood hematocrit and can be represented mathematically as

$$Sh = Sh_{0.25} + 0.84(Hct - 0.25) \quad (8.6)$$

In Eq. (8.6), Hct is the hematocrit, which is represented as the decimal equivalent of the percent hematocrit. $Sh_{0.25}$ is the Sherwood number at a hematocrit of 0.25 (25%), which has been experimentally found to be equal to 1.3. Knowing the hematocrit and the characteristic plasma thickness, one can easily calculate the mass transfer coefficient that describes the particular flow conditions and then relate this to the other diffusion/permeability steps. This event also must be considered during normal red blood cell oxygenation because of the length scale that is involved; making this a significant contributor to oxygenation time.

The fourth diffusion event during red blood cell oxygenation is the diffusion of oxygen across the red blood cell wall. The thickness of the red blood cell membrane is on the order of 10 nm, which is similar compared with that of most human cells. The diffusion coefficient

for oxygen across the red blood cell membrane has been found to be similar to the diffusion coefficient for oxygen within plasma. Using Eq. (8.4), it can be seen that the permeability of oxygen through the red blood cell wall will be approximately 100 times greater than the permeability of oxygen across the respiratory boundary (because of thickness differences). This assumes that the partition coefficient is close to 1 for both cases (this is actually a good assumption). Therefore, this diffusion event occurs significantly faster than the second diffusion event during blood oxygenation and does not need to be considered in the overall red blood cell oxygenation model; the diffusion of oxygen through two cells (epithelial and endothelial) takes a significantly longer amount of time compared with the diffusion through one cell membrane.

The fifth diffusion event that occurs for the oxygenation of blood is the diffusion of oxygen within the red blood cell until the oxygen comes into contact with and reacts with hemoglobin. Similar to the convection and diffusion that oxygen experiences while moving within the plasma, once in the red blood cell, oxygen molecules can either react immediately with nearby available hemoglobin or diffuse through the red blood cell to interact with a different available hemoglobin molecule. The Thiele modulus is a dimensionless parameter that relates the kinetic reaction (in this case, oxygen–hemoglobin binding) to the molecular diffusion through the particular medium. The Thiele modulus is defined as

$$\phi = \sqrt{\frac{kx^2}{D}} \quad (8.7)$$

where k is the kinetic association constant, x is a characteristic length, and D is the diffusion coefficient. The oxygen–hemoglobin kinetic association constant within red blood cells is equal to 128 s^{-1} , and the diffusion coefficient for oxygen within red blood cells is on the order of $6 \times 10^{-6} \text{ cm}^2/\text{s}$. If we take the characteristic length of the red blood cell to be $1.5 \text{ }\mu\text{m}$, which is the average thickness of the red blood cell, then the Thiele modulus is

$$\phi = \sqrt{\frac{128 \text{ s}^{-1} (1.5 \text{ }\mu\text{m})^2}{6 \times 10^{-6} \text{ cm}^2/\text{s}}} = 0.6928$$

This diffusion/kinetic event must be considered as well because the kinetic reactions take a significant amount of time compared with the diffusion events.

Combining the five diffusion events for the oxygenation of red blood cells, we can see that only the diffusion of oxygen across the respiratory boundary, the convection/diffusion of oxygen within plasma, and the association of oxygen with hemoglobin can significantly limit the time it takes for red blood cells to become oxygenated. The remaining two events occur so rapidly that they will have little to no effect on the overall time required for red blood cell oxygenation under normal conditions. The first two diffusion events that we will consider are described by permeability coefficients through a particular medium. To combine these coefficients, we will consider that the barriers to diffusion are in series and that they act to resist the motion of oxygen. Permeability coefficients are equivalent to conductances in circuit theory, and therefore, the combined oxygen permeability across the respiratory boundary can be represented as

$$\frac{1}{P_{\text{barrier}+\text{plasma}}} = \frac{1}{P_{\text{barrier}}} + \frac{1}{K_{\text{plasma}}} \quad (8.8)$$

$$\frac{1}{P_{\text{barrier}+\text{plasma}}} = \frac{x_{\text{barrier}}}{p_{c-\text{barrier}} D_{\text{barrier}}} + \frac{x_{\text{plasma}}}{Sh_{\text{plasma}} D_{\text{plasma}}}$$

$$\frac{1}{P_{\text{barrier}+\text{plasma}}} = \frac{x_{\text{barrier}}}{p_{c-\text{barrier}} D_{\text{barrier}}} + \frac{x_{\text{plasma}}}{[Sh_{0.25} + 0.84(\text{Hct} - 0.25)] D_{\text{plasma}}}$$

$$\frac{1}{P_{\text{barrier}+\text{plasma}}} = \frac{2.2 \mu\text{m}}{1(2.3_E - 5 \text{ cm}^2/\text{s})} + \frac{0.875 \mu\text{m}}{[1.3 + 0.84(0.4 - 0.25)](2_E - 5 \text{ cm}^2/\text{s})}$$

$$P_{\text{barrier}+\text{plasma}} = 792 \mu\text{m}/\text{s}$$

assuming that the hematocrit is 40%. To add the resistance of oxygen diffusion through the red blood cell into this combined permeability, a mass transfer Biot number and an effectiveness factor are needed. The Biot number relates the mass transfer of the molecules to the diffusion of the molecules with the following relationship

$$Bi = \frac{Px}{D} \quad (8.9)$$

For our case the Biot number will equal

$$Bi = \frac{(792 \mu\text{m}/\text{s})(1.5 \mu\text{m})}{6_E - 6 \text{ cm}^2/\text{s}} = 1.98$$

for the mass transfer/diffusion of oxygen within the red blood cell (using the red blood cell characteristics). To combine all of the resistances and diffusion along with the kinetic reaction rates, the effectiveness factor should be used. The effectiveness factor can determine the effect of diffusion on a reaction and whether diffusion or the kinetic reactions are limiting the entire process. A modified effectiveness factor for our case of red blood cell oxygenation within the pulmonary microcirculation can be defined as

$$\eta = \frac{\tanh(\phi)}{\phi \left[\frac{\phi}{Bi} \tanh(\phi) + 1 \right]} \quad (8.10)$$

$$\eta = \frac{\tanh(0.6928)}{0.6928 \left[\left(\frac{0.6928}{1.98} \right) \tanh(0.6928) + 1 \right]} = 0.7155$$

An effectiveness factor less than 1 suggests that mass transfer is limiting the reaction more significantly than the kinetic reaction rates. However, in this process, the kinetics can change drastically based on percent oxygenation and the partial pressure of oxygen within the blood. Therefore, under normal conditions, oxygen mass transfer across the respiratory boundary and the red blood cell membrane limit the overall oxygenation of red blood cells.

The second case of gas diffusion that we will consider is the delivery of oxygen to the tissues within the systemic circulation. One of the first physiologists to tackle the problem of oxygen delivery to the tissues and to develop a feasible solution to the problem was August Krogh. Similar to the example of blood oxygenation, this process can be simplified into five diffusion events. The first is the dissociation of oxygen from hemoglobin and the red blood cells, then the diffusion and convection of oxygen through plasma, then the diffusion of oxygen across the endothelial cell barrier, then the diffusion of oxygen through the interstitial space, and finally the diffusion of oxygen into cells/mitochondria. Krogh realized that many tissues are arranged with a very regular spacing between the capillaries in 3D space. Assuming that a capillary has a perfectly cylindrical cross-section, Krogh made the argument that oxygen would be able to diffuse with an equal probability along any azimuthal direction surrounding the blood vessel. This primarily assumes that there is no diffusion restriction (or accelerant) in one particular direction. In other words, the rate of diffusion is the same in each direction (we know this is not true because the endothelial cell thickness will vary at different radial directions). Therefore, under this model/assumption, each capillary would supply a perfect cylindrical area of tissue with oxygen (Fig. 8.2). Additionally, the oxygen

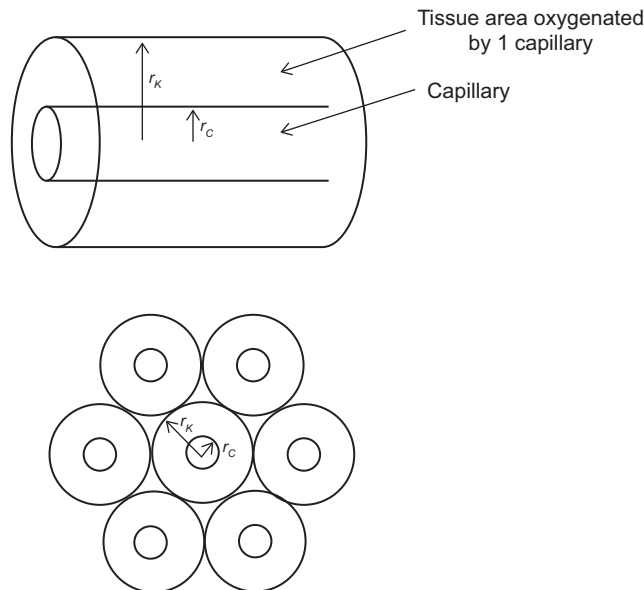


FIG. 8.2 Krogh model for tissue oxygenation around uniformly spaced capillaries. r_K is the Krogh radius and r_c is the capillary radius. This model assumes that each capillary can supply a uniform area of tissue with oxygen and is very accurate for predicting the oxygenation of tissue with ordered arrays of capillaries (like muscle). However, this model does not take into account the decrease in oxygen along the capillary length, inhomogeneities within the tissue, and nonordered arrays of capillaries (as seen in brain tissue). Even accounting for these limitations, the Krogh model can calculate an accurate estimate of tissue oxygenation.

concentration at one particular radial position would be equal for any changes in the azimuthal direction because it was assumed that the tissue consumption and diffusion through the tissue is uniform. Similarly, it was assumed that the oxygen concentration would decrease as the distance away from the capillary increases (e.g., distance along the radial direction), because oxygen is not generated by tissue. Fig. 8.2 illustrates that with this model, there are some areas of tissue that do not receive oxygen (or other nutrients) from the capillaries, if the oxygenation cylinders (e.g., the tissue) have zero overlap. Overlap within the tissue cylinder could be beneficial for redundancy but could be detrimental from an energy expenditure point of view. Regardless, at this point, the assumptions made by A. Krogh are a good first approximation for tissue oxygenation. This model is accurate only if the tissue capillaries are arranged in this most efficient organization array. In this model, r_K is the Krogh radius, and its value depicts how effective the capillary is at supplying oxygen to the surrounding tissue. Tissue with a larger r_K can have a smaller number of capillaries with a larger spacing between the capillaries, whereas tissues with a smaller r_K need more capillaries to supply the same area as tissues with a larger r_K . This is a similar analysis for the overlapping of blood vessels, because more capillaries would be needed to supply the same area, if overlapping vessels were found.

To develop the mathematics for tissue oxygenation, let us consider that the diffusion of oxygen is steady and occurs only in the radial direction. We can also neglect the oxygen convection because the blood velocity is relatively slow compared with the oxygen permeability throughout the tissue. A mass balance across this tissue can be obtained by converting the radial component of Eq. (3.61) to a convective/diffusion 1D steady diffusion scenario.

$$\frac{D}{r} \frac{d}{dr} \left(r \frac{dC}{dr} \right) = R \quad (8.11)$$

In Eq. (8.11), D is the diffusion coefficient, r is the radius, C is the concentration of a particular molecule, and R is the reaction rate for that molecule. Integrating Eq. (8.11) twice with respect to r yields a formulation for the concentration of a diffusing molecule with respect to the radial direction.

$$C(r) = \frac{r^2 R}{4D} + C_1 \ln(r) + C_2 \quad (8.12)$$

As with other differential equations, boundary conditions are needed to solve this equation in terms of the particular conditions of the problem of interest (i.e., to find the two integration constants C_1 and C_2). Let us assume that the plasma concentration of oxygen is uniform throughout the capillary at a given blood vessel cross-section and is denoted as C_p . This allows us to formulate the first boundary condition of

$$C(r = r_C) = C_p$$

which states that the concentration of oxygen at the wall of the capillary (r_C) is equal to the plasma concentration of oxygen. Our second boundary condition uses the Krogh radius. At r_K , the diffusion of oxygen out of the Krogh cylinder is balanced by the diffusion of oxygen

into the Krogh cylinder (from the neighboring cylinder). In other words, the flux of oxygen is equal to zero at the Krogh radius, because this is the farthest point that each capillary can effectively supply and thus oxygen motion is balanced at this location. Note that the oxygen concentration is not typically zero at the Krogh radius, although some students may want to use this value as the second boundary condition; if the oxygen concentration were zero at the Krogh radius, the tissue at this location would not obtain sufficient (or any) oxygen. Furthermore, tissue close to this location would also not receive sufficient oxygen. This second boundary condition states that the movement of oxygen is balanced at the Krogh radius. Therefore, the second boundary condition is

$$\left. \frac{dC}{dr} \right|_{r=r_K} = 0$$

Solving Eq. (8.12) using the two boundary conditions provides a means to obtain the integration constants, which are

$$C_1 = -\frac{r_K^2 R}{2D}$$

and

$$C_2 = C_p + \frac{r_K^2 R}{2D} \ln(r_C) - \frac{r_C^2 R}{4D}$$

Substituting and simplifying the derived integration constants into Eq. (8.12) develops a mathematical relationship for the change in concentration of a molecule with radial distance. This relationship is normally represented as

$$\frac{C(r)}{C_p} = 1 + \frac{r_K^2 R}{4C_p D} \left[\frac{r^2 - r_C^2}{r_K^2} + 2 \ln\left(\frac{r_C}{r}\right) \right] \quad (8.13)$$

Example 8.1

Calculate the oxygen concentration at a distance of 10 and 20 μm from a capillary with a radius of 4 μm . Assume that the Krogh radius is 35 μm , the diffusion coefficient for oxygen is $2 \times 10^{-5} \text{ cm}^2/\text{s}$, the plasma oxygen concentration is $4 \times 10^{-8} \text{ mol}/\text{cm}^3$, and that the oxygen reaction rate is $5 \times 10^{-8} \text{ mol}/\text{cm}^3 \cdot \text{s}$. In addition, plot the oxygen concentration as a function of radial distance. How does the plot change if the Krogh radius reduces to 25 μm ?

Solution

$$C(r) = C_p + \frac{r_K^2 R}{4D} \left[\frac{r^2 - r_C^2}{r_K^2} + 2 \ln\left(\frac{r_C}{r}\right) \right]$$

Example 8.1 (*cont'd*)

$$C(r) = 4_E - 8 \text{ mol/cm}^3 + \frac{(35 \text{ } \mu\text{m})^2(5_E - 8 \text{ mol/cm}^3\text{s})}{4(2_E - 5 \text{ cm}^2/\text{s})} \left[\frac{r^2 - (4 \text{ } \mu\text{m})^2}{(35 \text{ } \mu\text{m})^2} + 2\ln\left(\frac{4 \text{ } \mu\text{m}}{r}\right) \right]$$

$$C(10 \text{ } \mu\text{m}) = 4_E - 8 \text{ mol/cm}^3 + \frac{(35 \text{ } \mu\text{m})^2(5_E - 8 \text{ mol/cm}^3\text{s})}{4(2_E - 5 \text{ cm}^2/\text{s})} \left[\frac{(10 \text{ } \mu\text{m})^2 - (4 \text{ } \mu\text{m})^2}{(35 \text{ } \mu\text{m})^2} + 2\ln\left(\frac{4 \text{ } \mu\text{m}}{10 \text{ } \mu\text{m}}\right) \right]$$

$$= 2.65_E - 8 \text{ mol/cm}^3$$

$$C(20 \text{ } \mu\text{m}) = 4_E - 8 \text{ mol/cm}^3 + \frac{(35 \text{ } \mu\text{m})^2(5_E - 8 \text{ mol/cm}^3\text{s})}{4(2_E - 5 \text{ cm}^2/\text{s})} \left[\frac{(20 \text{ } \mu\text{m})^2 - (4 \text{ } \mu\text{m})^2}{(35 \text{ } \mu\text{m})^2} + 2\ln\left(\frac{4 \text{ } \mu\text{m}}{20 \text{ } \mu\text{m}}\right) \right]$$

$$= 1.78_E - 8 \text{ mol/cm}^3$$

The oxygen concentration as a function of Krogh radius and distance is plotted in Fig. 8.3.

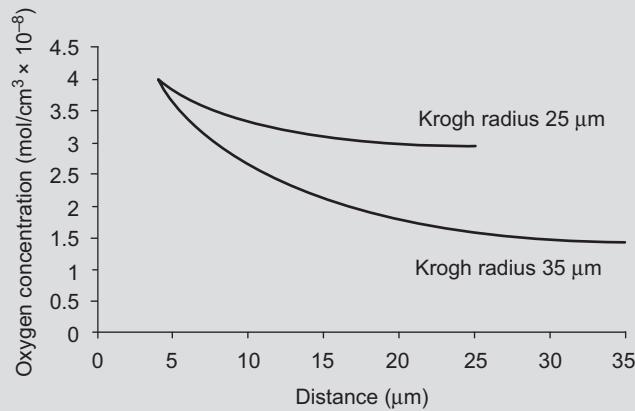


FIG. 8.3 Oxygen concentration as a function of distance and the Krogh radius.

Although the Krogh method to calculate tissue oxygenation is possibly the most famous and the most often used model, there are some limitations associated with this model. First, Krogh did not consider the reduction in plasma oxygenation concentration along the capillary length. This model also assumes that the capillaries are uniformly distributed in a regular array throughout the tissue. This is fairly accurate for some tissue, such as skeletal muscle, but for other tissues (especially the brain), the capillary distribution is seemingly random and not organized in a regular array. Krogh also assumed that diffusion occurs in only one direction in both the plasma and the tissue (i.e., radial). If these assumptions are not met, there may be a drastic effect on the movement of oxygen throughout the tissue, and it is likely that the tissue oxygen concentration will not be uniform at one particular radial location.

The same analysis can be conducted for carbon dioxide exchange. The formulations are the same, and it turns out that the same processes are the rate-limiting steps for carbon dioxide movement. The following are experimentally determined diffusion coefficients/kinetic rate constants for carbon dioxide. The diffusion coefficient for carbon dioxide movement through the respiratory boundary is $8.3 \times 10^{-4} \text{ cm}^2/\text{s}$. The diffusion coefficient for carbon dioxide through plasma is on the order of $4 \times 10^{-4} \text{ cm}^2/\text{s}$. Within the red blood cell the diffusion coefficient for carbon dioxide is $1.6 \times 10^{-4} \text{ cm}^2/\text{s}$ and the kinetic association constant for the formation of bicarbonate within the red blood cell is 0.13 s^{-1} (again, recall that the majority of carbon dioxide does not associate with hemoglobin). One typically does not discuss a Krogh radius for carbon dioxide because the tissue is supplying the capillary with carbon dioxide and not the reverse.

8.2 Glucose transport

Glucose diffusion out of the vascular system is similar to the diffusion of oxygen and carbon dioxide; however, because glucose is not lipid soluble, there are other mechanisms present to efficiently move glucose into the interstitial space. This is typically termed *glucose transport*. Once glucose passes through the intercellular cleft (see [Section 8.3](#)), a carrier protein is required to move glucose into individual cells, so that the glucose can be used as an energy source within the individual cells. In most cases, glucose transport is mediated by a coupled transport protein that moves some molecule along the direction of its electrochemical gradient and at the same time moves glucose against its electrochemical gradient. The energy gained by moving the first molecule down its concentration gradient is harnessed to move glucose against its gradient. Remember that glucose is typically in a higher concentration within the cells than outside of the cell. In the most common transport mechanism for glucose, sodium is moved in the direction of its concentration gradient (i.e., into cells) at the same time that glucose is moved into the cell. The type of transporter that is responsible for this is termed a *symporter*. The energy that is gained from sodium movement along its concentration gradient is used to transport glucose against its gradient. This transporter only works after both sodium and glucose have interacted with the protein, which most likely occurs when the protein is open to the extracellular space (because sodium is in a much higher concentration in the extracellular space). Once sodium and glucose bind to the protein, there is a conformational change that closes the protein to the extracellular space and opens it to the intracellular space. The conformational change also causes the release of sodium and glucose molecules into the cell after the conformational change. Many of these types of transporters exist for various compounds coupled to glucose movement; however, the abundance of sodium makes this an ideal compound to use in a coupled transporter. In the case of sodium–glucose cotransport, the sodium concentration gradient would be maintained through the presence of sodium–potassium ATPase molecules on both the apical and basolateral side of the endothelial cell. The glucose that enters the endothelial cell would then typically leave the endothelial cell via a glucose transporter that is present on the basolateral side of the endothelial cell. Once glucose has entered the extravascular space, it can be transported, by diffusion, to other cells within the system.

In many tissues, this asymmetrical distribution is used to move glucose through cells that line a cavity/lumen, for example, the epithelial cells that line the intestines. Within the epithelial cells there is a high concentration of glucose, but there is also a low concentration of glucose on either the intestinal side or the basal side of the cells. To effectively transport glucose through the intestinal wall, the sodium–glucose cotransporter transports glucose and sodium from the intestine into the epithelial cells. A carrier protein specific for glucose is also found on the basolateral side of the cell and uses the glucose concentration gradient to move glucose out of the cell (the additional sodium that enters is pumped out of the cell by other mechanisms). Similar mechanisms exist within the kidneys. Glucose transport is difficult to model because of the coupling of the proteins' conformational changes and binding kinetics. The affinity of the protein for glucose depends on the presence of other ions (e.g., sodium and its concentration gradient), the pH of the solution, the quantity of proteins within the cell membrane, and the concentration gradient of glucose. Therefore, for most molecules that use this mechanism of transport, many assumptions must be made to conduct some form of analysis.

8.3 Vascular permeability

We will now move our discussion to generalizations about how molecules move out of and into the vascular system. Diffusion accounts for the majority of exchange between the vascular system and the cells throughout the body. The amount of water and dissolved solutes that move allow for a constant mixing between these two compartments and therefore the constituents of the plasma are very similar to the constituents of the interstitial fluid. As we know, diffusion is a result of random thermal motion of molecules. If the molecule is lipid soluble (i.e., hydrophobic), it can diffuse directly through the endothelial cell membrane. Physiologically relevant lipid-soluble molecules are typically small and uncharged. There are no direct transport mechanisms (e.g., channels, transporters) for these types of molecules present within the cell membrane. The permeability of these molecules is typically much greater than that of other molecules that are transported within the microvascular networks such as proteins. The permeability of these molecules tends to be very high because the endothelial cells do not restrict the movement of these molecules; it is as if the endothelial barrier does not exist toward the movement of these molecules. Examples of these types of molecules are oxygen and carbon dioxide.

Most molecules, however, are not lipid soluble and cannot diffuse readily through the cell membrane. These molecules are typically soluble in water and can pass through the microvascular wall only between endothelial cells at the intercellular clefts or by active transport mechanisms within the endothelial cell membrane. As discussed in the previous chapter, the intercellular cleft accounts for less than 1/1000 of the total capillary surface area. However, this very small area accounts for the vast majority of the movement of non-lipid-soluble molecules, such as ions, glucose, and water. The diffusion of molecules through the intercellular cleft is so fast that it allows for solutes to rapidly approach equilibrium across the capillary wall (e.g., plasma concentration versus the interstitial space concentration). In fact, equilibrium of solutes is typically reached within half of the capillary length because

of the overall slow velocity of blood and the very strong diffusional forces across the capillary wall. The remaining portion of the capillary is left as a safety reservoir (this is a similar mechanism that is found within the pulmonary capillaries for blood oxygenation and removal of wastes). The diffusion of molecules through the intercellular cleft occurs at a rate that is approximately 80 times greater than the blood flow through the capillary.

The process of diffusion through the intercellular cleft is principally regulated by the permeability of the pore to the specific molecule. As noted in Chapter 7, the intercellular cleft pore diameter is on the order of 7 nm. Water molecules, ions, glucose, and some other metabolically important molecules all have a molecular radius that is smaller than the 7nm pore size and therefore can permeate through the pore relatively easily. Plasma proteins typically have a molecular size that is greater than 7 nm and therefore cannot diffuse through the pore under physiological conditions. However, in inflammatory diseases and some pathological scenarios, the size of these pores can increase and they can become permeable to plasma proteins. In the early 1950s, studies were conducted to determine the average permeability of the intercellular cleft to physiologically important molecules. From these studies, it was found that most physiologically important molecules have a permeability that is in the range of that of water. For instance, sodium chloride in solution has a permeability that is equal to 96% of water's permeability through the intercellular cleft. Glucose, a molecule that is 10 times the weight of water, has a permeability in the range of 60% of water's permeability through the intercellular cleft. Albumin, which has a molecular weight that is approximately 4000 times greater than that of water, has a permeability of 0.1% of water's permeability through the intercellular cleft and thus is effectively impermeable across the endothelial cell wall.

In most engineering applications, diffusion is principally regulated by the concentration gradient across the membrane. Although that is partially true within capillaries, the permeability is much more easily controlled than the concentration gradient and is therefore the principal regulator of diffusion within the microcirculation (e.g., the concentration gradient is not the primary regulator of diffusion in the capillary as with most standard engineering applications). For most physiologically important molecules (i.e., glucose, salts, water), the permeability is so large that very small differences (or changes) in the concentration gradient can induce very large changes in the rate of movement across the capillary wall. The energy that would be required to maintain a large concentration gradient for each biologically important molecule would exceed the body's capacity to store energy and in some instances would vary from the concentration that is needed for other physiologically relevant processes. Furthermore, the concentration is variable depending on diet and meals, etc., so it would be challenging for the body to predict and accommodate to these changes. For instance, for cells to function in the innate environment, it is required that sodium be present in the extracellular fluid at a concentration that is approximately 100 times that concentration within the cell. However, if concentration gradient were the principle regulator of diffusion, the concentration in the extracellular fluid would need to be lower than the blood sodium concentration to allow for diffusion of sodium into the extracellular fluid. However, because the blood sodium concentration is variable, is not easily controlled, and is not something that the body would want to maintain at a constant value as digestion/absorption alters the

sodium concentration, using concentration gradients as the primary regulator of diffusion does not make sense and would not be efficient. If we extend this to every metabolically important molecule that diffuses across the capillary wall, each molecule would need to be regulated, controlled, and monitored to maintain a concentration gradient that favors diffusion in a particular direction. The majority of these metabolically important molecules have a variable concentration with time. Therefore, it is much easier to control the cellular permeability of the diffusing molecule, which is independent of the concentration.

Recall that some molecules, like glucose as described in the previous section, also can be transported through the endothelial cells that line the capillary walls, instead of being transported in between the endothelial cells. In this case, specific transport proteins are needed on the apical side (side that faces the blood) and on the basolateral side (side that faces the extravascular space) of the endothelial cell. Most of these transporters derive their energy through the motion of a molecule, such as sodium, down its concentration gradient to move a second molecule up its concentration gradient and into the cell. These types of transporters would be present on the apical side of the tissue. On the basolateral side of the tissue, transporters would be present that allow for the motion of the metabolically important molecule down its concentration gradient and out of the cell. To ensure that these proteins function properly, active transport mechanisms, such as the sodium–potassium ATPase, would need to be present to maintain the concentration gradient of the specific molecules used in the first stage of the transport. This requires significant energy and is not a feasible transport mechanism for every metabolically important compound.

An important application of vascular permeability is therapeutic delivery mechanisms. In general, there are two methods to deliver therapeutics to the body: local delivery and systemic delivery. Local delivery is of less interest to biofluid mechanics analysis because the therapeutic is typically directly injected into the site of interest (or very close to the site of interest), allowing for pure diffusion to account for therapeutic uptake/function. However, for systemic delivery, the therapeutic can be given orally, injected into a muscle, injected into the interstitial space, or injected into a vein. For all of these routes, except for intravenous injection, the therapeutic will enter the vascular system by diffusion through microcirculation beds. For all injection methods, the therapeutic will typically bind to plasma proteins and be delivered to all of the organs/tissues in the body. In some instances, the metabolites of the therapeutics are active. Therefore, the therapeutic would need to make it to an organ that can metabolize the therapeutic, usually the liver, and then the metabolites are transported through the vascular system to have some effect. In general, the therapeutic or its metabolites are then removed by the liver or the kidneys. The importance of therapeutic delivery is that the size of therapeutic molecules and the molecular weight of therapeutic molecules are typically larger than the usual molecules transported through these mechanisms. Combined with this, the permeability and diffusion coefficient can be significantly lower than with other molecules. Therefore, the design of therapeutics, including their mode of delivery, needs to be carefully considered to ensure proper delivery.

It is also important to differentiate among diffusion, active transport, cellular transport, and organ-level transport. We discussed diffusion in [Section 8.1](#), and we will relate this to some of the more physiological transport mechanisms. Active transport requires the presence

of a particular receptor within the cell membrane. These receptors are proteins that function to transfer signals, possibly in the form of molecules, from one side of the membrane to the other (for clarification, this also includes transfer across the nuclear membrane and other organelle membranes). Under most conditions, the binding of the ligand, which is the molecule that will be transported, to the receptor induces a conformational change in the protein structure of the receptor. This change can cause the ligand to be brought into the cell, a pinocytosis process to cause the molecule to be put into the cell, or signal a cascade that may result in a cellular level functional change. Most receptor–ligand events can be described by kinetic reactions that describe the association and the dissociation of the receptor–ligand complex. Depending on the magnitude of the association rate constant compared with the dissociation constant, the outcome of these kinetic events can be determined and then statements about the favorability of certain reactions can be made. At the cellular level, transport of molecules will occur by either diffusion through the cytoplasm or a coupled diffusion, where the molecule of interest is associated with some other molecule (an example of this is the motor proteins). This has been discussed previously, but the only new considerations would be that the diffusion coefficients would differ because the media that the molecules are moving through are different.

Organ level transport is actually fairly intuitive to model; however, in practice the information that is necessary to complete this type of modeling is typically missing. For instance, the exact blood/lymph flow characteristics would need to be known for the organ that is being modeled. If we assume a Krogh type of model, with uniform or some clearly defined spacing, these concentrations/characteristics may be known and applied to the model. However, the fluid velocity through each blood vessel and lymph vessel would need to be known, and as we have learned earlier, fluid velocity differs temporally and each capillary is not fully perfused at one instant in time. Therefore, many simplifications/assumptions would be needed to determine the location of blood vessels along with the flow rate of blood through those vessels, over some period of time. The second issue that complicates the modeling of molecules at the organ level is that permeability, diffusion coefficients, and other transport phenomena are generally not known along the entire path throughout the organ. We may be able to develop a formulation that simplifies this transport (recall oxygen transport across the respiratory boundary as discussed in [Section 8.1](#)), but then the accuracy of the solution may vary greatly. Also, the diffusion properties depend on the homogeneity of the tissues/organs and as we can imagine, there is a significant amount of inhomogeneities in biological specimens. The last issue with organ level transport, which confounds the solution methods, is that multiple length and time scales are involved in the transport. If we are discussing transport of a species through the digestive tract, we can concern ourselves with the transport across a cell membrane, which is typically 7 to 8 nm, or we can be concerned with the transport along the tract, which is approximately 30 m in length. This is an astounding difference in length scales, which would need to be coupled if solving an organ transport problem. For a time-scale problem in the digestive tract, molecular transport can occur within a few microseconds or as long as a few days. Thus, the solutions to these types of problems would need to couple both length and time scales that vary along a few orders of magnitude. Compartmental modeling is a good way to handle these types of problems, and it will be presented in Chapter 13.

8.4 Energy considerations

The transfer of nutrients can be classified as an adhesion reaction between the nutrient and the transporter (e.g., glucose) or as an interaction between the nutrient and water (e.g., ions). In either case, some energy is required to either maintain that adhesion or break the adhesion. In other words, there is a force required to break the adhesive interactions between the two molecules that are involved in the diffusion process so that one molecule can diffuse away freely. Recall that all ions are hydrated in physiological conditions and their transport would require some alteration to the hydrated form. In the case of an adhesion-based transporter, there must be some interaction so that the molecule can associate with the transporter. This adhesion would help localize the molecule that is being transported but would hinder the overall diffusion of the molecule if the association energy were too high. In addition, it may be required for the molecule to shed the water that is associated with it so that it can interact with the transporter and/or be transported across a cell membrane. Adhesion forces are typically small, on the nano- to micro-Newton range, and the adhesive forces increase with a decreasing surface roughness. It is also typical that flexible surfaces have a larger adhesive force than stiffer surfaces because the flexible surface can conform to the surface profile of the material that it is adhering to (thus, there would be a higher contact area). In general, four forces contribute to adhesion: molecular forces, electrostatic forces, capillary forces, and excessive charge forces (which will not be discussed because this force is not typically found in common biological systems).

Molecular forces act over the shortest range and are typically the weakest types of forces that play a role in adhesion. These types of attractive forces typically arise as a result of changes in the electronic structure of the atoms that compose the molecules. This means that electrically neutral molecules can exhibit molecular forces, through transient dipoles created by these fluctuations. Any molecule that has a permanent dipole (e.g., water) will experience molecular forces. This type of interaction is termed a *van der Waals interaction*. Van der Waals forces are composed of two components: an attractive force and a repulsive force. The attractive force arises from transient dipoles within electrically neutral molecules. The repulsive component arises because two molecules cannot enter the same space, and therefore, no matter how strong the attractive force is, the two molecules cannot exist in one location. Mathematically, the force associated with molecular interactions can be described by

$$\vec{\psi}(d) = \vec{\psi}_0 \left[\left(\frac{d'}{d} \right)^{12} - \left(\frac{d'}{d} \right)^6 \right] \quad (8.14)$$

where ψ_0 is the strength of the molecular interactions when the molecules are in contact, d is the distance between molecules, and d' is the range of the interactions. Therefore, if $d = d'$, the molecular forces will be equal to zero.

The second type of force that makes up the adhesive forces is electrostatic forces. These can arise from either excess charge on a molecule or an electric double layer. The force associated with charge should be familiar from a previous classic physics class and is described by Coulomb's law, which states that

$$F = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{r^2} \quad (8.15)$$

where q is the excess charge on molecule 1 and 2, respectively, r is the distance between the two molecules, and ϵ_0 is the permittivity of free space. These charges can be removed if the substances are “grounded” or more likely the charges can be transferred to another molecule. The electric double layer is more of a concern in biological applications, in which one encounters the interaction of a small particle (that may or may not have a charge associated with it) with a larger particle with a surface charge that acts as a boundary. For biological applications, this can be considered the intercellular cleft (or a protein channel), in which small potentially charged molecules will permeate a larger channel that has a charge associated with it. The charge on the boundary attracts opposite charges within the solution; in the case of biological solutions the majority of the fluid is water. As an example, if the surface has a partial positive charge, the partial negative charge present on the oxygen atom within water will be attracted to the surface (Fig. 8.4; we use the example of water because this is likely the most significant component of bathing medium in the body, but this process can be extended to any bathing medium that is a dipole). This suggests that a second, potentially less strong, partial positive layer will be formed from the aligned hydrogen atoms that compose water. A second layer of water will form on top of the original aligned layer, until the electric field generated by the boundary (cell membrane wall or protein backbone) weakens to a point that it can no longer maintain this organized charge structure. The surface potential on the boundary is termed the *Nernst potential*, and the potential at the point that the layer begins to break up is termed the *Stern potential*. The entire distance between the boundary and the point at which the charges in solution break up is called the *Stern layer*. The Stern layer is characterized by highly organized solutes, and again in physiological bathing mediums this is typically water. Directly adjacent to the Stern layer there is a slight

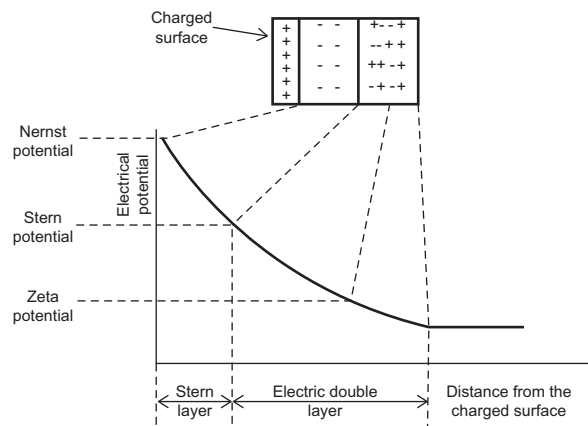


FIG. 8.4 Electrostatic forces near a charged surface, which tend to organize water (or other ions) close to the boundary. The layer that is closest to the charged boundary and has the highest organization is termed the *Stern layer*. A second layer, of mostly organized charged species, is termed the *electric double layer*. Beyond the electric double layer, the charged species would resemble the bulk properties.

organization of the charged molecules until the shearing plane. Between the Stern layer and the shearing plane there is some organization of the bathing medium, but one can observe significantly less organization. At the end of the shearing plane, the organization of the bathing medium resembles a solution in contact with an uncharged surface and is therefore organized randomly. This is characterized as the bulk organization of the fluid. In the layer between the Stern layer and the shearing plane, water is partially organized and partially random. The attractive force at the shearing plane is termed the *zeta potential*. The entire distance from the Stern layer to the point at which the electric field equilibrates to the bulk fluid properties is termed the *electric double layer*. All of these potentials and distances are shown in Fig. 8.4.

If there are two charged surfaces that come into close contact with each other, for example, a charged protein and an ion in solution, the attractive force between these two surfaces can be described by

$$F_{ef}(d) = \frac{2\xi_1\xi_2}{\epsilon_l\epsilon_0} A e^{-\frac{d}{\lambda_D}} \quad (8.16)$$

where ξ is the surface charge densities for the surface and the molecules within the fluid, A is the potential area of contact between the surface and the molecules, ϵ_0 is the dielectric constant of vacuum, ϵ_l is the dielectric constant of the liquid, and λ_D is the Debye length. The Debye length quantifies the electrostatic double-layer thickness and is calculated from

$$\lambda_D = \sqrt{\frac{\epsilon_l\epsilon_0 k_B T}{e^2 \sum_i^n (c_i \chi_i^2)}} \quad (8.17)$$

where k_B is the Boltzmann constant (1.38×10^{-23} J/K), T is the temperature (in Kelvin), e is the charge of an electron, and c is the concentration of molecule i with a valence of χ . Eq. (8.16) is a modification of the electric double-layer formulation, taking into account that the layer from each of the two surfaces will overlap as they approach. The summation in Eq. (8.17) takes into account the valence and concentration of particular species. This tends to be difficult to approximate for biological specimens because it is typical that charged surfaces (e.g., cell membranes) are composed of multiple charged species that can have a time-varying concentration.

Example 8.2

Calculate the attractive force between an endothelial cell and a red blood cell that are $3 \mu\text{m}$ apart. The surface charge density for the endothelial cell is -12 mC/m^2 , and that for the red blood cell is -3 mC/m^2 . Assume that the dielectric constant of the liquid is 75 and that the blood is flowing at a temperature of 32°C . The summation of all molecular species and valences on these two cell types is $1.7 \mu\text{m}^{-3}$. Approximate the potential area of contact between the two cells, using geometrical constraints.

Example 8.2 (cont'd)**Solution**

First, calculate the Debye length for this interaction

$$\lambda_D = \sqrt{\frac{75 \left(8.85_E - 12 \frac{C^2}{Nm^2} \right) \left(1.38_E - 23 \frac{J}{K} \right) (273 + 32)K}{(1.6_E - 19C)^2 (1.7 \mu m^{-3})}} = 8.012 \mu m$$

Now calculate the attractive force between the endothelial cell and the red blood cell.

$$F_{ef}(d) = \frac{2(-12 mC/m^2)(-3 mC/m^2)}{75 \left(8.85_E - 12 \frac{C^2}{Nm^2} \right)} A e^{\frac{-3 \mu m}{8.012 \mu m}}$$

To approximate the area of interaction, we need to make some assumptions about the cells' contact area. If we assume that the endothelial cell can be represented as a stiff plane and the red blood cell as a sphere, we can make some simple estimates of the contact area; however, these estimates may not represent the actual contact area. Using these assumptions would suggest that the contact area would be only one point on the red blood cell membrane. However, we know that the red blood cell can deform when it comes into contact with the endothelial cell (which can also deform). If we make the assumption that the deformation will encompass a 60-degree arc length (in 3D space) of the original red blood cell, we get that the potential contact area is

$$A_{60^\circ} = \frac{4\pi(4 \mu m)^2}{6} = 33.51 \mu m^2$$

For interest, we will show other area calculations as well

$$A_{30^\circ} = \frac{4\pi(4 \mu m)^2}{12} = 16.75 \mu m^2$$

$$A_{120^\circ} = \frac{4\pi(4 \mu m)^2}{3} = 67.02 \mu m^2$$

The effective forces of interaction for these three contact areas are

$$F_{ef}(d) = \frac{2 \left(-\frac{12 mC}{m^2} \right) \left(-\frac{3 mC}{m^2} \right)}{75 \left(8.85_E - 12 \frac{C^2}{Nm^2} \right)} (33.51 \mu m^2) e^{\frac{-3 \mu m}{8.012 \mu m}} = 2.50 \mu N$$

$$F_{ef}(d) = \frac{2 \left(-\frac{12 mC}{m^2} \right) \left(-\frac{3 mC}{m^2} \right)}{75 \left(8.85_E - 12 \frac{C^2}{Nm^2} \right)} (16.75 \mu m^2) e^{\frac{-3 \mu m}{8.012 \mu m}} = 1.25 \mu N$$

Example 8.2 (*cont'd*)

$$F_{ef}(d) = \frac{2\left(-\frac{12 \text{ mC}}{\text{m}^2}\right)\left(-\frac{3 \text{ mC}}{\text{m}^2}\right)}{75\left(8.85_{\text{E}} - 12 \frac{\text{C}^2}{\text{Nm}^2}\right)} (67.02 \text{ } \mu\text{m}^2) e^{\frac{-3 \text{ } \mu\text{m}}{8.012 \text{ } \mu\text{m}}} = 5 \text{ } \mu\text{N}$$

As we can see, with an increasing contact area, the effective force increases as well, which is important in biological systems in which the cells can deform when impacting each other.

The third type of force that makes up adhesive forces in biological systems are capillary forces, which are subdivided into adhesion, cohesion, and surface tension. Surface tension is a fluid property that causes a surface of liquid to be attracted to another surface (e.g., a bounding container that becomes wet when in contact with the fluid). Surface tension arises as a result of the intermolecular forces within the fluid. For a fluid element within the bulk fluid phase, the intermolecular forces acting on that element are balanced in all directions. However, at the surface of the fluid, there is an interface between the fluid elements and the surrounding medium (e.g., for a glass of water, the fluid at the surface will tend to be pulled into the water because the intermolecular forces for water–water are stronger than the intermolecular forces for water–air). This inward force is balanced by the tendency of the fluid to resist compression until the energy (and hence the fluid surfaces) reaches equilibrium at a low energy state. The surface tension is defined as the force that is required to maintain the fluid in this low-energy state per unit length. Surface tension (γ) is quantified by the pressure difference across the surface and the curvature that the surface takes in the low energy state, using the Young-Laplace equation

$$\Delta p = \gamma \left(\frac{1}{r_x} + \frac{1}{r_y} \right) \quad (8.18)$$

where Δp is the pressure difference across the fluid surface, and r is the radius of curvature measured in the x - and y -directions. This can be normalized to a force by considering the area of contact between the two surfaces, where A_C is the contact area.

$$F_{ST} = \gamma A_C \left(\frac{1}{r_x} + \frac{1}{r_y} \right) \quad (8.19)$$

The surface tension of water is approximately 71 kPa/m, which can be used to approximate the forces or pressures associated with cells coming into contact with other structures. In fact, the surface tension of biomaterials is a common property to manipulate/optimize to promote cell adhesion or inhibit cell adhesion. For instance, for cardiovascular devices, it has become common to make the surface tension very large, so that platelets will not adhere to

the device. The reverse is also true: if the device is designed to become endothelialized, the surface tension would be reduced to promote endothelial cell adhesion.

Adhesion occurs when two different molecules tend to stick together because of an attractive force between the molecules. Adhesion is typically quantified by the amount of work that is required to separate the two materials; this depends on the surface tension of the materials, as follows

$$W_A^{12\delta} = \gamma^{1\delta} + \gamma^{2\delta} - \gamma^{12} \quad (8.20)$$

where γ is the surface tension generated between materials 1 and 2 or the medium, δ , within which the materials are bathed. The force associated with adhesion can be calculated from the distance that is required to separate the materials and the work that is input into the system to separate the materials. Cohesion arises as a result of the interaction of the same molecules within the material. This attraction is caused by intermolecular forces, such as the common hydrogen bonding that occurs between individual water molecules. Dipole interactions can also lead to a cohesive interaction between molecules. Cohesion is also quantified through the surface tension of the material, as follows

$$W_C^1 = 2\gamma^1 \quad (8.21)$$

where γ is the surface tension between the material phase of material 1 and its equilibrium vapor phase. Again, the force associated with cohesion can be calculated from the distance required to separate two molecules in solution.

Cellular adhesion can be divided into three basic categories, which include cell contact, cell adhesion/attachment, and cell separation. Cell contact is based on random connections that occur as a result of cells coming into contact with each other. These connections can act over varying ranges and may have a large force associated with them. Cell adhesion/attachment is based on chemical bonds, which can be subdivided into the different molecular forces that we have described previously. These typically act over a range of no more than 0.5 nm and are typically in the nano-Newton range. Cell separation is based on the same attachment forces when there are other forces acting to pull the cells apart. Initial adhesion and separation are based on the cell surface properties and geometries. We have hinted at this before: to model these interactions, many simplifying assumptions on these relationships would need to be made because cells are homogeneous neither in the expression of surface molecules nor in contact geometry. Furthermore, both of these properties are time varying based on the input biochemical or biomechanical stimuli.

8.5 Transport through porous media*

Porous media are solid materials that are composed of pore structures, which are typically fluid filled in biological applications. Porous media can have very different topographical and morphological properties, based on the internal organization of the pores. The most common

*This section is considered advanced and can be skipped without a loss of continuity.

porous media in biological systems is the interstitial space, which is composed of the extracellular matrix and interstitial fluid. As we have learned, the extracellular matrix is mostly composed of proteins and functions as a mechanical scaffolding for cells. This structure is required for the normal functioning of cells, including migration, proliferation, and apoptosis.

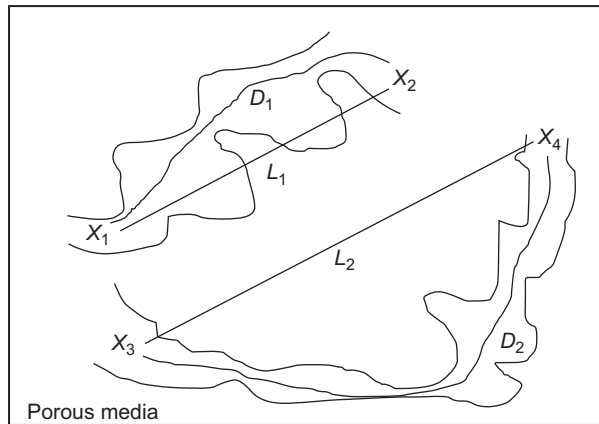
It is common to describe porous media based on the porosity, which is defined as follows.

$$\varepsilon = \frac{\text{Volume associated with voids}}{\text{Total volume}} \quad (8.22)$$

The values that make up porosity may need to be approximated from microscopy images of the porous media, and porosity can depend on the loading conditions of the porous media and whether cells can interact with and/or modify the pore structure. For instance, the extracellular matrix is deformable, and thus the porosity may appear to change under particular loading conditions because both the volume associated with voids and the total volume of the extracellular matrix can change. The porosity of the interstitial space, neglecting blood vessels and cells, approaches 0.9, whereas the porosity of general biological tissues (including blood vessels and cells) would be closer to 0.25.

Porous media also can be classified based on the tortuosity of the pores within the media. Tortuosity is a measure of the random orientation and random spacing of pores throughout the media. Clearly, not all pores will be able to be classified as straight channels through the media, and tortuosity quantifies the degree of bending and/or twisting of the pores (Fig. 8.5). Tortuosity is defined as

$$T = \frac{L_{\text{actual}}}{L} \quad (8.23)$$



$$T_{X_1 \rightarrow X_2} = \frac{D_1}{L_1}, T_{X_3 \rightarrow X_4} = \frac{D_2}{L_2}$$

FIG. 8.5 Tortuosity is defined as the actual minimum distance between two points connected by a pore divided by the straight line path between the points. This value can only be greater than or equal to 1.

where L_{actual} is the minimum actual distance between two points that are connected by pores, and L is the straight-line distance between the two points. Thus, tortuosity can be only equal to or greater than 1, and as tortuosity values approach 1, the pores more closely resemble a straight pass through the channel. Note that the quantification of tortuosity values does not account for the 3D shape of the channel and has no need to, as long as the channel is open to some extent along its entire length.

Fluid flow through porous media is most typically quantified by Darcy's law, which relates the pressure gradient (as the driving force for fluid flow) to the flow rate of fluid through the porous media. Darcy's law is an idealized case that is not applicable for non-Newtonian fluids and for fluids when there is a large momentum transfer between the fluid and the solid particles. Under these conditions, Darcy's law states that the fluid velocity ($\vec{v}$) will be defined by

$$\vec{v} = -K \nabla \vec{p} \quad (8.24)$$

where K is the hydraulic conductivity of the medium and p is the driving pressure. If the porous media is nonisotropic, the hydraulic conductivity is not constant and must be included within the gradient operator. Also, if blood flow and lymph flow are accounted for in Darcy's law, we can obtain a slightly modified formulation, as

$$\vec{v}_{blood} - \vec{v}_{lymph} = -\nabla(K \vec{p}) \quad (8.25)$$

which is a more accurate representation of actual biological flows through porous media. The inflow and outflow conditions can be time varying, spatially varying, or some average value of the flow conditions throughout the tissue. Gravitational or other forces can be included within Eq. (8.25) if necessary. The hydraulic conductivity is related to the viscosity of the fluid that is moving through the porous media. The hydraulic conductivity can be defined as

$$K = \frac{c\epsilon^3}{\mu \left(\frac{SA}{V}\right)^2} \quad (8.26)$$

where c is a shape factor, ϵ is the porosity, μ is the viscosity, SA is the interface surface area of the pores, and V is the total volume of the porous media. The hydraulic conductivity is a measure of how readily fluid can move through porous media. The larger the hydraulic conductivity, the more readily the porous media is permeated. The flow through porous media can also be described, in a more general case, by the Brinkman equation

$$\mu \nabla^2 \vec{v} - \frac{1}{\kappa} \vec{v} - \nabla \vec{p} = 0 \quad (8.27)$$

which can account for transitional flows between the porous media. The Brinkman equation is also used when one would like to account for the flow through the porous media and the flow through particles (e.g., cells) suspended within the media. This formulation is somewhat

difficult to use because experimentally or empirically deriving the constants is not easy and depends on many biological and physical factors that can change with time. Thus, altering the conditions that describe the flow may drastically alter the constants that describe the flow.

8.6 Microcirculatory heat transfer*

Heat transfer is an important principle in biological systems (introductory heat transfer concepts were developed in Chapter 4). We will reiterate some of those concepts here, but please refer to Chapter 4 (and traditional engineering heat transfer textbooks) for a more complete discussion on these topics. As described earlier, one of the most important functions of the cardiovascular system is to maintain the temperature of the body. In particular, the cardiovascular system is arranged as a countercurrent heat exchanger, so that blood that loses heat as it passes into the extremities can gain heat back as it passes through the venous circulation back toward the heart. The role of this arrangement is to ensure that the core body temperature maintains a near constant temperature under any external conditions. A second example of heat transfer in the body is for air entering the lungs. This air must be warmed (or cooled in some extreme conditions) to body temperature. The purpose of altering the inspired air temperature to body temperature is first to ensure that the lungs, which are in the core body, maintain a near constant temperature; and second, to ensure there is minimal heat flux from the lungs to other organs within the chest cavity and the blood, with which the oxygen and carbon dioxide are exchanged. Significant heat flux to these other locations would induce changes in the core body temperature and possible changes to the physiology as we know it. Cardiovascular heat transfer occurs through all blood vessels, but we will focus on the vessels with the thinnest wall to make our analysis easier. In thicker vessels, the wall can act as an insulator and heat can be transferred along the length of the blood vessel wall or even stored within the wall of the blood vessel itself. If we assume that the wall is thin, the analysis of heat transfer is significantly easier. Heat transfer for inspired air occurs primarily within the nasal passages. We will not analyze this situation, but similar assumptions would need to be made and an extra simplifying assumption regarding the geometry of the nasal passages would be needed.

There are many different forms of energy in this universe; for this section we will focus on one of these, heat, which is the form of energy that is transferred from two systems as a result of a temperature difference between the two systems (see Chapter 4). The study of the rate of energy transfer in the form of heat as a function of temperature difference is termed *heat transfer*. As stated earlier, heat transfer is a property of the cardiovascular system, but many other engineering systems that involve temperature differences must consider heat transfer. The first two laws of thermodynamics lay the foundation for heat transfer analyses, but other principles, some of which will be developed here in the context of the cardiovascular system, are also needed. The driving force for heat transfer is a temperature difference, in the same way that pressure differences are the driving force for fluid flow. The rates of heat transfer are dictated by the temperature difference and the overall resistance to heat transfer between

*This section is considered advanced and can be skipped without a loss of continuity.

the two systems. Although this was thoroughly defined in Chapter 4, recall that there are three basic mechanisms for heat transfer to occur between two media. These will be reviewed quickly here. These mechanisms are conduction, which is the transfer of energy between adjacent nonmoving particles; convection, which is the transfer of energy between a solid surface and flowing fluid (liquid or gas); and radiation, which is the transfer of energy through electromagnetic waves (e.g., photons). Conduction can take place in solids, liquids, and gases. In solids, conduction occurs as a result of the vibrations of the molecules in the molecular structure and energy transport of free energy, whereas in liquids and gases, conduction occurs because of the collisions and random diffusion of the molecules within the material. In general, conduction depends on the materials, the thickness of the materials, the geometry of the materials, and the temperature difference between the materials. The differential governing equation for conduction is termed *Fourier's Law of Heat Conduction* and was defined in Chapter 4. Conduction is a function of the thermal conductivity of the material, which is a measure of how readily the material conducts heat. As the thermal conductivity of the material increases, the material can more readily conduct heat, and therefore thermal insulators tend to have a very low conductivity. The second mode of heat transfer, convection, is the mode of heat transfer between a solid surface and the adjacent fluid layer, which must be in motion (if the fluid layer is not in motion, conduction principles apply). The rate of convection depends on the fluid properties, the nature of the fluid motion (e.g., laminar versus turbulence), fluid velocity, geometrical features of the flow (e.g., surface roughness), the area of interaction, and the temperature difference. Although the fluid motion complicates the heat transfer properties, a convenient way to express the rate of heat transfer by convection is through Newton's Law of Cooling, which was defined in Chapter 4. Convection is a function of the convection heat transfer coefficient (h), the surface area for exchange, and the temperature difference between the surface and the free temperature. Unfortunately, the convection heat transfer coefficient is not easily tabulated because it encompasses many fluid and material considerations that we discussed earlier. The value must be experimentally obtained, is valid only within a particular range of fluid properties (e.g., velocity, motions), and thus care must be used when using heat transfer coefficients. Radiation, the final mode of heat transfer, does not require the presence of an intervening medium; it can occur through a vacuum. All solids, liquids, and gases emit, absorb, and/or transmit radiation at various rates and it is principally dependent on the surface area of the material and the temperature of the material. The various relationships to describe radiation were developed in Chapter 4. Finally, in general, more than one mode of heat transfer can occur at a time, and the heat transfer can be described by a lumped heat transfer equation and combined heat transfer parameters (note that all of this was discussed in Chapter 4).

Each of these heat-transfer mechanisms can be subdivided further into special cases of heat transfer (e.g., convection can be divided into forced convection compared with natural convection; forced convection can be divided into internal or external forced convection). The analysis methods for each of these particular cases of heat transfer will be slightly different because the modes of heat transfer are different. However, the general heat transfer properties would be similar in all of these cases.

For our discussion of heat transfer in the cardiovascular system, we will focus on internal forced convection because this is the most applicable heat-transfer modality within the vascular system. Internal forced convection is concerned with fluids that are bound on all

surfaces (e.g., flow through blood vessels, the respiratory tract, or heat exchangers; this is why it is termed *internal*—all of the flow is internal to the container) and is driven by some pressure gradient (e.g., the heart, a pump, or a turbine; this is why it is termed *forced*). For these types of situations, the velocity profile, which has been described in earlier chapters, and the temperature profile are of primary interest. From these two profiles we can obtain heat transfer rates and other properties of interest.

We will begin by developing the temperature profile for a fluid in cylindrical coordinates. The temperature within the fluid must satisfy the energy conservation laws, which state that the actual energy transported through a fluid must be equal to the energy transported through a fluid that has a uniform temperature profile throughout the fluid. This is analogous to analyzing fluids as if they are inviscid (and thus have a uniform velocity profile) but make statements about viscous fluids (as if they have a parabolic or some other velocity profile) from this simplified analysis. For this analysis we are going to make relationships between a uniform temperature profile and compare them to some other temperature profile. Mathematically, the conservation of energy equation states that

$$\dot{E}_{fluid} = \dot{m}c_p T_m = \int_{area} \rho c_p T(r) u(r) dA \quad (8.28)$$

where $\dot{m}$ is the fluid's mass flow rate, c_p is the fluid's specific heat at constant pressure (normally assumed to be a constant), T_m is the mean fluid temperature, ρ is the fluid density (also, normally assumed to be a constant), and $T(r)$ and $u(r)$ are the temperature and velocity profile in radial coordinates, respectively. In this analysis, we assume that the velocity and temperature profiles are only functions of the radial direction (this is analogous to the velocity profile assumptions that we used for the Navier–Stokes equation). Eq. (8.28) can be rearranged to calculate the mean temperature of the fluid, if needed, as follows

$$T_m = \frac{\int_0^R \rho c_p T(r) u(r) 2\pi r dr}{\rho v_{average} (\pi R^2) c_p} = \frac{2}{v_{average} R^2} \int_0^R T(r) u(r) r dr \quad (8.29)$$

Solving Eq. (8.28) for a steady 2D (Cartesian coordinates) flow of a fluid with constant fluid properties with negligible stresses, the solution to the energy balance equation is

$$\rho c_p \left(u \frac{\partial T}{\partial x} + v \frac{\partial T}{\partial y} \right) = k \left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} \right) \quad (8.30)$$

or in radial coordinates

$$u \frac{\partial T}{\partial z} = \frac{k}{\rho r c_p} \frac{\partial}{\partial r} \left(r \frac{\partial T}{\partial r} \right) \quad (8.31)$$

Eqs. (8.30) or (8.31) can be used to solve for the temperature profile within a fluid as the Navier–Stokes equations were used to determine the velocity profile of the fluid. Note

that some information about velocity is needed to solve for the temperature because this is a coupled convection problem. Thus, the components of velocity would need to be known before initiating the analysis of the temperature distribution (e.g., one may need to solve the Navier–Stokes equations in parallel to and before attempting a solution for the temperature profile).

Using this same type of energy balance analysis, we can obtain general heat transfer equations for blood vessels that are assumed to have either a constant surface temperature or a constant surface heat flux. In most biological applications, neither the surface temperature nor the surface heat flux will be constant, but we may be able to use these simplifications to approximate certain conditions and obtain meaningful results. Constant surface temperature (or the approximation of a constant surface temperature) would suggest that the entire surface of the blood vessel is held at a fixed temperature along the entire length of the blood vessel. When the vessel length within the particular heat transfer problem is relatively short, this may be a valid approximation; however, as the vessel length increases, the probability of obtaining a constant surface temperature along the entire vessel length decreases. Constant surface heat flux (or the approximation of a constant surface heat flux) would suggest that the heat flux into the blood vessel from the blood vessel wall is constant along the entire vessel length. Similarly, as the vessel length increases, the likelihood for that vessel wall to subject the blood to a constant heat flux diminishes. However, in this case, because the heat flux may change along a single cell depending on that cell's metabolic activity, one may need to take care when using this assumption. In the absence of any work by the fluid, the conservation of energy can be solved to obtain the heat transfer rate, $\dot{Q}$, to or from the fluid. This is represented as

$$\dot{Q} = \dot{m}c_p(T_o - T_i) \quad (8.32)$$

where T_o is the mean outlet temperature and T_i is the mean inlet temperature. You may recall from a previous course in heat transfer that the surface heat flux ($\dot{q}_s$) can be defined as

$$\dot{q}_s = h_x(T_s - T_m) \quad (8.33)$$

where h_x is the local convection heat transfer coefficient, T_s is the surface temperature, and T_m is the mean fluid temperature. Using Eqs. (8.32) and (8.33), we can now analyze our idealized conditions for constant surface heat flux or constant surface temperature. In the case in which we can assume that $\dot{q}_s$ is a constant, the rate of heat transfer also can be expressed as

$$\dot{Q} = \dot{q}_s A_s = \dot{m}c_p(T_o - T_i) \quad (8.34)$$

where A_s is the area available for heat transfer and is equal to πDL for perfectly circular blood vessels (or those assumed to be perfectly circular in cross-section) with a length of L . The mean fluid outflow temperature and the mean surface temperature become

$$T_o = T_i + \frac{\dot{q}_s A_s}{\dot{m}c_p} \quad (8.35)$$

$$T_s = T_m + \frac{\dot{q}_s}{h} \quad (8.36)$$

which both vary linearly with the surface heat flux. By recognizing that $\dot{q}_s$ and h are constants with respect to the z -direction (radial coordinates, along the blood vessel length), we can then obtain

$$T_m = T_i + \frac{2\pi R \dot{q}_s}{\dot{m} c_p} z \quad (8.37)$$

by differentiating and equating the equations that describe the linear variation of the mean outlet temperature and the surface temperature. In Eq. (8.37), R is the blood vessel radius and z is the axial distance along the vessel. Note that for a circular tube,

$$\dot{m} = \rho v_{average} A_c = \rho v_{average} (\pi R^2)$$

Eqs. (8.34) through (8.37) can be used to solve for various heat transfer properties under the constant surface heat flux assumption.

If the conditions are such that we can make the assumption of a constant surface temperature, instead of a constant surface heat flux, the heat transfer and temperature conditions will be modified from those described in the preceding section to represent the new surface properties. Here, the rate of heat transfer can be expressed as

$$\dot{Q} = h A_s \Delta T_{average} \quad (8.38)$$

The average temperature difference can be calculated by

$$\Delta T_{average} \approx T_s - \frac{T_i + T_o}{2}$$

where the second term on the right side is the bulk mean fluid temperature, and this is the temperature at which all fluid properties are analyzed for heat transfer problems (e.g., density, viscosity). We can further relate the heat transfer rates to the fluid temperatures by

$$\ln \left[\frac{T_s - T_o}{T_s - T_i} \right] = - \frac{h A_s}{\dot{m} c_p} \quad (8.39)$$

or

$$T_o = T_s - (T_s - T_i) e^{-\frac{h A_s}{\dot{m} c_p}}$$

where A_s is the surface area of the tube and can be represented as $A_s = 2\pi RL$. Using the log mean temperature difference approach, which tends to be a bit easier, mathematically, under these conditions, the heat transfer rate can also be calculated from

$$\dot{Q} = hA_s\Delta T_{lm} \quad (8.41)$$

where ΔT_{lm} is the log mean temperature difference, and is defined as

$$\Delta T_{lm} = \frac{T_i - T_o}{\ln \left[\frac{T_s - T_o}{T_s - T_i} \right]} \quad (8.42)$$

Example 8.3

Determine the outflow temperature and the surface inlet and outlet temperatures, assuming that there is fully developed blood flow through a 300 μm -long capillary (Fig. 8.6). The capillary can be considered to provide the blood with a constant surface heat flux of -1000 W/m^2 . The diameter of the capillary is $15 \mu\text{m}$, and its convection heat transfer coefficient is $2500 \text{ W/m}^2\text{K}$. Blood is flowing with a mass flow rate of 50 g/s at an inlet temperature of 25°C .

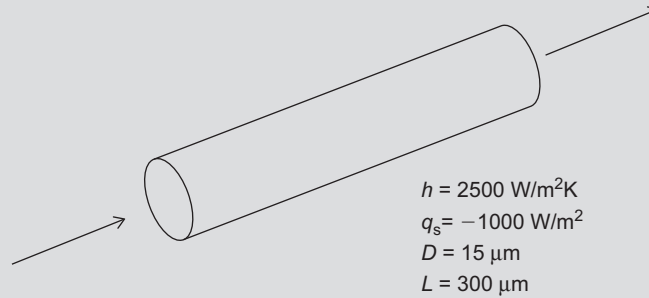


FIG. 8.6 Heat transfer through a capillary.

Solution

The specific heat at constant pressure for blood is 3.8 kJ/kgK .

First, determine the blood vessel heat transfer rate to obtain the outlet temperature:

$$\begin{aligned} \dot{Q} &= \dot{q}_s A_s = \dot{q}_s \pi D L = -1000 \frac{\text{W}}{\text{m}^2} (\pi)(15 \mu\text{m})(300 \mu\text{m}) = -1.414 \times 10^{-5} \text{ W} \\ T_o &= T_i + \frac{\dot{Q}}{mc_p} = 25^\circ\text{C} + \frac{-1.414 \times 10^{-5} \text{ W}}{50 \text{ g/s}(3.8 \text{ kJ/kgK})} \approx 24.99992^\circ\text{C} \end{aligned}$$

Example 8.3 (cont'd)

The surface inlet and outlet temperatures can be found by

$$T_{s,i} = T_i + \frac{\dot{q}_s}{h} = 25^\circ\text{C} + \frac{-1000\text{W}/\text{m}^2}{2500\text{W}/\text{m}^2\text{K}} = 24.6^\circ\text{C}$$

$$T_{s,o} = T_o + \frac{\dot{q}_s}{h} = 24.99992^\circ\text{C} + \frac{-1000\text{W}/\text{m}^2}{2500\text{W}/\text{m}^2\text{K}} = 24.59992^\circ\text{C}$$

Example 8.3 illustrates that for a relatively short blood vessel length, we do not observe a significant change in the temperature along the blood vessel length.

Example 8.4

Determine the outflow temperature, the log mean temperature difference, and the heat transfer rate, assuming that there is fully developed blood flow through a 300 μm -long capillary (Fig. 8.7). The capillary can be considered to provide the blood with a constant surface temperature of 24°C. The diameter of the capillary is 15 μm , and its convection heat transfer coefficient is 2250 W/m²K. Blood is flowing with a mass flow rate of 50 g/s at an inlet temperature of 25°C.

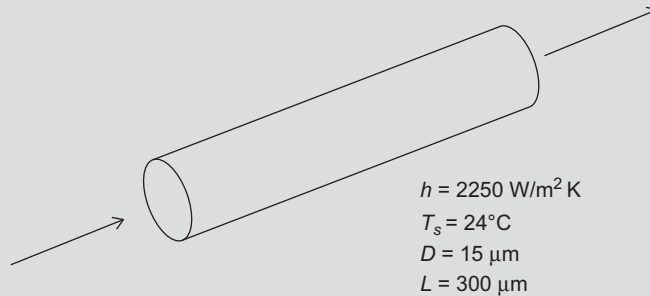


FIG. 8.7 Heat transfer through a capillary.

Solution

To calculate the outflow temperature, we use

$$T_o = T_s - (T_s - T_i)e^{-\frac{pLh}{\dot{m}c_p}} = 24^\circ\text{C} - (24^\circ\text{C} - 25^\circ\text{C})e^{-\frac{\pi(15 \mu\text{m})(300 \mu\text{m})(2250\text{W}/\text{m}^2\text{K})}{50\text{g/s}(3.8\text{kJ}/\text{kgK})}} = 24.99998^\circ\text{C}$$

Example 8.4 (*cont'd*)

The log mean temperature difference is

$$\Delta T_{lm} = \frac{T_i - T_o}{\ln\left(\frac{T_s - T_o}{T_s - T_i}\right)} = \frac{(25 - 24.99998)^\circ\text{C}}{\ln\left(\frac{24 - 24.99998}{24 - 25}\right)} = -0.9999^\circ\text{C}$$

The heat transfer rate will be

$$\dot{Q} = hA_s\Delta T_{lm} = 2250 \frac{\text{W}}{\text{m}^2\text{K}} (\pi)(15 \mu\text{m})(300 \mu\text{m})(-0.9999^\circ\text{C}) = -0.000032\text{W}$$

Extending this work, we can include the countercurrent heat transfer properties of blood vessels within our analysis. Under normal physiological conditions, arteries are always paired with veins, so that any heat that is lost from an artery can potentially be gained back by a vein along the path back to the core body (Fig. 8.8). In fact, all warm-blooded animals have this type of arrangement for their cardiovascular system. To begin to analyze this scenario, we assume that blood that is transiting from the core body to the capillaries has a constant rate of heat transfer from the paired artery to the paired vein. Additionally, there is some quantifiable value for the rate of heat transfer from the artery to the environment and a separate rate of heat transfer from the vein to the environment. To begin this analysis, we will use all of the same governing equations discussed earlier in this section but extend them to the scenario represented by Fig. 8.8. Furthermore, there is energy in the form of heat carried by the blood. This can be quantified using

$$\dot{Q}_{blood} = \dot{m} \frac{dh}{dx} = \dot{m} c_p \frac{dT}{dx} \quad (8.43)$$

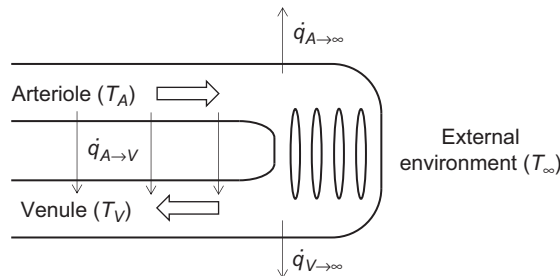


FIG. 8.8 Representation of an arteriole–venule pair as a countercurrent heat exchanger. There are at least three heat transfer events that occur within each arteriole–venule pair: heat transfer from the artery to the external environment, heat transfer from the vein to the external environment, and heat transfer from the artery to vein. Mathematically, this can be represented using convection methods, as outlined in the text.

where $\dot{m}$ is the blood mass flow rate and h is the enthalpy of blood. As shown in Fig. 8.8, there are also three heat transfer events that occur (heat transfer from artery to vein, heat transfer from artery to environment, and heat transfer from vein to environment). As with most heat exchangers, we begin the analysis of these heat transfer events using a total heat transfer equation, which attempts to summate all of the parameters/properties of the heat transfer events. The total heat transfer for this heat exchanger can be described by

$$\dot{Q} = UA_S \Delta T_{average} \quad (8.44)$$

where U is the overall heat transfer coefficient, A_s is the surface area, and $\Delta T_{average}$ is an appropriate mean temperature difference between the arterial side and the venous side of the blood vessel. Therefore, the total heat transfer for the cardiovascular countercurrent system can be represented by combining Eqs. (8.43) and (8.44) as follows.

$$\dot{Q}_{blood} + \dot{Q} = \dot{m}c_p \frac{dT}{dx} + UA_S \Delta T_m \quad (8.45)$$

The previous equation would need to be written for the arterial side and the venous side of the heat exchanger, and then these two equations will need to be solved simultaneously. An example of the system that can be written for this heat exchanger scenario is

$$\begin{aligned} \dot{m}c_p \frac{dT_A}{dx} + (UA_S)_{AV}(T_A - T_V) + (UA_S)_A(T_A - T_\infty) &= 0 \rightarrow \text{Arterial side} \\ \dot{m}c_p \frac{dT_V}{dx} + (UA_S)_{AV}(T_A - T_V) - (UA_S)_V(T_V - T_\infty) &= 0 \rightarrow \text{Venous side} \end{aligned} \quad (8.46)$$

where the subscript A designates arterial side parameters, the subscript V denotes venous side parameters, and the subscript ∞ denotes the environmental parameter(s). We assume that the mass flow rate and the specific heat do not change between the arterial circulation and the venous circulation in deriving Eq. (8.46). As we have learned, the mass flow rate is likely different between the arterial side and the venous side of the circulation, so these formulations may not be the most accurate. This equation can be solved in a number of ways to obtain a value for the heat transfer within a cardiovascular countercurrent exchanger, using the assumptions that were stated earlier.

It is important to note that under many conditions the convective heat transfer coefficient cannot be empirically measured because of many of the variables that influence heat transfer. However, under many of the conditions that we have discussed, the heat transfer coefficient can be calculated (or approximated) from the Nusselt number. The Nusselt number is a dimensionless number that relates the influence of the convective heat transfer to the conductive heat transfer. The Nusselt number can be defined as

$$Nu = \frac{hd}{k} = \frac{\text{Convective heat transfer}}{\text{Conductive heat transfer}} \quad (8.47)$$

where h is the convective heat transfer coefficient, d is a characteristic length, and k is the thermal conductivity. Unfortunately, a true thermal conductivity can be calculated only under stagnant flow, which is not the case during a convection problem. Therefore, during the convection scenario, the thermal conductivity is quantified assuming stagnant flow. Regardless of the difficulties in calculating the thermal conductivity, values for k can be tabulated. Luckily, for laminar flow in a circular tube, the Nusselt number is constant if we can apply the constant surface heat flux assumption or the constant surface temperature assumption. Using these assumptions, and the calculated value for the Nusselt number, one can obtain a value for the convective heat transfer coefficient. The appropriate Nusselt numbers under constant surface heat flux or constant surface temperature are

$$\begin{aligned} Nu &= \frac{hd}{k} = 4.36 \quad \dot{q}_s = \text{Constant} \\ Nu &= \frac{hd}{k} = 3.66 \quad T_s = \text{Constant} \end{aligned} \quad (8.48)$$

Although we will not go through the entire derivation to obtain Eq. (8.48), it begins by obtaining the temperature profile under either constant surface heat flux or constant surface temperature conditions. For the constant surface heat flux conditions, the temperature profile can be found to be equal to

$$T = T_s - \frac{\dot{q}_s R}{k} \left(\frac{3}{4} - \frac{r^2}{R^2} + \frac{r^4}{4R^4} \right) \quad (8.49)$$

if we assume a radial coordinate system and the following boundary conditions

$$\begin{aligned} \frac{\partial T}{\partial r} &= 0 \quad r = 0 \\ T &= T_s \quad r = R \end{aligned}$$

The mean temperature under these conditions can be found to be

$$T_m = T_s - \frac{11}{24} \frac{\dot{q}_s R}{k} \quad (8.50)$$

If the previous equation is combined with Eq. (8.33), one can obtain the Nusselt number formulation as

$$h = \frac{24}{11} \frac{k}{R} = \frac{48}{11} \frac{k}{D} = 4.36 \frac{k}{D}$$

A similar procedure can be completed for the constant surface temperature scenario, but we will not complete the derivation here and suggest the reader refer to a more complete heat transfer textbook.

A large area of cardiovascular heat transfer research has been conducted under the assumption that conduction is the primary mode of heat transfer in the body. Within this assumption, one must consider that heat can be transferred (gained or lost) by metabolism and convection, but that they can be represented in simple heat source (or sink) terms. In a 1D problem, this is represented with the bioheat transfer equation that was described in Chapter 4. A significant amount of work, initially by Pennes et al., has been conducted to find an accurate representation for these values. To apply this formulation, most studies assume that all of the properties that are associated with blood and the metabolic heat generation term are all constant with respect to the local tissue temperature. In practice, the simplifications that were made to analyze this system are not accurate under a wide range of conditions. For instance, it is difficult and impractical to quantify the thermal properties of biological tissues. It is also likely that there will be some variance in the thermal properties and fluid properties that were assumed to be constant in this formulation. Additionally, the human body can adjust to the thermal environment in many ways that cannot be quantified in this conduction heat transfer formulation. For instance, sweating and shivering, which are two methods by which humans can compensate for significantly altered heat transfer situations, cannot be included in this type of formulation in a very easy or accurate manner. Therefore, although heat transfer and the maintenance of the core body temperature are significant functions for the cardiovascular system, in practice it is quite difficult to represent these salient features with the classic heat transfer equations. One must make many assumptions about the heat transfer parameters and the conditions to apply the formulations that were discussed here.

8.7 Cell transfer during inflammation and white blood cell rolling and sticking*

One of the most important properties of the endothelium is to allow white blood cells to pass through the endothelial cell wall during inflammatory conditions. From our previous discussion we have stated that white blood cells, although there are many different types of these cells, are all involved in the removal and/or elimination of foreign particles. This task could not be accomplished if the white blood cells are segregated within the circulatory system because foreign particles can propagate anywhere within the body. Additionally, we discussed that the endothelial cell wall has an extremely low permeability toward large matter, including cells; thus, a special mechanism must be present to account for cellular motion.

To aid in this special mechanism, one of the earliest responses to an infection is the expression of adhesion molecules on the capillary endothelial cell surface (e.g., E-selectin and various integrins). White blood cells can bind to these receptors to make an initial contact with the endothelial cells. White blood cells tend to roll along the capillary, making and breaking adhesions along the way. At some point, the adhesion between the white blood cell and the endothelial cell wall becomes more stable and the cell does not roll along the blood vessel anymore and, thus, stays in one location. Once this stable adhesion occurs, it

*This section is considered advanced and can be skipped without a loss of continuity.

is possible for the white blood cell to cross the endothelial cell barrier, in a process termed *transmigration* or *extravasation*. Once this process occurs, the white blood cells migrate toward the site of infection along a chemotactic gradient. Again, the initial attachment of white blood cells to the endothelial cell wall is typically mediated through various selectin molecules. These adhesions are characterized by rapid association and dissociation constants. After selectin binding, there is a reorganization of the white blood cell membrane-bound integrins, which facilitates a more stable adhesion (the kinetic constants are slower). As more selectins make contact with the endothelial cells, the reorganization of integrins occurs much more rapidly.

Typically, the white blood cell selectin density changes depending on factors such as shear stress, and presence of cytokines. At a selectin density of less than 15 molecules/cm², white blood cell adhesion is unstable, even at low fluid velocities. At higher selectin densities, white blood cell adhesion is more stable but transient, and it is likely that integrins will be redistributed and activated to mediate more stable adhesion. The force required to break one selectin bond is on the order of 20 pN, and the bond typically acts over a distance of approximately 0.5 Å. As the adhesion becomes stronger, from either more selectin bonds or more integrin bonds, the white blood cell becomes stationary even though the largest fluid shear forces are acting on the bound white blood cell (because the white blood cells would be located along the blood vessel wall). The strength of a single integrin adhesion has been reported to be in the range of 50 pN. This process of tight adhesion normally occurs within the venous side of capillaries or within postcapillary venules, where the fluid flow rates, pressure differences, and shearing forces are typically lower than the arterial side. At the point of stable adhesion, the cytoskeleton of the white blood cell is reorganized so that the cell flattens out over the endothelial cell wall. This reduces the face-on exposure area to the fluid velocity (thus minimizing the face-on pressure). Pseudopods from the leukocyte locate the intercellular cleft between neighboring endothelial cells. Pseudopods typically express many adhesion molecules. The white blood cell passes through the cleft primarily by the action of the platelet endothelial cell adhesion molecule (PECAM), which acts to pull the cell through the gap. The strength of a PECAM bond can be as large as 1 to 10 nN. The leukocytes then migrate through the basement membrane along a chemotactic gradient to reach the site of inflammation. It is important to note that the white blood cell may release vasoactive compounds to increase the diameter of the intercellular cleft. Also, invading pathogens or other inflammatory cells can release cytokines that increase the spacing of the intercellular cleft.

Many groups have tried to model the adhesion of white blood cells to endothelial cells using the empirical data discussed previously. Binding association, dissociation constants, and the forces acting on the cell are relatively easy to model. However, the selectin density, the location of selectins on the cell, and actual binding of the white blood cell to the endothelial cell wall are more problematic and complex to model. Selectin density can be assumed to have some initial value, but this can change drastically based on the conditions described previously (shear stress and cytokines, among others). This level of involvement within the model can greatly increase the number of simultaneous equations to solve. In addition, probability functions are likely needed to model the association and dissociation of bonds along with the likelihood for contact. Probability functions are never perfectly accurate and typically depend on the selectin density and the distance between the white blood cell and the

endothelial cell. As the reader can imagine, as the selectin density increases and the distance decreases, there should be a higher likelihood for selectin adhesion to occur within the model. However, the exact probabilities are not known and assumptions have to be made to model this phenomenon. Therefore, the accuracy of these assumptions limits the predictive capability of the model.

It is typical in models of this kind to initiate the adhesion through one receptor–ligand binding event. This event is governed by the receptor density and/or distance between cells, as discussed previously. All remaining association and dissociation events are then described by receptor kinetics and the density of the receptors/ligands present and how this may change from the current state. This principal can be used to define the receptor association/dissociation because it is typically assumed that if one bond can be formed, the other receptors are close enough to bind to other expressed ligands. In addition, it is typical to make the time steps in the model small enough that the quantity of receptors–ligand events can only increase by 1, decrease by 1, or remain the same during each subsequent time step (this significantly simplifies the modeling and can only work with small time steps). In equation form, the quantity of bonds in a time step would be the summation of the amount of bonds in the previous time step, plus the association of a new bond (which depends on kinetics) and the dissociation of any one bond (again based on kinetics). This type of modeling will be discussed in more detail in Chapter 15.

Summary

- 8.1.** To model red blood cell oxygenation within the pulmonary capillaries, there are five main diffusion events that we should consider. The first, alveolar diffusion, is governed by Fick's laws of diffusion

$$\vec{J} = -D\nabla\vec{C}$$

and

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}$$

Solving this differential equation, we can obtain a measure for the time needed to reach equilibrium. Using this formulation, we can show that alveolar diffusion occurs rapidly and does not limit the red blood cell oxygenation. The second diffusion event is the movement of the gas across the respiratory boundary. This would be modeled with a partition coefficient for each of the boundaries that are included within the model (i.e., alveolus epithelial cells and capillary endothelial cells), as

$$P = \frac{p_c D}{x}$$

The third diffusion event is the convection and diffusion of oxygen to the red blood cell within the pulmonary capillaries. The dimensionless Sherwood number can be used to model this convection–diffusion event, as

$$\text{Sh} = \frac{Kx}{D}$$

and

$$\text{Sh} = \text{Sh}_{0.25} + 0.84(\text{Hct} - 0.25)$$

The fourth diffusion event is the diffusion of oxygen across the red blood cell membrane, which occurs approximately 100 times faster than the diffusion across the respiratory boundary. This event is also not a rate-limiting step in diffusion. The last diffusion event is the diffusion of oxygen to hemoglobin and the kinetic association of oxygen to hemoglobin. This is modeled with a Thiele modulus, which is defined as

$$\phi = \sqrt{\frac{kx^2}{D}}$$

A model of tissue oxygenation also should be formulated, and perhaps the most famous model is the Krogh model. Assuming that oxygen diffusion through tissue is homogeneous in all directions and that the capillaries are regularly spaced in three dimensions, the Krogh radius quantifies the area of tissue oxygenation per capillary. The relationship of the capillary radius to the Krogh radius is represented as

$$\frac{C(r)}{C_p} = 1 + \frac{r_k^2 R}{4C_p D} \left[\frac{r^2 - r_c^2}{r_k^2} + 2\ln\left(\frac{r_c}{r}\right) \right]$$

- 8.2. Glucose transport is also a salient transport mechanism to discuss within the microcirculation. Under most normal conditions, glucose cannot freely diffuse through the capillary wall. Its movement is coupled to the movement of a second ion (e.g., sodium), and the energy gained by moving this second ion down its electrochemical gradient is used to move glucose up its concentration gradient. Cotransporters are typically used in these processes.
- 8.3. Lipid-soluble molecules can freely permeate the endothelial cells that line the capillaries. Non-lipid-soluble molecules cannot diffuse freely through the endothelial cells, but typically they move through the intercellular cleft. It has been experimentally determined that physiologically important molecules generally have a permeability through the intercellular cleft that is in the range of water's permeability through the intercellular cleft. For instance, sodium chloride has a permeability that is approximately 96% of water's permeability. Large plasma proteins, such as albumin, have a permeability that is significantly lower than the permeability of water.

8.4. The critical adhesive forces that play a role in biological applications are the molecular forces, the electrostatic forces, and the capillary forces. Molecular forces are the weakest, act over the smallest range, and are sometimes transient. The mechanical force associated with these types of adhesive forces can be quantified with

$$\vec{\psi}(d) = \vec{\psi}_0 \left[\left(\frac{d'}{d} \right)^{12} - \left(\frac{d'}{d} \right)^6 \right]$$

Electrostatic forces may arise in biological situations if there is a net charge on one of the molecules. These forces can be calculated from Coulomb's law

$$F = \frac{1}{4\pi\epsilon_0} \frac{q_1 q_2}{r^2}$$

A charged surface would have some potential associated with it, which is termed the *Nernst potential*. Because of this net charge, the ions in solution or water can organize near the charged surface. This highly organized layer is termed the *Stern layer*, and the potential at which the layer ends is termed the *Stern potential*. The electric double layer describes the remaining distance that has some organization because of the presence of the charged surface. The Debye length quantifies the electric double layer

$$\lambda_D = \sqrt{\frac{\epsilon_l \epsilon_o k_B T}{e^2 \sum_i^n (c_i \chi_i)}}$$

Capillary forces are composed of adhesion, cohesion, and surface tension. Adhesion occurs when two different molecules tend to stick to each other because of an attractive force. Cohesion is the likelihood for two of the same molecules to stick together. Surface tension is a fluid property that arises as a result of the intermolecular forces within the fluid that occur at the boundary of a fluid and another substance.

8.5. Porous media are solid materials that are composed of pore structures, which are typically fluid filled in biological applications. Porous media can be described by the physical parameter porosity, which is defined as

$$\epsilon = \frac{\text{Volume associated with voids}}{\text{Total volume}}$$

The porosity of the interstitial space, neglecting blood vessels and cells, approaches 0.9, whereas the porosity of general biological tissues (including blood vessels and cells) would be closer to 0.25. Porous media also can be classified based on the channel's tortuosity, which

is a measure of the random orientation and random spacing of pores. Tortuosity is typically defined as

$$T = \frac{L_{actual}}{L}$$

Fluid flow through porous media is most typically quantified via Darcy's law, which is

$$\vec{v} = -K \nabla \vec{p}$$

which also can be related to the viscous forces present within the media or fluid by

$$\mu \nabla^2 \vec{v} - \frac{1}{\kappa} \vec{v} - \nabla \vec{p} = 0$$

8.6. Heat transfer is an integral component to many biological systems. Three basic mechanisms for heat transfer include conduction, convection, and radiation. Most heat transfer formulations begin with the conservation of energy principle, which states that

$$\dot{E}_{fluid} = \dot{m} c_p T_m = \int_{area} \rho c_p(r) u(r) dA$$

From this equation, the temperature difference within a fully developed, two-dimensional flow scenario can be solved from

$$\rho c_p \left(u \frac{\partial T}{\partial x} + v \frac{\partial T}{\partial y} \right) = k \left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} \right)$$

or

$$u \frac{\partial T}{\partial z} = \frac{k}{\rho r c_p} \frac{\partial}{\partial r} \left(r \frac{\partial T}{\partial r} \right)$$

if the viscous forces are negligible. This leads to two specialized problems, one in which there is a constant surface heat flux and a second in which there is a constant surface temperature. In the case in which we can assume that $\dot{q}_s$ is a constant, the rate of heat of transfer can be expressed as

$$\dot{Q} = \dot{q}_s A_s = \dot{m} c_p (T_o - T_i)$$

and the mean fluid outflow temperature and the mean surface temperature become

$$T_o = T_i + \frac{\dot{q}_s A_s}{\dot{m} c_p}$$

If the conditions are such that we can make the assumption of a constant surface temperature, the heat transfer and temperature conditions will be modified as

$$\dot{Q} = h A_s \Delta T_{average}$$

$$T_o = T_s - (T_s - T_i) e^{-\frac{h A_s}{\dot{m} c_p}}$$

Using the log mean temperature difference, the heat transfer rate also can be calculated from

$$\dot{Q} = h A_s \Delta T_{lm}$$

$$\Delta T_{lm} = \frac{T_i - T_o}{\ln \left[\frac{T_s - T_o}{T_s - T_i} \right]}$$

In fact, all arteriole and venule pairs are organized as a countercurrent heat exchanger, so that blood that experiences a temperature reduction as a result of heat transfer to the environment does not reduce the temperature of the core body. The total heat transfer within a countercurrent mechanism can be estimated by

$$\dot{Q}_{blood} + \dot{Q} = \dot{m} c_p \frac{dT}{dx} + U A_s \Delta T_m$$

The Nusselt number is a dimensionless number that is used to relate the heat transfer that occurs via convection to the heat transfer that occurs via conduction.

8.7. White blood cells express many adhesion molecules that allow them to adhere to and roll along the endothelium. Once a more stable adhesion occurs, the white blood cells can stay in one location and transmigrate into the extravascular space. Most of these adhesions are modulated through the actions of selectins that have an average bond strength of 20 pN or integrins that have an average bond strength of 50 pN. Most of these adhesion properties occur during inflammatory reactions, although white blood cells always express a low quantity of adhesion molecules.

Homework problems

- 8.1. Discuss the steps necessary for red blood cells to become oxygenated. What are the rate-limiting steps of this process?
- 8.2. Make a mathematical prediction of the changes in oxygen diffusion with either an increased hematocrit or a decreased hematocrit.
- 8.3. Determine the permeability coefficient (barrier plus plasma) for oxygen assuming that the thickness of the barrier increases to $5\text{ }\mu\text{m}$ and the diffusion coefficient decreases to $0.8D - 5\text{ cm}^2/\text{s}$ (e.g., the patient has edema). Assume that the hematocrit is 38% and that there are no changes in the rate of diffusion characteristics for plasma.
- 8.4. What is the Biot number and effectiveness factor for Homework Problem 8.3 (assuming that no changes occur in the kinetics of oxygen saturation)? What does this suggest?
- 8.5. What is the maximum capillary spacing (using the Krogh model) for a capillary with a radius of $4.5\text{ }\mu\text{m}$ and a plasma oxygen concentration of $5 \times 10^{-8}\text{ mol/cm}^3$? The oxygen reaction rate is $4 \times 10^{-8}\text{ mol/cm}^3 \cdot \text{s}$. Assume that at maximum spacing the oxygen concentration at the Krogh radius will be $3 \times 10^{-8}\text{ mol/cm}^3$.
- 8.6. In the previous homework example, we used a standard Krogh model to determine the oxygen concentration as a function of distance from the capillary. Extend this model and consider a scenario in which there is a differential oxygen usage (as measured by a different oxygen reaction rate) in the extravascular space. Assume that the oxygen reaction rate is $4 \times 10^{-8}\text{ mol/cm}^3 \cdot \text{s}$ for $4.5\text{ }\mu\text{m} < r < 12\text{ }\mu\text{m}$. For r greater than $12\text{ }\mu\text{m}$, the oxygen reaction rate decreases to $1.5 \times 10^{-8}\text{ mol/cm}^3 \cdot \text{s}$. Calculate the maximal spacing under these conditions.
- 8.7. Under tumorigenic conditions, oxygen use increases significantly. Assume a two-cylinder Krogh model (as in Homework Problem 8.6) with an oxygen reaction rate of $2 \times 10^{-7}\text{ mol/cm}^3 \cdot \text{s}$ for a radius between 4.5 and $10\text{ }\mu\text{m}$. For radii greater than $10\text{ }\mu\text{m}$, the oxygen reaction rate is $4 \times 10^{-8}\text{ mol/cm}^3 \cdot \text{s}$. What is the maximal capillary spacing under these conditions? Do new blood vessels need to grow to meet this need?
- 8.8. (Modeling) Make a model for glucose transport considering the discussion of permeability and transporters needed to move glucose across the vascular wall. Test this model with empirical data.
- 8.9. A charged element is moving through a protein channel in the microvasculature. The charged element has an excess charge of 50 pC and the protein has an excess charge of 200 pC . If the channel has a mean radius of 100 nm , what is the force associated with these excess charges? Consider that the charged element has a diameter of 5 nm and is centered within the channel, is a half radius from the wall and a quarter radius from the wall.
- 8.10. Knowing that there are channels that restrict the movement of ions based on charge and size, propose a formulation that can represent this phenomenon.
- 8.11. Calculate the Debye length for a 120 mM sodium ion ($\sum c_i \chi_i = 5\text{ }\mu\text{m}^{-3}$) that is being transported through the interstitial space (where ϵ_l is 60; this is a relative number with no units) at body temperature.
- 8.12. Calculate the surface tension and the force associated with the surface tension for a red blood cell moving through blood. Assume that the radius of curvature for the red blood cell is $4\text{ }\mu\text{m}$ and the radius of curvature for the blood can be approximated at a value of 1 cm . The pressure difference across the cell and blood is 25 mmHg . Assume that a red blood cell is a perfect sphere when estimating contact area.

Homework problems (cont'd)

- 8.13.** Determine the velocity of interstitial fluid through the extracellular matrix where the pressure gradient in the fluid direction is equal to -0.10 mmHg/cm. Assume that the porosity of the media is 60%, the surface area to volume ratio is 8/cm and the shape factor is 2.
- 8.14.** Solve for the velocity profile of a unidirectional pressure-driven flow, through a small porous channel, in which the hydraulic conductivity can be represented as $K = \frac{k}{\mu}$, where k is a measure of the permeability of the media. Assume that k , μ , and the pressure gradient are constant.
- 8.15.** Blood is flowing through the aorta at a temperature of 37°C . The aortic wall can be considered isothermal with a temperature of 30°C (on a cool day). The aorta has a diameter of 24 mm. If blood enters the aorta at 75 cm/s and leaves the 0.5 m section of the aorta at 33°C , determine the average heat transfer coefficient between the blood and the aorta. Assume that the specific heat for blood is 3.8 kJ/kg $^\circ\text{C}$ and that the density of blood is 1050 kg/m³.
- 8.16.** The trachea is 0.20 m long and 12 mm in diameter and is used to heat air that enters at 25°C ($v = 0.4$ m/s). A uniform heat flux is maintained by the body so that the air enters the lungs at a temperature of 35°C . Assume that the average properties of air to be $\rho = 1000$ kg/m³, and $c_p = 4000$ J/kgK, and determine the required surface heat flux.
- 8.17.** Consider that the velocity and temperature profiles for blood flow in a vessel with a diameter of 100 μm can be expressed as

$$u(r) = 0.35 \left[1 - \left(\frac{r}{R} \right)^2 \right]$$

$$T(r) = 2.1 \left[150 + 35 \left(\frac{r}{R} \right)^2 - 65 \left(\frac{r}{R} \right)^3 \right]$$

with units in micrometers per second and K , respectively. Determine the average velocity and the mean temperature from the given profiles.

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The lymphatic system

LEARNING OUTCOMES

- Identify the components of the lymphatic system
- Compare the structure of lymphatic vessels to that of blood vessels
- Describe the movement of water from the blood capillaries to the lymphatic capillaries
- Discuss the function of lymph-collecting vessels
- Identify salient lymphatic organs
- Explain the function of lymphatic organs
- Identify the major regulators that act during lymph formation
- Compare the composition of lymph to the composition of extracellular fluid and blood
- Model lymph flow rate and the direction of flow through the lymphatic system
- Describe the lymphatic pump and compare this pump to the venous pump
- Discuss the lymph node structure
- Identify the direction of lymph flow through the lymph node
- Explain cancer metastasis and why the lymphatic system is important during cancer
- Analyze edema and the role of the lymphatic system during edema

9.1 Lymphatic physiology

The lymphatic system consists of lymphatic vessels, lymphoid tissues and organs, lymph, and a small quantity of lymphocytes. We will discuss the first three components of the lymphatic system in this chapter. The remaining component, lymphocytes, was discussed briefly in [Section 6.3](#) with the other types of white blood cells that circulate in the blood and will be only reviewed here. The function of the lymphatic vessels is to carry lymph (and excess fluid) away from tissue spaces and back to the venous side of the cardiovascular system or to the right side of the heart. Unlike the cardiovascular network, the first vessels in

the lymphatic network are the lymphatic capillaries. Lymphatic capillaries are present in most tissues of the body and are absent only from tissues that do not have a direct blood supply. They tend to permeate microvascular beds to aid in the absorption of interstitial fluid that has not entered cells or returned to the cardiovascular system along the venous side of the capillary (Fig. 9.1). If lymphatic capillaries did not collect this excess fluid, the interstitial space would swell because of continual diffusion of water out of the blood capillaries (recall that overall there was a net water loss from the capillaries into the interstitial space as a result of the favorable pressure difference for movement out of the vasculature). In the hypothetical in which the lymphatic system did not exist (or something similar to the lymphatic system), the hydrostatic pressures (capillary and interstitial) and osmotic pressures (capillary and interstitial) would eventually reach equilibrium across the capillary wall. This means that there would be no net movement of nutrients or water between the blood and the interstitial space, and thus this would severely restrict overall nutrient delivery and waste removal and would force a change in the physiology because a new mechanism would be required to transport these nutrients and wastes. Similar to the blood vessels of the cardiovascular network, lymphatic vessels are lined by endothelial cells. However, the endothelial cells in lymphatic capillaries are not bound as tightly as those in blood capillaries. Instead, the lymphatic endothelial cells tend to overlap one another, forming channels that allow for the unidirectional flow of fluids, large molecules (such as proteins), and cells from the

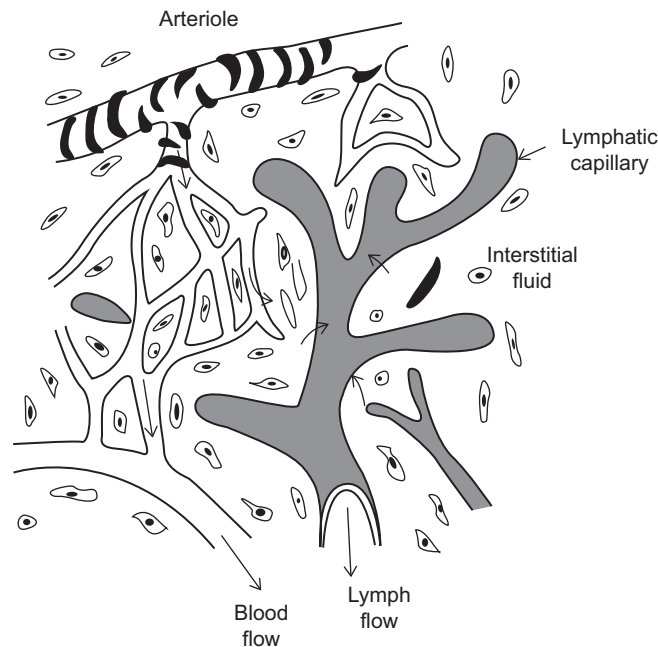


FIG. 9.1 The association of a lymphatic capillary and a capillary network. *Arrows indicate the movement of fluid from the blood vessel into the interstitial space and then into the lymphatic system. The lymphatic system is an open-ended system that initiates at the lymphatic capillaries and progresses to larger lymphatic vessels.* (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, 2018, Pearson, New York.)

interstitial space into the lymphatic capillaries. Lymphatic capillaries are generally larger than blood capillaries, with a typical diameter in the range of 20 to 30 μm . In addition, lymphatic vessels are not circular in cross section, because they experience a very low hydrostatic pressure (gauge, approximately -4 to -6 mmHg). In this regard, they mimic the venous blood vessels of the cardiovascular system. As the reader can imagine, the lymphatic system is not a closed system by itself because the lymphatic capillaries are open-ended.

Multiple lymphatic capillaries converge to form small lymphatic vessels, which in turn converge to form large lymphatic vessels. These vessels are comparable in wall structure and size to venules and veins, respectively, and have a function similar to that of veins. Similar to veins, lymphatic vessels contain valves that are spaced very close together to prevent the backflow of lymph toward the interstitial space. At the valve location, the lymphatic vessel wall bulges to accommodate the opening and closing of the lymphatic valves. Without these bulges, the valves would not form a tight seal and there would be a continual (but perhaps small amount) backflow of lymph toward the interstitial space. In vivo, lymphatic vessels appear to resemble a string of pearls because the diameter changes abruptly and quite often at the valve locations. Finally, after multiple convergences, large lymphatic vessels join to form major lymph-collecting vessels that are typically located within the abdomen or chest cavity.

Major lymph-collecting vessels are divided into two different types, the deep lymphatic vessels and the superficial lymphatic vessels. The major difference between these two types of lymph-collecting vessels is their location within the body. Deep lymphatic vessels are located alongside the deep veins that collect interstitial fluid or blood from the skeletal muscles of the limbs. Superficial lymphatic vessels are primarily located within the skin. Both of these types of lymph-collecting vessels transport lymph to the collecting lymphatic trunks, which lead to the two main lymph-collecting vessels of the body. The first major lymph-collecting vessel is the thoracic duct. The thoracic duct begins inferior to the diaphragm and then continues upward through the chest cavity parallel to the aorta. The major lymph vessels from the lower body and those from the left side of the upper body/torso transport lymph back to the cardiovascular system by the thoracic duct. The thoracic duct terminates and empties its contents into the left subclavian vein, which is located alongside the left clavicle. The second major lymph-collecting vessel is the right lymphatic duct. This lymphatic vessel collects all of the lymph from the right side of the upper body/torso. This duct forms as a convergence of the major collecting ducts of the right arm and the right trunk. This occurs near the right clavicle, and then the vessel empties into the right subclavian vein. For both major lymph-collecting vessels, the connection with the cardiovascular system forms a “closed-loop” circuit for the fluid that has exited the cardiovascular system, such that the lymph that is collected near the blood capillaries is returned to the cardiovascular system. This also prevents the loss of fluid volume through capillary filtration and cellular absorption. Some argue that in a sense, if you combine the cardiovascular system and the lymphatic system, you have a true closed system, whereas others see these two systems as distinct and unique but complementary. Both thoughts are true, but if one isolates and considers all of the functions of the lymphatics as a contained system, this must be considered an open-ended system. Be cautious on how you are defining your system of interest and which functions are of interest to you during your example.

The lymphatic system is also composed of lymphatic tissue and organs. The lymphatic tissues are composed of many nodules that are associated with a large number of circulating lymphocytes. The two most important lymphatic tissues are the tonsils and the mucosa-associated lymphoid tissue (MALT). The tonsils are large nodules located in the pharynx. MALT is all of the lymphoid tissues associated with the digestive system. The majority of the MALT tissue is found within the lining of the intestines and resembles the tonsils except that they are more spread out along the entire intestinal system. The function of the lymphatic tissue is to provide a centralized location for production of mature lymphocytes, which can then function to protect the body against inflammation.

Lymphatic organs are more specialized than the lymphatic tissue, and they consist of the spleen, the thymus, and the lymph nodes. The spleen has a number of functions in the body. First, it acts as a blood filter that removes damaged red blood cells, damaged white blood cells, and activated platelets. The spleen can also initiate an immune response, by bringing B cells and T cells in close contact with any antigen present in the bloodstream. Finally, there is a small storage of iron in the spleen obtained from the recycling of damaged red blood cells. This iron store may be used to produce new hemoglobin molecules for red blood cell production. The spleen consists of two major parts: the red pulp and the white pulp. The red pulp contains a significant quantity of blood cells and gets its color from red blood cells. The white pulp is similar to lymphatic tissues and also functions as a site for lymphocyte production. It is the red pulp that acts as a blood filter, and it is in that region where an inflammatory response can be initiated. Mature lymphocytes from the white pulp can migrate into the red pulp and enter the blood to circulate throughout the body.

The thymus is located just beneath the sternum and wraps around the trachea. The thymus is divided into a right and left lobe, each consisting of many lobules. The exterior portion of each lobule is composed of dividing and maturing lymphocytes. As the lymphocytes fully mature (primarily T lymphocytes), they migrate into the interior portion of each lobule, where they exit through blood vessels that permeate the entire thymus. In this way, the thymus acts as lymphatic tissue by producing mature lymphocytes. The thymus also produces hormones that are critical for the immune system development. Upon release, these hormones promote the development and maturation of lymphocytes within other lymphatic tissues and organs. Therefore, the thymus is primarily responsible for the maturation of T cells and the production of hormones that aid in lymphocyte production in other lymphatic tissues.

The last major lymphatic organs are the lymph nodes. Lymph nodes are relatively small organs (typically do not exceed 25 mm) that resemble the shape of a kidney bean. Each lymph node is innervated and supplied by its own blood vessel. Every lymph node is also directly connected to lymph flow by lymphatic vessels. The lymphatic vessels that bring lymph to the nodes are termed *afferent lymphatic vessels*, and those that collect lymph and remove it from the nodes are termed *efferent lymphatic vessels*. Lymph nodes function to filter the lymph before it is returned to the cardiovascular system by the lymphatic ducts. Close to 100% of the antigens within lymph are removed within the lymph nodes by macrophages that are fixed on the lymph node wall. These macrophages engulf and digest the antigens and then present them to lymphocytes within the node. This initiates an immune response and is a warning system for the rest of the body that an antigen has been found within the blood. When there is a major inflammatory process initiated within the body, these glands become

swollen because of an increase in the production of lymphocytes, which destroy any invading particles found within the blood. [Section 9.3](#) will discuss in more detail the flow of lymph through the lymph nodes and the rest of the lymphatic system.

The last component of the lymphatic system, which has not been discussed previously, is the fluid that circulates throughout the lymphatic system termed *lymph*. Lymph has a composition very similar to that of interstitial fluid. One of the primary functions of lymph is to return proteins that have been transported out of the blood vessel or cells back into the cardiovascular system. In this way, there is a very small loss of protein concentration within the cardiovascular system, and thus proteins would not need to be continually produced. Lymph derived from the gastrointestinal system provides a second rapid mechanism for nutrient absorption for any nutrients that do not directly enter the cardiovascular system. The remaining sections of this chapter will discuss how lymph is formed and its path through the lymphatic system.

Lymphocytes are the last component of the lymphatic system and are specialized cells that can circulate within the blood or the lymphatic system. Lymphocytes account for approximately 25% of the entire circulating leukocyte cell population. Under normal conditions, only a small portion of the lymphocyte population is circulating throughout the body and the vast majority of these cells are stored in lymphatic tissues and organs. The body contains more than 10^{12} lymphocytes. There are three major classes of lymphocytes circulating within the blood: the T cells (thymus-dependent), the B cells (bone marrow-derived), and the natural killer (NK) cells. Approximately 75% of the lymphocytes are T cells, which can be subdivided into the cytotoxic T cells, the helper T cells, and the suppressor T cells. The primary function of the cytotoxic T cells is to attack foreign cells or destroy the body's cells that have been infected by a virus. The helper T cells stimulate the activation and production of T cells and B cells during an inflammatory response. Suppressor T cells inhibit the activation of T cells and B cells. B cells account for approximately 15% of the lymphocyte population. Activated B cells differentiate into plasma cells, which are responsible for mass production and secretion of antibodies in response to an infection. Therefore, T cells play a critical role during the cell-mediated immunity responses and B cells play a critical role during the antibody-mediated immunity. The NK cells make up the remaining 10% of the lymphocyte population. These lymphocytes are responsible for attacking foreign cells and innate cells that become infected with a virus. NK cells continuously monitor the quantity of foreign particles, and therefore, their function is termed *immunological surveillance*. The life span of lymphocytes varies, but the vast majority of these cell types last for at least 5 years (approximately 80%). Some lymphocytes can last as long as 20 to 30 years in circulation and, therefore, act as a “memory” for past foreign particle invasions and can help stem a secondary attack.

9.2 Lymph formation

Lymph is composed of only the compounds of the interstitial fluid that enter the lymphatic system. Therefore, as stated before, the composition of lymph is very similar to that of the interstitial fluid when it first enters the lymphatic vessels. However, under normal conditions,

the protein concentration of lymph is higher than the interstitial fluid protein concentration because a large percentage of lymph is derived from the liver. The liver has a protein concentration in the range of 6 g/dL, and lymph derived from the liver composes approximately 50% of all lymph within the lymphatic system. The remaining portions of lymph have a protein concentration that ranges from 2 to 4 g/dL, which is the average interstitial protein concentration (recall that the interstitial fluid protein concentration will vary based on the tissue). This makes the total bulk lymphatic protein concentration in the range of 3 to 5 g/dL. A second difference between lymph and interstitial fluid is the presence of large bacteria. Large bacterial cells can invade the lymphatic system after they migrate into the interstitial space. These cells will typically be cleared after the lymph flows through the lymph nodes, but the bacteria themselves appear in a higher concentration than within the interstitial fluid.

Lymph is formed through a process already discussed in Chapter 7, the movement of water and nutrients out of the capillaries into the extracellular space. This means that lymph formation rate depends on the hydrostatic pressure of the capillary, the hydrostatic pressure of the interstitial space, and the osmotic pressure within the capillary and the osmotic pressure within the interstitial space. This is described by the same equation that we discussed in Chapter 7, which is repeated here

$$\dot{m} = K_p(P_B - P_I - \Pi_B + \Pi_I) \quad (7.8)$$

However, lymph is not solely derived from the blood. As cells perform work, they can take up substances from the extracellular space (e.g., nutrients) and add substances to the extracellular space (e.g., wastes). Therefore, the composition of lymph changes continually and it is slightly different within each tissue. As lymph enters the lymphatic capillaries, its composition is very similar to that of the interstitial fluid of that tissue. However, as lymph moves throughout the lymphatic system, it comes into contact with other cells (particularly lymphocytes), other proteins, other molecules, and lymph derived from other tissues that change the overall composition of lymph. Therefore, in some sense, lymph is continually being formed until it is returned to the cardiovascular system by the lymphatic ducts. A modified lymph formation equation can be described by

$$\dot{m} = K_p(P_B - P_I - \Pi_B + \Pi_I) + \dot{m}_t \quad (9.1)$$

where $\dot{m}_t$ is the formation rate of lymph from other cells that may come in contact with lymph within the lymphatic vessels. Note that this can be positive, if the cells are adding lymph or other constituents to the fluid, or negative, if the cells are removing constituents.

9.3 Flow through the lymphatic system

The total flow rate throughout the lymphatic system is approximately 125 mL/h. Close to 100 mL of this is returned each hour through the thoracic duct to the cardiovascular system. The remaining portion is returned via the right lymphatic duct. Every day, approximately 3 L of lymph is formed and returned to the cardiovascular system. If you recall that the total blood volume of an average person is around 5 L and the plasma component of this is close

to 60% (or 3 L), this suggests that without the lymphatic system, a person would lose the entire plasma portion of blood each day (assuming that the hydrostatic and osmotic pressures do not change significantly during this process). If the body had to continually produce plasma to make up for this 3L loss every day, this would be an inefficient/ineffective process and the body would not function as we know it. Under these conditions, a significant energy input would be needed to form and replace plasma on a daily basis, and this energy would be diverted from other critical functions. Additionally, continual ingestion and absorption of water would be needed to make up some of the volume, and it would be unlikely that the kidneys, if they were present, would produce urine as they currently do (maybe a similar mechanism to that used in avian species would be present). Therefore, the lymphatic system prevents this inefficient process of continually producing blood plasma, which has been filtered within the capillary beds into the interstitial space. Additionally, lymph flow provides a safety mechanism to screen for invading pathogens, because the entire plasma volume can flow through the lymphatics every day; this suggests that the lymphatic tissue can screen and filter the same volume every day.

One of the largest regulators of flow through the lymphatic system is the interstitial hydrostatic pressure. As the hydrostatic pressure increases, the rate of flow within the lymphatic system also increases. At an interstitial pressure of approximately 0 mmHg, the rate of lymph flow increases 10 times over the normal lymphatic flow rate (recall interstitial hydrostatic pressure is typically -3 to -4 mmHg). As the interstitial pressure increases to 2 mmHg, the lymphatic flow rate approaches a maximum of approximately 20 times of the normal lymphatic flow rate. The lymph flow cannot exceed this capacity because at higher interstitial pressures (>3 mmHg), the lymphatic vessels compress because they cannot withstand the external pressure forces. Lymphatic vessels do not have a thick muscular wall like some of the vessels within the cardiovascular system and thus are susceptible to significant changes in the external pressure. The possible compression of lymph vessels effectively increases the resistance to flow through the lymphatic vessels to a point that the driving force cannot overcome. Therefore, for small deviations from the normal interstitial pressure, the rate of lymph flow does not increase significantly. As the interstitial pressure increases significantly above the normal interstitial hydrostatic pressure level, the rate of lymph flow increases to remove the excess fluid within the interstitial space. The major contributors to the interstitial hydrostatic pressure are the capillary hydrostatic pressure, the osmotic pressures of the capillary and the interstitial space, and the endothelial cell permeability. Small changes in any of these values can have a significant effect on the hydrostatic pressure of the interstitial space and therefore a major effect on the flow rate of the lymphatic system.

Example 9.1

Assume for this example that the osmotic pressure of the blood vessel, the osmotic pressure of the interstitial space, and the hydrostatic pressure of the blood vessel remain the same. Make an approximation of the lymph flow rate at various interstitial pressures (as given in the main text) using a first-order polynomial and a second-order polynomial. Plot the changes in lymph flow rate versus pressure under both conditions.

Example 9.1 (cont'd)**Solution**

Using linear algebra to solve for the least squares regression line through the following data points, we get

$$X = [-4, 0, 2] \text{ mmHg}$$

$$Y = [1, 10, 20] \text{ relative flow rate}$$

First-Order Polynomial	Second-Order Polynomial
$\begin{bmatrix} 3 & -2 \\ -2 & 20 \end{bmatrix} \begin{bmatrix} a \\ b \end{bmatrix} = \begin{bmatrix} 31 \\ 36 \end{bmatrix}$	$\begin{bmatrix} 3 & -2 & 20 \\ -2 & 20 & -56 \\ 20 & -56 & 272 \end{bmatrix} \begin{bmatrix} a \\ b \\ c \end{bmatrix} = \begin{bmatrix} 31 \\ 36 \\ 96 \end{bmatrix}$
$Y = 3.036X + 12.357$	$Y = 0.4583X^2 + 4.083X + 10$

In these formulations, Y is the relative flow rate and X is the average interstitial pressure in mmHg. With a second-order polynomial, the approximated function passes through each of the three data points, and this may be the better approximation for lymph flow rate changes (Y -axis) with changes in interstitial pressure (X -axis), within the range of given values. However, we know that lymph flow rate cannot exceed approximately 20 times its normal flow rate, so outside of this range each approximation will fail (see Fig. 9.2). A better approximation should include more data points and possibly better approximation methods.

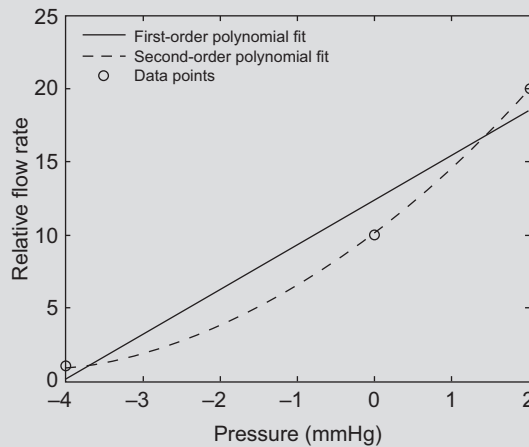


FIG. 9.2 Regression analysis of data presented in the Example 9.1.

The lymphatic system has a pump mechanism similar to the one seen in venous flow. As lymphatic vessels fill with lymph, they can mechanically stretch. This stretch causes an automatic contraction of the smooth muscle cells that surround the lymphatic vessels. The contraction of smooth muscle cells forces lymph through a small lymphatic section (divided by valves) into a downstream lymphatic section. As the fluid fills the next section, the lymphatic vessel stretches again, causing an automatic smooth muscle cell contraction. This pumping mechanism propels the lymph along the entire lymphatic vascular system. Pressure within the lymphatic vessel, as a result of smooth muscle cell contraction, can be as high as 100 mmHg (in the thoracic duct), but is generally significantly lower than this. Furthermore, this pumping mechanism is transient and would experience these high-pressure forces for only a relatively short time. Smooth muscle cells are not the only mechanism that aids in the contraction of lymphatic vessels. A contraction of neighboring skeletal muscle can propel lymph through the lymphatic system, similar to the venous system. Compression of any tissues that transmits a compressive load to the lymphatic system can also help move lymph throughout the lymphatic system. Remember that the lymphatic system is a low-pressure system.

Lymph flow through the lymph nodes is also important to discuss (Fig. 9.3). Lymph is delivered to the lymph nodes through a few afferent lymphatic vessels (typically in the range of five) per node. Within the lymph node, there are hundreds of lymph node sinuses, which are open passageways throughout the node. Lymph can flow freely through these sinuses.

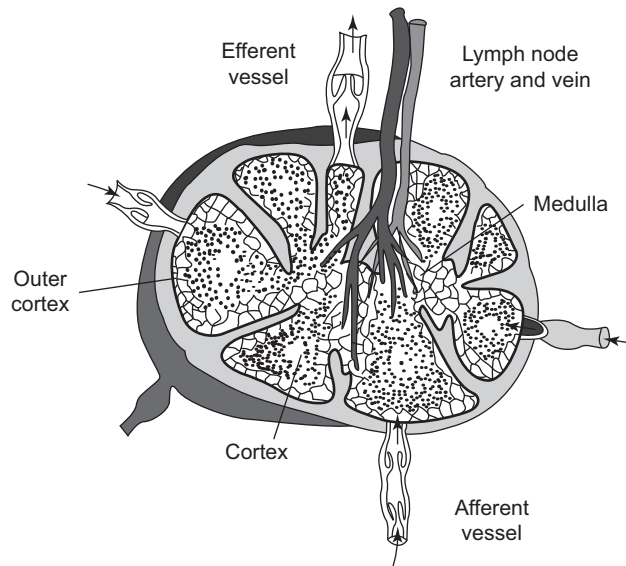


FIG. 9.3 Structure of a lymph node, showing the internal arrangement of the lymph node sinuses. Each lymph node is associated with one artery and one vein that provide a direct connection between foreign particles within the cardiovascular system and lymphocytes within the lymphatic system. Lymph enters the lymph node from multiple afferent vessels that pass through various chambers of the lymph node. These chambers have multiple lymphocytes to monitor the presence of inflammatory mediators. After passing through these chambers, lymph flows out of the lymph node from one efferent vessel. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, 2018, Pearson, New York.)

The first set of sinuses that lymph flows through is termed the *subcapsular space*; it houses a large number of macrophages and other cells to initiate an immune response, if necessary. The subcapsular space is typically on the order of three to five cells in thickness (50 to 100 μm). After flowing through this space, lymph enters the outer cortex of the lymph node, which contains a large concentration of B cells. The outer cortex also is the location for B-cell division, termed the *germinal center*. The outer cortex is typically on the order of 10 to 20 cells in thickness (200 to 400 μm). Lymph then enters the cortex of the lymph node, which surrounds the lymph's cardiovascular artery and vein, connecting the lymph node to the circulatory system. The cortex is composed mainly of T cells, but many lymphocytes can migrate out of the cardiovascular system into the lymph nodes at this location. Lymph then continues into the medulla of the lymph node, which consists primarily of B cells and plasma cells. The medulla collects lymph entering from all of the afferent lymphatic vessels and shunts it toward the single efferent lymphatic vessel. At any of these locations within the lymph nodes, lymph can come into contact with immune cells to help initiate an immune response, if needed. Each lymph node is connected to the cardiovascular system by one artery and one vein, as shown in Figure 9.3. The lymph nodes are very efficient at removing antigens from lymph, and it has been suggested that over 99% of all antigens are cleared from lymph within lymph nodes. Interestingly, lymph nodes are typically found along the periphery of the chest cavity to prevent infections from entering the vital organs. The largest collection of lymph nodes is found in the groin region and in the neck, but there is a large concentration of lymph glands associated with the mesenteric flow to protect the body from invading pathogens from the respiratory system and the gastrointestinal system.

Lymphatic flow is a pressure-driven flow. The viscosity of lymph is close to that of water (1 cP). All of the fluid mechanics relationships that we have discussed so far apply to the lymphatic system. In particular, most of the flow scenarios within the lymphatic system will mimic what is seen in the venous system because of the presence of valves, slow pressure-driven flow, a muscular pumping system, and a large elasticity of the vascular walls. We will therefore not reiterate the relationships here because they can be found elsewhere in this textbook.

9.4 Disease conditions

9.4.1 Cancer metastasis by the lymphatic system

Metastasis is defined as the spreading of malignant tumor cells from the primary tumor location to a separate secondary location within the body. Before we discuss the role that the lymphatic system plays in metastasis, it is important to discuss some characteristics of cancer itself. Cancer is a disease that is characterized by uncontrollable cell division. This is typically caused by a destruction and/or modification of some of the genes within the cell. Additionally, more recent data have shown that when some of the gene regulatory molecules are altered, cancer can begin to progress. If the rate of cell division exceeds the rate of cell death, then a tumor forms. Tumors are defined as a mass of abnormally dividing cells. Tumors can be benign, which rarely leads to death, or malignant, which are cells that no longer function normally and are typically more problematic for the patient.

The primary tumor is the location where the first cells start to divide uncontrollably. As this process continues, the tissue becomes exceedingly large and it cannot contain all of the tumor cells within that space. Additionally, tumor cells require a significant amount of energy (typically in the form of glucose) and instead of competing with other cancerous cells for limited nutrients, it may be more efficient for the cancerous cells to relocate to a new location. Metastasis occurs when tumor cells break away from the primary tumor and invade other nearby locations of the body. To accomplish this, tumor cells migrate through the interstitial space, in a process termed *local invasion*. Once in the interstitial space, tumor cells can be taken into the lymphatic system or enter the bloodstream by a process termed *intravasation*. Intravasation is characterized by cancerous cells passing through the wall of lymphatic capillaries or cardiovascular capillaries. Regardless of which capillary (blood or lymphatic) the tumor cells enter, they can be carried throughout the body relatively easily. This circulation through the vascular system initiates secondary tumor sites, which are typically more difficult to locate and difficult to treat. At the secondary tumor site, the cancerous cells arrest in the capillaries. This can be caused by a size restriction (e.g., they cannot fit through capillaries at this location) or the result of an overexpression of adhesion molecules at a particular location (e.g., in a process similar to inflammatory cell adhesion). Regardless of the cause, the cancerous cells begin to extravasate from the lymphatic or cardiovascular capillaries by migrating across the wall. Once the tumor cell has exited the lymphatic system or blood vessels and has reestablished itself in a new location, this location is defined as the secondary tumor site. The cancerous cells can proliferate and induce angiogenesis at this secondary site once established in a similar manner as at the primary site. If tumor cells have penetrated the lymphatic system, it is also typical for them to amass within lymph nodes, preventing immune cells from recognizing invading particles. It is then likely for a patient to succumb to an infection because the inflammatory process will not proceed normally.

If the cancer cells enter the bloodstream, they also can be carried to other locations within the body to establish secondary tumors. Tumor cells use a great deal of energy at the expense of the surrounding healthy tissue. To accommodate this new demand, cancer cells have the ability to stimulate new blood vessel growth (or angiogenesis). The additional blood supply unfortunately acts to accelerate the rate of cancer cell growth and does not provide the noncancerous tissue with the nutrients it needs. This leads to the death of noncancerous tissue and tissue or organ malfunction because of a lack of nutrients. In addition, the simple compression of a large mass of tumor cells on a healthy organ can cause the organ to not function properly. Cancer is a disease that is intimately associated with the cardiovascular system, and currently there is not a great deal of information available on how tumor cells interact and use the cardiovascular system to its advantage.

The ability of a tumor cell to metastasize within the lymphatic system or with the cardiovascular system depends on a number of properties. First, if the lymphatics or the vascular system is cancerous to begin with, it is relatively easy for the cells to metastasize based on the mechanical loading conditions of the tissue. If the cancerous tissue is not part of either circulation, properties of the cancerous cell itself can allow it to metastasize or not. Surrounding noncancerous tissue can inhibit or accelerate metastasis based on the responses that it is undergoing. The vasculature (lymphatic or cardiovascular) at the primary tumor site and a potential secondary tumor site can also affect the rate of metastasis. In general, many factors are needed to promote the metastasis of tissue. In addition to all of these factors working

together to promote metastasis, a metastatic cancer cell can establish itself at a secondary site, but it may not proliferate for many years. This is part of the reason why locating and treating these secondary sites (which can include multiple secondary sites) is very difficult.

9.4.2 Lymphedema

Lymphedema is very similar to edema associated with microvascular networks. A common characteristic of lymphedema is that a lymphatic vessel becomes blocked and prevents lymph from passing through the lymphatic system and being returned to the cardiovascular system. In this scenario, lymph collects within the lymphatic vessel and interstitial fluid collects within the interstitial space. The region upstream of the blocked lymphatic vessel becomes swollen because fluid cannot pass through the blockage. The danger of lymphedema is associated with an infectious outbreak secondary to the decrease in lymph flow. Since a major initiator of the inflammatory response is associated with the lymph tissues and organs, it is likely that during lymphedema infectious agents never arrive at these lymph tissues and organs. Furthermore, because the interstitial fluid and lymph is stagnant, it is unlikely that many white blood cells will be in the vicinity of the infectious agents. Therefore, the infectious agents can overcome the local immune response and reach a very serious level. In addition, with any edema, the increased pressure can affect local tissue function and local blood flow.

Lymphedema may be inherited (primary lymphedema) or caused by lymphatic vessel injury (secondary lymphedema). Primary lymphedema can be classified by the time of onset. If it is present at birth, it is termed *congenital lymphedema*; if it appears around puberty, it is termed *praecox lymphedema*; if it appears around age 35, it is termed *tarda lymphedema*; and if manifests for genetic reasons at birth, it is then termed *Milroy's disease*. Primary lymphedema is more prevalent in women than men; women account for approximately 90% of lymphedema cases. Additionally, the onset of lymphedema manifests before the age of 40 in more than 90% of cases. Secondary lymphedema is most commonly caused by inflammation that follows some injury to lymphatic tissue. It is most frequently seen after lymph node dissection, surgery, and/or radiation therapy, in which damage to the lymphatic system occurred during the treatment itself.

The exact cause of primary lymphedema is unknown, but it generally occurs as a result of missing lymph nodes or channels between the lymph nodes. Secondary lymphedema affects both men and women, but it occurs in different locations. In women, secondary lymphedema is most commonly found in the upper limbs. In men, it is most commonly found at the location of an injury or the legs. Regardless of the type or location of the lymphedema, it develops in stages. The first stage, stage 0, is termed the *latent stage* and is classified by damage to the lymphatic vessels that has not become apparent yet. Transport of interstitial fluid still occurs, but it is typically shunted away from the damaged vessels. Therefore, there is not a significant pooling of lymph. Stage 1 is termed the *spontaneously reversible stage* and is characterized by pooling of lymph that reverses during rest conditions. In most cases, after depressing the affected area, an indentation will remain on the surface for some time in these early stages. Stage 2 is termed the *spontaneously irreversible stage*. This stage is characterized by morphological and biochemical changes to the tissue because of the presence of excess interstitial fluid.

The affected region is hardened, and there is a general increase in tissue size. The final stage, stage 3, is termed the *lymphostatic elephantiasis stage*. The swelling in this stage is irreversible, and the affected area is relatively large. The tissue is very hard and does not depress when indented.

Treatments for lymphedema are somewhat palliative. For primary lymphedema, it is most common to elevate the affected limb to prevent fibrosis and/or recurrent infections. In some instances, elastic supporting structures can be worn to maintain an elevated external pressure on the effected limb. These elastic supports help prevent pooling and can typically work for a limited range of lymphedema cases. There have been a number of studies that have shown that treatment with benzopyrones can increase the degradation of proteins within lymph, to aid in flow through the lymphatic system; however, the majority of these molecules have wide-ranging effects, and thus care should be used when applying them to patients.

Summary

- 9.1. The lymphatic system is composed of lymphatic vessels, lymphoid tissues and organs, lymph, and lymphocytes. Lymphatic vessels function to transport lymph away from microvascular beds and into the cardiovascular system. The first vessel within the lymphatic system is the lymphatic capillary, which is composed of loosely bound endothelial cells to facilitate the movement of water into the lymphatic system. Lymphatic capillaries converge into larger lymphatic vessels, which are similar in structure and function to venules. Lymphatic vessels contain valves to prevent lymph backflow. The major function of lymphatic tissues and organs is to produce and control lymphocytes and to bring blood into proximity with lymphocytes. Lymphocytes either directly destroy invading pathogens or associate them with antibodies so that other cells can recognize and remove them.
- 9.2. Lymph is formed as a filtrate of interstitial fluid, except that there is typically a higher protein concentration in lymph than the interstitial fluid. The regulation of lymph formation is therefore governed by the formation of interstitial fluid. Recall that the major players in interstitial fluid formation are the capillary hydrostatic pressure, the interstitial space hydrostatic pressure, the plasma colloidal osmotic pressure, and the interstitial colloidal osmotic pressure. There is an added component that lymph can be continually formed by cells within the lymphatic system. Therefore, lymph formation can be described by

$$\dot{m} = K_p(P_B - P_I - \Pi_B + \Pi_I) + \dot{m}_t$$

- 9.3. Lymph flows through the lymphatic system at a rate of approximately 125 mL/h for a total of approximately 3 L of lymph formed per day. This is approximately 60% of the average blood volume, and this would account for a significant loss of body fluids per day if it was not returned to the cardiovascular system. The principal regulator of

lymph flow is the interstitial hydrostatic pressure, because the lymphatic system is also under a very low pressure throughout the entire system. Small changes in the interstitial pressure can have a significant effect on lymph flow through lymphatic vessels. Lymph is also propelled through the lymphatic vessels by compression of surrounding tissue (e.g., muscle contraction). Finally, lymph must flow through lymph nodes, before being returned to the cardiovascular system. As lymph enters the lymph node, it passes through many sinuses that contain multiple lymphocytes to investigate the cells within the lymph. These cells can initiate an inflammatory response if they come into contact with pathogens.

- 9.4. Two diseases that are associated with the lymphatic system are cancer and edema. Cancerous cells can easily enter the lymphatic system and then move to other locations within the body. This would possibly initiate a secondary tumor site somewhere else in the body. Interestingly, tumor cells can metastasize through the lymphatic system or the cardiovascular system. Lymphedema is similar to edema and is defined as an increase in extravascular space water volume (and pressure) resulting from a blockage or a defect of the lymphatic system. This can potentially cause a large inflammatory response because it is possible that pathogens do not come into contact with lymphocytes in the lymphatic tissues.

Homework problems

- 9.1. What type of blood vessels do the lymphatic vessels most closely match? Are the functions of these two vessels similar?
- 9.2. Which lymphatic organ removes damaged red blood cells from circulation? What other functions does this organ have?
- 9.3. Describe the differences between the deep lymphatic vessels and the superficial lymphatic vessels.
- 9.4. What functions do the T lymphocytes and the B lymphocytes perform?
- 9.5. Why is the protein concentration in lymph typically more concentrated than interstitial fluid?
- 9.6. Lymphatic vessels have valves that prevent the movement of lymph back toward the capillary beds. What will happen to water movement across the capillary wall if the lymphatic valves are not functioning properly?
- 9.7. Approximate the flow rate through a lymphatic vessel with a radius of $75\ \mu\text{m}$, a pressure difference of 5 mmHg, and an overall length of 1 mm. The viscosity of lymph in this section of lymphatic vessels is 1.1 cP. If a muscle surrounding the lymphatic vessel constricts the vessel so that the radius reduces to $25\ \mu\text{m}$ and the pressure difference increases to 25 mmHg, what does the flow rate become under these conditions?
- 9.7. There are no active pumping mechanisms to propel lymph movement through a lymph node, which is composed of many interconnected chambers. Discuss the movement of lymph through these structures. Is it likely to be laminar, steady, turbulent, and so on? How does the body ensure the proper mixing of lymph within these chambers?

Homework problems (cont'd)

9.8. The permeability constant can be approximated from

$$K_p = \frac{Ar}{8\mu}$$

where A is the vessel area. Discuss and plot variations in this permeability in relation to the mass flow rate through the lymphatic system. Consider that lymph is continually being added to the system at a constant rate.

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Flow in the lungs

LEARNING OUTCOMES

- Identify the salient components of the respiratory system
- Describe the physiology of the lungs
- Compare the branching structure within the respiratory system to that found within the vascular system
- Explain the alveolar structure
- Use Boyle's law to predict changes in the lung size
- Model lung movement during inspiration and expiration
- Formulate a relationship for lung blood-vessel elasticity
- Analyze the separation distance between the alveoli and the capillaries
- Discuss the air volumes associated with normal breathing
- Describe the lungs' reserve volumes for breathing
- Analyze the composition of air in the atmosphere and in the lungs
- Formulate the diffusion rate within the alveoli
- Understand ventilation perfusion matching
- Calculate changes in breathing rate associated with changes in atmospheric conditions
- Model the respiratory boundary as a semi-permeable membrane
- Describe the mechanisms for gas transport within the blood
- Explain the role of hemoglobin in oxygen and carbon dioxide transport
- Discuss compressible fluid flow
- Discuss diseases that affect the respiratory system

10.1 Lung physiology

The respiratory system provides the means for gas exchange between the air within the atmosphere and the cardiovascular system. Before atmospheric air flows into the lungs, it

passes through the upper portion of the respiratory system, which is composed of various passageways that deliver air to the lungs. The initial conduits for air to flow through are typically the nose, the nasal cavity, the mouth, the pharynx, the larynx, and the trachea (Fig. 10.1). All of these passageways, with the exception of the mouth, are lined with a mucous membrane, which acts as a first-line defense against toxins or particulate matter within the air. The mucous membrane traps toxins and particulate matter and brings this matter into close proximity to white blood cells for removal and/or destruction. The other major function of these conducting passages is to warm atmospheric air to body temperature and to humidify atmospheric air to body conditions (or to cool air temperature and de-humidify, although these would be rarer). Under very dry conditions, it is common for the nasal cavity to lose its moisture. Once this happens to a significant level, it is common for the blood capillaries in the nose to rupture, causing a nosebleed, because all of the moisture has been used to humidify the atmospheric air.

The respiratory system is composed of many branching conducting pathways, to effectively transport and deliver the air into a close proximity with the cardiovascular system. This branching pathway also increases the available surface area for gas exchange at the level of the pulmonary capillaries. The branching respiratory passageways begin with the trachea, which branches into the right and left bronchi (Fig. 10.2). Each bronchi divides into smaller secondary bronchi, which branch into smaller tertiary bronchi. These tertiary bronchi divide approximately three to five times into smaller bronchi within the lungs. Eventually, the bronchi give rise to bronchioles, which themselves divide approximately five times, eventually branching into the terminal bronchioles. Terminal bronchioles have an internal diameter in the range of 500 μm , and there are approximately 6000 terminal bronchioles that arise from

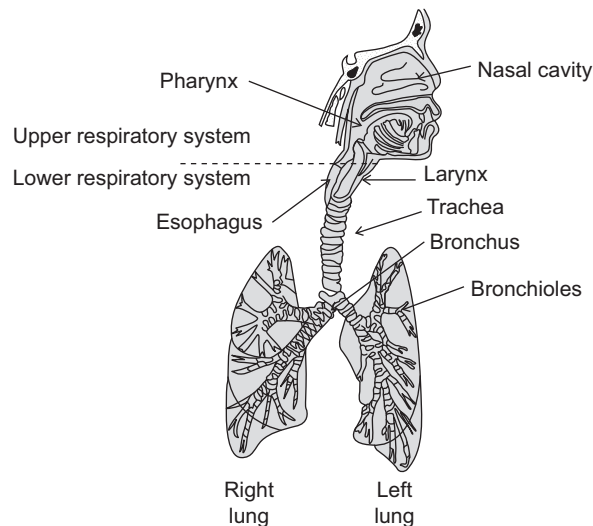


FIG. 10.1 Anatomical arrangement of the components of the respiratory system. Air enters from either the nose (nasal cavity) or the mouth and passes into the pharynx. From here, air passes through the larynx, the trachea, and the primary bronchi. The bronchioles continually divide until the air reaches the alveoli where gas is exchanged with the cardiovascular system. Only the conducting portion of the respiratory system is shown in this figure.

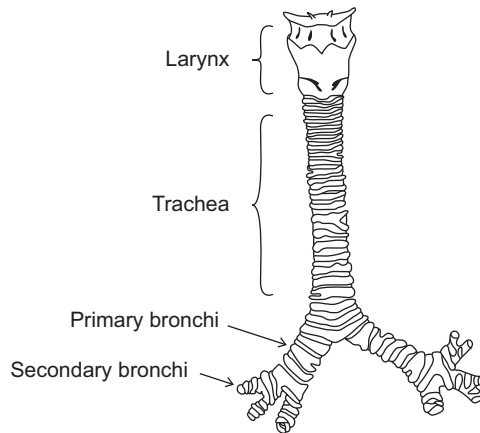


FIG. 10.2 Schematic of the lower respiratory system, which is composed of the larynx, the trachea, and the bronchi. The trachea and the bronchi are surrounded by cartilage to maintain the rigid shape of this portion of the respiratory system.

each tertiary bronchus (there are approximately 20 tertiary bronchioles in the lungs). This branching structure is very similar to the arterial vascular branching pattern between the single large aorta and the many terminal arterioles.

The larger conducting pathways within the lungs are surrounded by cartilage. Cartilage is relatively stiff and acts to protect the airways from collapsing or overexpanding during respiratory pressure changes. The tracheal cartilage wraps around the circumference of the trachea in a C shape, and the ends of the cartilage are connected by a single smooth muscle cell. The contraction and dilation of this smooth muscle cell changes the diameter of the trachea, which regulates the tracheal airflow by either increasing or decreasing the overall resistance to flow through the trachea. The exterior walls of each bronchus are also wrapped with cartilage; however, the cartilage coverage is not as regular as seen along the trachea. This cartilage also acts to stiffen the conducting pathways and can partially regulate airflow through this portion of the lungs. The walls of bronchioles do not contain cartilage but do contain a large number of smooth muscle cells to regulate the diameter of the vessel. Bronchioles are similar to the arterioles of the cardiovascular system because they are the major resistance vessels to airflow in the lungs. These vessels are innervated by the autonomic nervous system, which can induce bronchodilation or bronchoconstriction, to change the airflow pattern throughout the lungs.

Each terminal bronchiole is connected to multiple alveolar sacs by small respiratory bronchioles. The alveolar sacs are common chambers that lead to the individual alveolus (Fig. 10.3). Combined, there are approximately 300 million alveoli in the lungs. Each alveolus is directly associated with blood capillaries, allowing for a large surface area for gas exchange between the respiratory and cardiovascular systems (approximately 70 m^2 total). Alveolar walls are composed of thin epithelial cells. Macrophages (termed dust cells) monitor the lung epithelial surface and engulf any foreign particles that make it through the respiratory track and into the alveolar space. A second cell type, the pneumocyte type II cell, is interspersed throughout the epithelial surface. These cells produce and excrete a surfactant, which

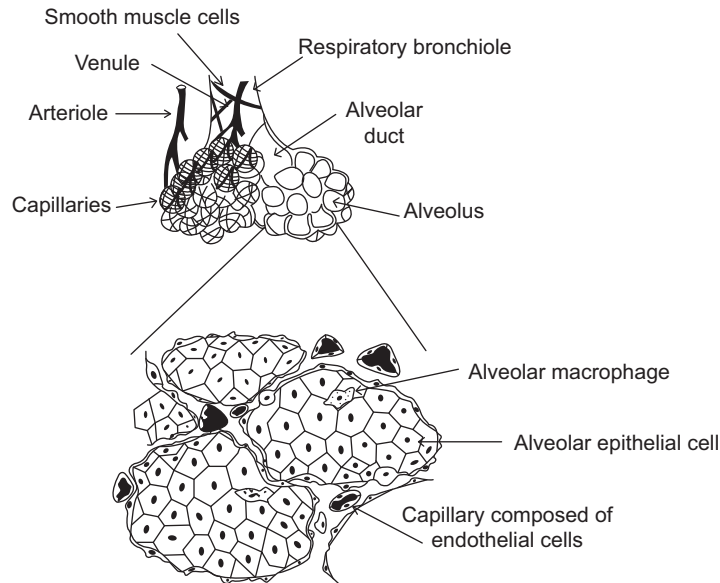


FIG. 10.3 The anatomical structure of a single alveolar lobule. Each lobule is surrounded by a capillary network to efficiently exchange gas with the alveolar space. Bronchioles are wrapped with smooth muscle cells to change the diameter of the bronchiole and increase or decrease the resistance of airflow into the alveolar sac. This figure also shows an expanded section of an alveolar sac, which is composed of epithelial cells and the surrounding capillaries. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, 2018, Pearson, New York.)

is a viscous fluid mainly composed of phospholipids. This surfactant covers the entire alveoli surface in a thin layer of fluid, which acts to reduce the surface tension of the alveoli. If the surfactant is not present, the surface tension increases to a level that would tend to collapse the alveoli. This is described by a pathological condition termed *adhesive atelectasis*, and during this disease it is observed that there is a severe reduction in gas exchange in the lungs. Therefore, the presence of the surfactant acts to reduce the surface tension of the respiratory surface to provide a large surface area for gas exchange to occur between the lungs and the cardiovascular system.

As we have stated, gas exchange occurs across the alveoli epithelial surface. Gases must cross the respiratory boundary, which is composed of three distinct layers, to enter the blood capillary (Fig. 10.4). The first layer of the respiratory boundary comprises the epithelial cells that line the alveoli. The second layer is termed the *fused basal laminae layer* and functions to anchor the alveolar epithelial cells to the capillary endothelial cells. The basal laminae are the extracellular matrix of each cell (epithelial and endothelial) and are primarily composed of elastin and collagen fibers within the respiratory boundary. The third layer is the single endothelial cell that forms the blood capillary wall. Because oxygen and carbon dioxide are uncharged and lipophilic, these molecules can easily and rapidly diffuse across the respiratory boundary. Remembering that in the lung circulation, the arterial vessels are deoxygenated, at the arterial end of the blood capillary, there is a large concentration gradient for oxygen to diffuse into the blood and a small concentration gradient for carbon dioxide to

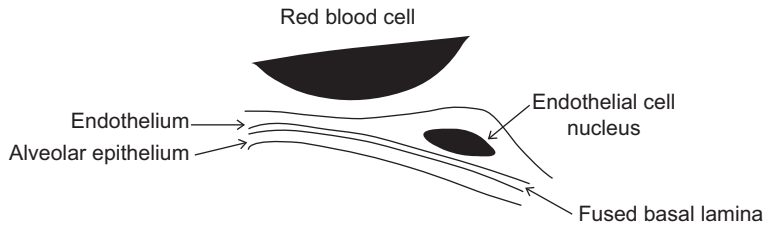


FIG. 10.4 The respiratory membrane, which is composed of an alveolar epithelial cell, a capillary endothelial cell, and their fused basal lamina layer. In general, a red blood cell would be within one cell diameter of the endothelial cell. As discussed in the text, this boundary can be modeled as a single permeable membrane or a composite permeable membrane (with different diffusion permeabilities). (Modified from Guyton and Hall, *Textbook of Medical Physiology*, 10th edition, Saunders, Philadelphia, PA, 2000).

diffuse out of the blood. Under normal conditions, at the venous end of the blood capillary, both the oxygen and carbon dioxide concentrations between the alveoli and the blood have reached an equilibrium (Section 10.3 will discuss oxygen and carbon dioxide exchange in more detail). The distance that separates air within the alveoli and blood within the capillary is approximately $0.5\ \mu\text{m}$ (which is the thickness of the respiratory boundary).

Moving to the gross anatomy of the lungs, each lung is composed of distinct lobes. The right lung has three lobes (the superior lobe, the middle lobe, and the inferior lobe) that are separated by the horizontal and oblique fissures, respectively. The left lung has two lobes (the superior lobe and the inferior lobe) that are separated by the oblique fissure. The right lung is wider than the left lung because the heart is located within the left thoracic cavity and requires some physical space; thus the presence of the heart requires some space from the left lung and reduces the lungs' overall width. The right lung is slightly shorter than the left lung to accommodate the liver, which is directly inferior to the right lung. Each lung is located within a space called the *pleural cavity* within the chest and is surrounded by a membrane termed the *pleura*. The pleural membrane is composed of two layers, the parietal pleura and the visceral pleura. The parietal pleura is the exterior layer, and it is physically connected to the thoracic wall, the diaphragm, and the ribs. The visceral pleura is the inner layer and covers the outer surface of each lung. Between the parietal pleura and the visceral pleura is a thin fluid layer. The fluid within this layer is termed the *pleural fluid* and is critical during respiration.

In fact, the relationship among the atmospheric pressure, the interpulmonary pressure, and the intrapleural pressure determines the direction of airflow in the lungs. Following simple fluid mechanics laws, if the atmospheric pressure and the interpulmonary pressure are the same, there is no net air movement within (either into or out of) the respiratory system. If the interpulmonary pressure drops below the atmospheric pressure, air will flow into the lungs. When the interpulmonary pressure rises above the atmospheric pressure, air will flow out of the lungs. However, there is no internal mechanism for the interpulmonary pressure to change by itself because of some demand on the system (e.g., the lungs do not actively change air pressure by contracting, relaxing, shape change, etc.). In addition, there is clearly no mechanism for the body to alter the atmospheric pressure in relation to the interpulmonary pressure. However, to accomplish this feat of altering interpulmonary pressure, the body makes use of Boyle's law. Boyle's law states that at a constant temperature the pressure of

a system is inversely related to the volume of the system. A constant temperature is a reasonably good assumption for most biological systems (especially when we are discussing internal body cavities), and under normal breathing we will typically assume that the temperature within the human body is constant (although the temperature of atmospheric air may differ). Furthermore, the air temperature in the majority of the respiratory track has little variation in temperature (especially after the air temperature has been altered in the nasal passageways). Mathematically, Boyle's law is represented as

$$P_1 V_1 = P_2 V_2 \quad (10.1)$$

if we assume there are negligible changes in temperature and amount of substance between the two different states that are being described. In addition, in this case, the two different states we are analyzing will typically be the difference in the lungs immediately before inhaling (denoted with a subscript of 1) and immediately after inhaling (denoted with a subscript of 2). Using the principle described by Boyle's law, the interpulmonary pressure is altered by changing the volume of the lungs, because there are no known mechanisms to directly alter the interpulmonary pressure. During inhalation, the rib cage moves upward and outward, while the diaphragm moves downward. Because the parietal pleura is attached to the diaphragm and the rib cage, it expands at the same rate as the diaphragm and ribs. This acts to decrease the intrapleural pressure because the parietal pleura moves outward as the visceral pleura remains in the same location, to approximately -5 mmHg (gauge pressure). Because of the surface tension of the pleural fluid, the visceral pleura is pulled toward the parietal pleura. The visceral pleura is attached to the lobes of the lungs, and thus, the lung tissue gets pulled outward as well. Under normal conditions, this accounts for an approximately 20% change in lung volume that decreases the interpulmonary pressure by 1 to 2 mmHg (gauge pressure), allowing for air to flow into the lungs. Before exhalation begins, the lung pressure becomes equilibrated with the atmospheric pressure once again because enough atmospheric air has entered the lungs. During exhalation the reverse occurs. The ribs move downward and inward as the diaphragm moves upward, which pushes the parietal pleura into close contact with the visceral pleura. This movement increases the intrapleural pressure slightly (because the pleural fluid is not highly compressible), which acts to push the visceral pleural and hence the lungs. The interpulmonary pressure increases by approximately 1 mmHg above atmospheric pressure, which helps force air out of the lungs. Again, before the next inhalation–exhalation cycle begins, the atmospheric pressure and the interpulmonary pressure equilibrate. Thus, the pressure changes that are required for lung ventilation are accomplished by volume changes. The pleural pressure is a measure of the elastic forces that tend to collapse or expand the lungs.

The lungs are supplied with blood through two pathways. The first supplies blood to the lung tissue, for nutrient delivery and waste exchange with the cells that compose the lungs (by the bronchial arteries). This is similar to the systemic circulation of every other tissue within the body and has been discussed through the earlier sections of this textbook. The second pathway is used for gas exchange to oxygenate blood (and remove excess carbon dioxide) and is termed *pulmonary circulation*. The later circulation is the one we will focus on for this section, because the standard previous governing equations apply to the flow through the bronchial arteries.

The pulmonary circulation receives blood from the right side of the heart. The right ventricle pumps deoxygenated blood to the alveolar capillaries by the left and right pulmonary arteries. These arteries enter the lungs at the level of the bronchi and branch at the same locations at which the respiratory vessels branch. Thus, the blood vessels that make up the pulmonary circulation follow the pulmonary tree down to the level of the alveoli. Each terminal bronchiole receives blood from one terminal arteriole and blood exits by one postcapillary venule. As stated earlier, each alveolus is surrounded by a dense mesh of capillaries to provide a surface for gas exchange. After the blood becomes reoxygenated, it passes into the postcapillary venule and follows the pulmonary tree back up to the level of the bronchi. The blood is returned to the heart by the pulmonary veins to continue through the systemic circulation. Recall that the pulmonary circulation flows at much lower pressures than the systemic circulation. It flows at approximately one-sixth of the systemic circulation, rarely exceeding a systolic pressure of 30 mmHg.

10.2 Elasticity of the lung blood vessels and alveoli

As we have discussed in previous chapters, blood flow through vessels is highly dependent on the cross-sectional area of the blood vessels. We discussed earlier in this chapter that during each breath the lungs and all of the tissues and cells within the lungs experience a deformation. Generally, during inhalation the lungs experience a 20% increase in volume (a tensile stretch) that is brought back to normal levels after expiration has occurred (a compressive deformation). From this knowledge, we would presume that the blood vessels in the lungs also would be subjected to large strains, and therefore, the cross-sectional area may change significantly, thus altering the blood flow through the pulmonary vasculature.

The pulmonary blood vessels are viscoelastic, and the stress–strain relationship must take into account the strain rate history. Strain rate history would be a function of loading rates and the applied loads. Since this biological material is under large deformations, the Kirchhoff stress (S_{ij}) and the Green's strain (E_{ij}) are the most applicable stress and strain values to use to describe the loading conditions. Experimentally, it was found that the stress–strain relationship is actually independent of the loading frequency (e.g., breathing rate) and therefore was pseudoelastic. In these same experiments, the results were fit to a classic two-dimensional (2D) strain energy function fairly accurately. From this experimental work, the circumferential stress (S_{xx}) and the longitudinal stress (S_{yy}) can be defined as

$$\begin{aligned} S_{xx} &= a_1 E_{xx} + 0.6429 E_{yy} \\ S_{yy} &= a_2 E_{yy} + 0.6429 E_{xx} \end{aligned} \tag{10.2}$$

where E_{xx} and E_{yy} are the Green's strains in the circumferential and longitudinal direction, respectively, and a_1 and a_2 are material properties. The material property constants change from person to person and can be altered during disease states. Other experimental work has shown that the relationship between pressure (blood pressure minus the pleural pressure) and vessel diameter is linear within the pulmonary blood vessels. In comparison, for systemic vessels this relationship is highly nonlinear. More than likely this is due to the fused

basal laminae layer that intimately links the pliant blood vessels to the stiffer lung tissue. Therefore, linear elastic relationships can be used when determining the blood vessel cross-sectional area change as a function of hydrostatic pressure, interpulmonary pressure, and intrapleural pressure.

Changes in the interpulmonary pressure and the blood hydrostatic pressure can also affect the size of the alveoli and the distance that separates the gas in the alveoli and the gas in the blood capillary. Under normal conditions, the alveolar size remains constant as a function of blood hydrostatic pressure but varies with interpulmonary pressure. In simple terms, the surface area of the alveoli will follow the inverse of Boyle's law, so that when the interpulmonary pressure increases, so does the size of the alveoli. This is a direct relationship so that mass is conserved during lung expansion. The separation distance is a slightly more difficult problem because it will be affected by the interpulmonary pressure and the capillary hydrostatic pressure. Let us define

$$\Delta P = P_{\text{capillary-hydrostatic}} - P_{\text{interpulmonary}} \quad (10.3)$$

This pressure difference is the pressure that causes the separation distance between the alveolar space and the blood. Using Eq. (10.3), we can define the separation distance between the alveolar gas and the capillary gas (this is a measure of the respiratory boundary thickness and not the exact diffusion distance, which may follow random paths). The values for separation distance have been quantified experimentally and agree with the following discussion. If ΔP is negative and has a value less than -0.7 mmHg, the separation distance is equal to 0. When ΔP is between -0.7 and 0 mmHg, the separation distance increases from zero to its nominal resting value of approximately $0.5 \mu\text{m}$. As ΔP increases from zero, the distance increases linearly to some limiting value of approximately $1.3 \mu\text{m}$ at a pressure of approximately 30 mmHg. Mathematically, this can be represented as a piecewise continuous function

$$h(\Delta P) = \begin{cases} 0 & \Delta P < -0.7 \text{ mmHg} \\ 0.5 \mu\text{m} + \frac{0.5 \mu\text{m}}{0.7 \text{ mmHg}} \Delta P & -0.7 \text{ mmHg} \leq \Delta P < 0 \text{ mmHg} \\ 0.5 \mu\text{m} + \frac{2 \mu\text{m}}{75 \text{ mmHg}} \Delta P & 0 \leq \Delta P < 30 \text{ mmHg} \\ 1.3 \mu\text{m} & \Delta P > 30 \text{ mmHg} \end{cases} \quad (10.4)$$

The "slope" values that appear before the ΔP in the second and third relationships are known as the *compliance coefficients of the alveolar wall*. Under disease conditions, these compliance values can change significantly, and this is what effectively inhibits or accelerates gas movement from the atmosphere to blood under pathological conditions. To understand the separation distance as a function of pressure, one must look into which pressure is larger and what phase of matter is associated with the greater pressure. When the blood pressure is greater than the interpulmonary pressure, the blood can exert a net force on the alveolar space. Because the alveolar space is filled with a gas, it would tend to collapse under these

conditions and pull away from the capillary. In the reverse scenario, the interpulmonary pressure is greater than the capillary hydrostatic pressure, and therefore, the net force pushes the alveolar space closer to the capillary space.

10.3 Pressure-volume relationship for airflow in the lungs

We have briefly discussed in a previous section that air movement into the lungs is caused by changes in the lung volume. Following Boyle's law, the gas pressure must change inversely with the change in volume (assuming that the temperature is constant and there is no change in the amount of gas within the system). Here we will briefly discuss some of the mechanics of breathing that bring about the changes in volume. Recall that we have stated that during inspiration, the rib cage moves outward and upward and the diaphragm moves downward. The movement of the rib cage is controlled by the intercostal muscles, and the diaphragm is a skeletal muscle. During inspiration the diaphragm and the external intercostal muscles contract, causing an increase in the thoracic cavity volume. The contraction of the diaphragm accounts for approximately 75% of the air movement during normal breathing. During strenuous activity, the increase in the speed of rib movement and the increase in rib displacement are controlled by the pectoralis minor, the scalene, and the sternocleidomastoid muscles, which completely accounts for the increased volume of the thoracic cavity. During expiration, the contraction of the internal intercostal muscles brings the rib cage back to its normal position and the abdominal muscles contract to assist the internal intercostal muscles and force the diaphragm upward.

The respiratory system can adapt rapidly to the oxygen demands of the body. The rate of breathing and the amount of air moved with each breath can vary significantly. Under extreme conditions, it is possible that the amount of air moved by the respiratory system can exceed 50 times the normal breathing capacity during strenuous exercise. The respiratory rate is defined as the number of breaths that are taken within 1 minute. Under normal resting conditions, this is close to 12 to 15 breaths per minute. The tidal volume is the amount of air inhaled during one breath, and this is approximately 500 mL for an average adult. Therefore, at rest the amount of air moved into the lungs per minute is 6000 to 7500 mL. Of the 500 mL of air that enters the respiratory system during each breath, only approximately 350 mL of this enters the alveolar space and is used for gas exchange. The remaining 150 mL fills and is contained in the dead space (nose, trachea, and bronchi, among others) within the conducting system and is never used for gas exchange. Therefore, the alveolar space is ventilated with 4200 to 5250 mL of air each minute (clearly this depends on the exact size of the lungs and the respiratory rate). Interestingly, the respiratory rate and tidal volume can be controlled independently of each other. If the respiratory rate increases to 25 breaths per minute, the tidal volume must drop to 300 mL to maintain the same lung ventilation per minute (7500 mL/min). However, because the dead space of the conducting system does not change, the alveolar ventilation rate drops to 3750 mL/min (compared with 5250 mL/min) because 150 mL of incoming air stays within the dead space during each breath.

Under extreme conditions, the respiratory system can move 4.8 L of air during each breath. This is termed the *vital capacity of the lungs*. The lungs never fully deflate because the alveolar

wall would adhere to itself (adhesion atelectasis) and then it would be difficult to inflate the alveoli again. There is approximately 1.2 L of air within the lungs that is used to keep the lungs and the alveoli open under the most strenuous breathing conditions. The extra 1.2 L is termed the *residual volume of the lungs*, which combined with the lung vital capacity suggests that the total lung volume is 6 L (Fig. 10.5). During extremely strenuous activity (when the lung is moving 4.8 L per breath), the respiratory rate can increase to approximately 50 breaths per minute. Under these conditions, the respiratory system would move a total of 240 L of air per minute. In practice, only extremely well-conditioned athletes can approach this theoretical maximum respiratory rate.

We will provide a few more definitions that are associated with Fig. 10.5 that relate to two ways to describe gas in the lungs: the volumes and the capacities. The expiratory reserve volume is the amount of air that can be voluntarily forced out of the lungs after the end of a normal expiration of the tidal volume. This is typically on the order of 1000 mL and is used during strenuous activities. The inspiratory reserve volume is the amount of air that can enter the lungs in addition to a normal inspiration of the tidal volume. On average this is close to 3300 mL, and again this is typically used only during strenuous activities. As defined before, the total lung capacity would be the residual volume plus the expiratory reserve volume plus the tidal volume plus the inspiratory residual volume ($1200 \text{ mL} + 1000 \text{ mL} + 500 \text{ mL} + 3300 \text{ mL} = 6000 \text{ mL}$). The inspiratory capacity is the total amount of air that can be taken into the lungs. This is equal to the tidal volume plus the inspiratory reserve volume ($500 \text{ mL} + 3300 \text{ mL} = 3800 \text{ mL}$). The vital capacity is the maximum amount of air that the lungs can take in or move out, which is equal to the expiratory reserve volume plus the tidal volume plus the inspiratory reserve volume

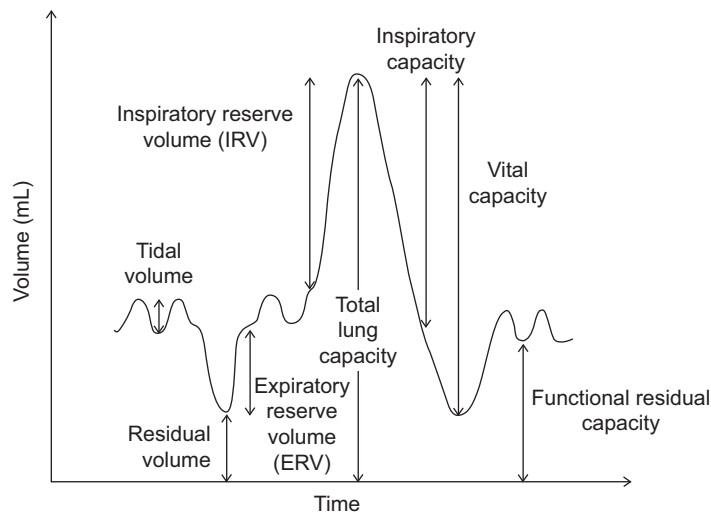


FIG. 10.5 The volume of the lungs under normal breathing and various other respiratory movements. Under normal conditions, the tidal volume will be approximately 500 mL for each breath and there is an inspiratory reserve volume of approximately 3300 mL and an expiratory reserve volume of approximately 1000 mL. The total lung volume is approximately 6000 mL.

(1000 mL + 500 mL + 3300 mL = 4800 mL) The functional residual capacity is the amount of air remaining in the lungs after a normal exhalation. This is equal to the residual volume plus the expiratory reserve volume (1200 mL + 1000 mL = 2200 mL)

Assuming that atmospheric air is uniform, all of the previous discussions on the pressure changes required to move air into or out of the lungs are still valid. Again, primarily Boyle's law will dictate the movement of air into the lungs.

10.4 Cardiopulmonary flows: ventilation perfusion matching

Adequate respiration means that the ventilation rate and blood flow rate must be matched so an optimal amount of oxygen is loaded into the erythrocytes of the blood and an optimal amount of carbon dioxide is unloaded into the alveolar gas space. This process is termed ventilation (V) perfusion (Q) matching and is described by the V/Q ratio. A simple way to think of this ratio is that alveoli without fresh gas cannot supply the blood with oxygen ($V/Q = 0$), and capillaries without flow cannot participate in gas exchange ($V/Q \sim \infty$) The physiologically normal V/Q ratio is 0.8, using a resting ventilation rate of 4000 mL/min and perfusion rate of 5000 mL/min. At this V/Q ratio, the partial pressure of oxygen will be close to 100 mmHg and the partial pressure of carbon dioxide will be close to 40 mmHg as blood enters the venous pulmonary circulation.

Because of both the lung anatomy and the force of gravity, the V/Q ratio of 0.8 is not uniform in all alveoli. In fact, in an upright position the upper lobes of the lung are better ventilated than the lower lobes. Thus, the upper lobes receive a larger volume of gas during each breath compared with the lower lungs. This is in part because the blood vessels that feed the lower lobes are fuller of blood than the blood vessels in the upper lobes. This phenomena occurs as a result of the force of gravity pulling the weight of the blood down toward the lower lobes of the lungs (remember that the overall blood pressure within the pulmonary circuit is relatively low). Thus, the upper lobes of the lungs have better ventilation and less flow; the V/Q ratio is greater than 0.8. The lower lobes have less ventilation and more flow; the V/Q ratio is less than 0.8. One can imagine a point in the middle of the lungs where $V/Q = 0.8$. This concept is illustrated in [Fig. 10.6](#), which shows one lung that has three different ventilation/perfusion zones. Under normal conditions, in a sitting position the upper zone has a V/Q ratio in the range of 3 and the lower zone has a V/Q ratio in the range of 0.5. It is important to note though that these V/Q ratios can change drastically depending on the activity level of the person and the presence of any pathological conditions.

Lung areas that are ventilated, but do not have gas exchange because of the absence of blood flow, are dead spaces. Likewise, lung areas that are not ventilated, but have sufficient blood flow, represent a shunt because there is no modification to the blood composition through this pathway. In various disease states, the V/Q ratio can become a diagnostic tool and is different from emphysema versus asthma, for instance. This is elaborated on in [Section 10.8](#).

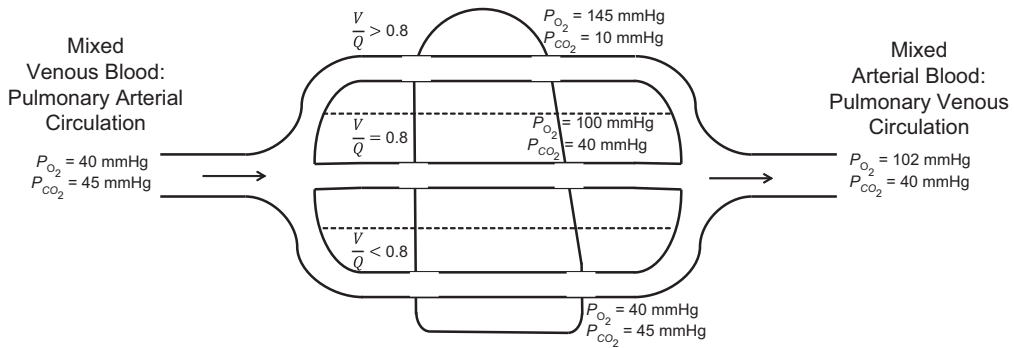


FIG. 10.6 Ventilation perfusion ratio for lungs in an elevated position. Under normal conditions the upper portion of the lungs has very low blood flow with a higher ventilation rate. This allows the blood from this zone to have an elevated oxygen and reduced carbon dioxide concentration compared with mixed arterial blood. The middle zone of the lungs has an oxygen and carbon dioxide concentration that is close to that of mixed arterial blood. Finally, the lowest zone of the lung has a reduced oxygen and an elevated carbon dioxide concentration compared with mixed arterial blood, because this portion of the lungs is not ventilated well.

10.5 Oxygen and carbon dioxide diffusion

Diffusion is the random thermal motion of molecules that results in a net movement of molecules from a higher concentration to a lower concentration. Diffusion is the only way that oxygen enters the blood from alveolar air and that carbon dioxide enters the alveolar air from the blood (meaning that there is no active transport mechanism for these molecules during these movements and the motions are entirely passive). Atmospheric air is composed of a number of molecules, and the pressure that each exerts is directly related to the concentration of that particular molecule within the air. For example, normal atmospheric air contains 21% oxygen; therefore, 21% of atmospheric pressure is contributed by oxygen (i.e., $0.21 \times 760 \text{ mmHg} = 160 \text{ mmHg}$). This partial pressure is denoted by P_{O_2} , for oxygen. Gases that are dissolved in liquids also exert a pressure. The partial pressure of a gas dissolved within a fluid is determined by its concentration and its solubility coefficient for that gas in the particular medium. Henry's law describes the relationship between a gas partial pressure and the factors that affect the pressure. Henry's law takes the form of

$$P = \frac{\text{Gas concentration}}{\text{Solubility coefficient}} \quad (10.5)$$

Looking at this relationship (Eq. (10.5)), it shows that for a given concentration, if the gas solubility is high, the gas will exert a lower pressure compared with a gas that has a lower solubility. Gases that are highly soluble exert a lower pressure because there will be an attraction between the liquid molecules and the gas molecules that prevents the gas from moving randomly and quickly through the fluid. Furthermore, for gases with a higher solubility in a particular medium, it is easier for those gas molecules to enter the liquid and those molecules would tend to prefer to be associated with the liquid molecules. However, when the solubility is low, there is a very small attraction between the liquid and gas molecules that allows

for the gas to move more freely. In addition, for gases with lower solubility coefficients for a particular medium, it becomes harder for gas molecules to enter the liquid and the molecules would prefer to not be in the liquid. At body temperature, the solubility coefficients for oxygen and carbon dioxide are 0.024 and 0.57, respectively. Therefore, the net movement of gas molecules across the respiration boundary depends on the relationship between the partial pressure of the gas in atmospheric air and the partial pressure of the gas within blood. Under normal conditions, the partial pressure for oxygen is higher in the alveoli, so that there is a net movement of oxygen into the blood. Additionally, the partial pressure for carbon dioxide is typically higher in the blood, so there is a net movement of carbon dioxide into the alveoli.

Like diffusion of any other molecule, the rate of diffusion is not solely based on the pressure gradient (for solids and liquids we typically talk about a concentration gradient; regardless of the phase of the molecule, there is some driving force for diffusion to occur). The other factors that affect gas diffusion are the temperature of the exchange medium, the distance that the gas must diffuse over, gas solubility, the cross-sectional area of a barrier separating the diffusing molecules, and the molecular weight of the gas. In equation form, the diffusion rate is proportional to

$$D \propto \frac{\Delta P A s}{\Delta x \sqrt{M}} \quad (10.6)$$

where D is the diffusion rate, ΔP is the pressure difference, A is the cross-sectional area, s is the solubility coefficient, Δx is the distance, and M is the molecular weight of the gas. This is intuitive because as the pressure difference, cross-sectional area, and solubility increase, more gas molecules should be able to diffuse into the medium. As the distance and molecular weight increase, the amount of molecules that can diffuse should decrease. From previous engineering or science courses, you may be familiar with the concept of a diffusion coefficient. For gases in solution, the diffusion coefficient is proportional to the solubility of the gas divided by the square root of the molecular weight of the gas. If we set the relative diffusion coefficient of oxygen to be 1.0 under normal physiological conditions, the relative diffusion coefficients for other physiologically relevant gases are listed in [Table 10.1](#).

Similar to the diffusion of gases through fluids, the diffusion of gas through the respiratory boundary is regulated by the same factors. Namely, the pressure difference, the thickness of the membrane, the cross-sectional area available for exchange, and the diffusion coefficient (solubility/molecular weight) are the most important factors that determine the diffusion

TABLE 10.1 Relative diffusion coefficients for important respiratory gases

Gas	Relative diffusion coefficient
Oxygen	1.0
Carbon dioxide	20.3
Nitrogen	0.53
Carbon monoxide	0.81

TABLE 10.2 Respiratory gas partial pressures

Gas	Atmospheric air (mmHg)	Alveolar air (mmHg)	Deoxygenated blood (mmHg)	Expired air (mmHg)
N ₂	597	569	563.3	566
O ₂	159	104	40	120
CO ₂	0.3	40	45	27
H ₂ O (as vapor)	3.7	47	Variable	47
Total	760	760	~760	760

of gas across the respiratory boundary. The pressure difference across the respiratory boundary is determined by the partial pressures of the gas in the alveolar air and in blood (which are listed in Table 10.2). The difference in these two pressure values (e.g., atmospheric air versus alveolar air for our particular examples) will provide a means to determine the net direction of movement for gas molecules across the respiratory boundary. The respiratory boundary thickness is a measure of the linear distance that the molecules must traverse to be exchanged. As this boundary increases in thickness, which commonly occurs under disease conditions, the rate of diffusion will decrease significantly. The surface area for diffusion determines the available regions for gases to be exchanged. As the surface area for exchange decreases, which again is common during disease conditions, the rate of diffusion will also decrease. Finally, the diffusion coefficient is directly related to the molecular properties of the gas. With a greater solubility and a lower molecular mass the diffusion coefficient will be larger, which in turn leads to a higher rate of diffusion. The changes in the rate of diffusion for gases across the respiratory boundary follow the same principles as discussed for diffusion through a fluid.

The same factors that regulate the diffusion of gases through fluids regulate the diffusion of gases through the respiratory boundary. The diffusing capacity is the ability for a boundary to exchange gas and is defined as the volume of gas that diffuses across a membrane at a pressure difference of 1 mmHg in 1 minute. Under normal resting conditions, the diffusing capacity of oxygen is 21 mL/min/mmHg. As blood enters the alveolar capillaries, the pressure difference for oxygen is approximately 60 mmHg, but this pressure gradient reduces to approximately 2 mmHg at the venous (oxygenated) side of the respiratory capillary (we are considering the mixed venous and arterial blood levels). If we approximate this to an average of 30 mmHg, this suggests that under normal conditions 630 mL of oxygen diffuses across the respiratory boundary every minute. During strenuous exercise, the diffusing capacity of oxygen can increase to 65 mL/min/mmHg. The diffusing capacity of carbon dioxide is approximately 20 times greater than oxygen because these values are directly related to the diffusion coefficients (see Table 10.1). Therefore, the diffusing capacity of carbon dioxide is approximately 425 mL/min/mmHg under normal conditions or approximately 1300 mL/min/mmHg during strenuous exercise.

Example 10.1

Imagine standing on the top of a mountain where the atmospheric pressure is 480 mmHg and the ambient temperature is 10°C. Assume that the percent composition of air is the same as described in Table 10.2 (although the exact partial pressures will be different). Calculate the respiration rate needed to maintain the body's oxygen requirements of 270 mL/min at standard body temperature and pressure (i.e., 760 mmHg, 37°C). Assume that your tidal volume increases to 750 mL, that 35% of the inspired oxygen enters the blood, and that all of this would meet the body's oxygen requirements.

Solution

First, let us determine the partial pressures of each of the major gases that are in air (calculated in Table 10.3):

TABLE 10.3 Partial pressure of gases calculated from the given values

Gas	Percent composition	Partial pressure (mmHg)
N ₂	78	374.4
O ₂	21	100.8
CO ₂	0.04	0.2
H ₂ O	0.5	2.4

Use a more general form of Boyle's law to determine the tidal volume needed at body temperature or pressure (assuming that the amount of substances remains the same).

$$\frac{P_B V_B}{T_B} = \frac{P_M V_M}{T_M}$$

$$V_B = \frac{T_B P_M V_M}{P_B T_M} = \frac{310 \text{ K}(480 \text{ mmHg})(750 \text{ mL})}{760 \text{ mmHg} (283 \text{ K})} = 520 \text{ mL}$$

The subscript *B* represents the normal body conditions, whereas the subscript *M* represents the "mountain top" conditions. Of this volume, 21% is oxygen, and of that your body can absorb only 35%.

$$520 \text{ mL} * 0.21 * 0.35 = 38.22 \text{ mL}$$

Thus, the body absorbs in 38.22 mL oxygen/breath under normal conditions.

The number of breaths needed on the mountain top would be

$$\frac{270 \text{ mL O}_2/\text{min}}{38.22 \text{ mL O}_2/\text{breath}} = 7 \frac{\text{breaths}}{\text{min}}$$

To model the diffusion of oxygen into blood or that of carbon dioxide out of blood, let us consider the respiratory boundary as a semipermeable membrane (Fig. 10.7). Blood flows

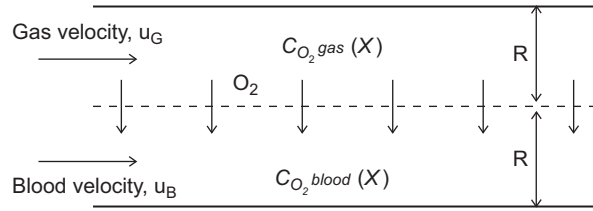


FIG. 10.7 Respiratory boundary modeled as a semipermeable membrane. Using this type of model, the diffusion of respiratory gases across the respiratory boundary can be calculated if we assume that the total concentration of the gas remains constant along the channel.

along one side of the membrane, and gas flows along the other side. For simplicity, let us assume that the membrane is permeable to only one respiratory gas (oxygen for this example). The net movement of oxygen across this channel will be from the gas side to the blood side. If we take the mass balance of the gas within each chamber across this semipermeable membrane and we assume that the concentration of oxygen is constant (i.e., $C_{O_2-gas} + C_{O_2-blood} = \text{constant}$), we get

$$Ru_G(C_{O_2-gas}(x + \Delta x) - C_{O_2-gas}(x)) + J\Delta x = 0 \quad (10.7)$$

and

$$Ru_B(C_{O_2-blood}(x + \Delta x) - C_{O_2-blood}(x)) - J\Delta x = 0 \quad (10.8)$$

where J is the flux of oxygen across the membrane defined by

$$J = \frac{D}{h}(C_{O_2-gas} - C_{O_2-blood}) \quad (10.9)$$

where h is the thickness of the respiratory boundary. If Δx approaches zero, Eqs. (10.7) and (10.8) become

$$\frac{dC_{O_2-gas}}{dx} = -\frac{D}{Ru_G h}(C_{O_2-gas} - C_{O_2-blood}) \quad (10.10)$$

and

$$\frac{dC_{O_2-blood}}{dx} = \frac{D}{Ru_B h}(C_{O_2-gas} - C_{O_2-blood}) \quad (10.11)$$

respectively. To prove the assumption of the oxygen concentration being constant, add Eqs. (10.10) and (10.11) together to get

$$\frac{dC_{O_2-gas}}{dx} + \frac{dC_{O_2-blood}}{dx} = 0$$

which leads to

$$C_{O_2-gas} + C_{O_2-blood} = \text{Constant}$$

if you integrate the differential equation with respect to distance. Eqs. (10.7) through (10.11) can be used to model the gas movement across any semipermeable membrane if the assumption regarding a constant concentration is valid.

10.6 Oxygen and carbon dioxide transport in the blood

Oxygen and carbon dioxide have a relatively low solubility in plasma, which limits the amount of oxygen and carbon dioxide blood can directly carry. Red blood cells, however, can “remove” the dissolved oxygen and carbon dioxide from blood and help transport oxygen and carbon dioxide through the blood in a more efficient and effective manner. In the case of oxygen, hemoglobin directly binds to oxygen molecules. Carbon dioxide, however, is modified into plasma-soluble molecules by proteins carried within red blood cells and is therefore indirectly transported by red blood cells. These processes solve the problem of the relatively low solubility of oxygen and carbon dioxide in plasma. It also allows for the gases to continually diffuse into the bloodstream as long as the red blood cells are not saturated, because the concentration gradient between alveolar air and plasma is never quenched.

Every 100 mL of blood leaving the alveolar capillaries carries approximately 20 mL of oxygen, of which only approximately 0.3 mL is pure oxygen dissolved in blood. The remaining 19.7 mL of oxygen is bound to hemoglobin (Hb). Each hemoglobin molecule consists of four protein subunits with one iron ion per protein subunit (Fig. 10.8). As hemoglobin becomes oxygenated, it is termed *oxyhemoglobin* (HbO_2). Each red blood cell carries over 250 million hemoglobin molecules. Oxygen-hemoglobin binding is a reversible process that can be described by kinetic rate constants that are dependent on the partial pressure of oxygen within the blood, and as we learned earlier these partial pressures depend on a number of factors. The hemoglobin-oxygen reaction can be defined with the following kinetic reaction:

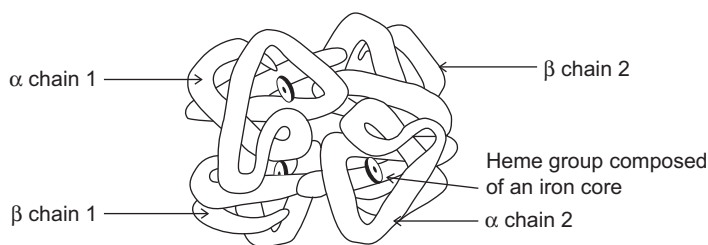
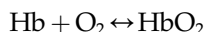


FIG. 10.8 The protein structure of hemoglobin, which consists of four globular protein subunits. Each subunit contains one heme molecule, which is a nonprotein compound that surrounds an iron core. It is this iron molecule that facilitates the transport of oxygen and carbon dioxide. Each red blood cell contains close to 300 million hemoglobin molecules. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, 2018, Pearson, New York.)

As the oxygen partial pressure increases, the rate of oxygen-hemoglobin binding increases, such that the equilibrium is shifted to favor more oxyhemoglobin. This is typically quantified by the percent saturation of hemoglobin. At a normal alveolar oxygen partial pressure of approximately 100 mmHg, nearly all of the hemoglobin in the blood becomes saturated with oxygen (approximately 98%). In tissues surrounding systemic capillaries, the partial pressure of oxygen is close to 40 mmHg, which would lead to only 75% hemoglobin saturation. Therefore, under normal conditions, hemoglobin remains fairly saturated with oxygen, even within the capillaries. Thus, not all of the oxygen that is transported by red blood cells diffuses into the tissue space. However, if (and when) the tissue is under slightly hypoxic conditions, the percent saturation drops rather quickly to bring the tissue oxygen level back to normal (at an oxygen partial pressure of 20 mmHg the hemoglobin saturation is close to 35%, meaning that a significant portion of oxygen has dissociated [or will dissociate] from hemoglobin under these conditions).

Carbon dioxide transport is slightly more complicated than oxygen transport within the blood. Upon entering the blood, carbon dioxide can follow one of three pathways at a carbon dioxide partial pressure of approximately 45 mmHg, which is commonly found within the systemic capillaries (Fig. 10.9). The first is the conversion of carbon dioxide to carbonic acid, which accounts for nearly 70% of all of the carbon dioxide transported through the blood. This reaction proceeds through the action of an enzyme, carbonic anhydrase, which

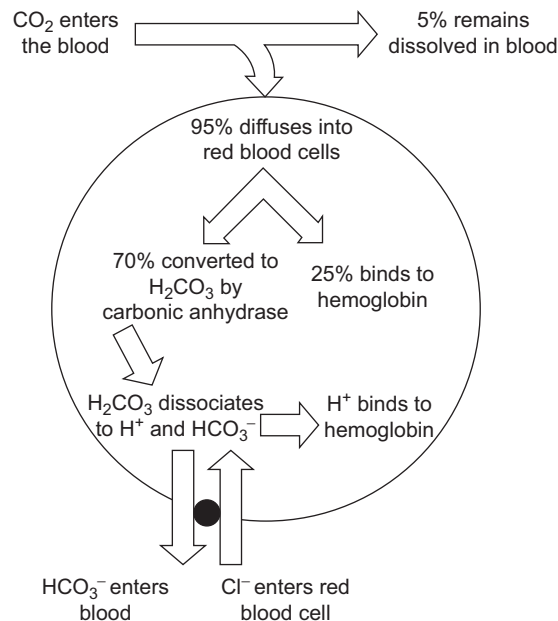
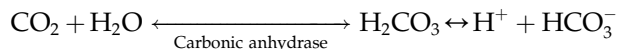
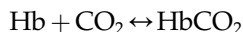


FIG. 10.9 Pathways for carbon dioxide transportation in blood at a carbon dioxide partial pressure of 45 mmHg. The majority of carbon dioxide is converted to hydrogen and bicarbonate ions. About 25% of the carbon dioxide binds directly to free amino groups in the hemoglobin protein. The remaining carbon dioxide is transported directly within the blood.

is stored within red blood cells. Carbonic acid immediately dissociates into a hydrogen ion and a bicarbonate ion. This kinetic reaction can be described by



Most of the hydrogen ions formed in this way bind to hemoglobin to maintain the pH of the plasma (e.g., if the hydrogen ion were transported into the plasma, the pH would decrease). Most of the bicarbonate ions are transported directly into the plasma phase through a membrane-bound transport protein. For each bicarbonate ion that enters the plasma, one chloride ion is transported into the red blood cell using the same transport protein (Band 3 anion transport protein). No energy is required for this transport, and it results in a large movement of chloride ions into the red blood cells, which is known as the *chloride shift*. The second possible outcome for carbon dioxide is adhesion to hemoglobin. Close to 25% of carbon dioxide follows this path. Carbon dioxide binds to the hemoglobin protein and not the iron ions like oxygen. Specifically, carbon dioxide binds to free amino groups (NH_2), forming carbaminohemoglobin (HbCO_2) in the following reaction:



The remaining portion of carbon dioxide (approximately 5% to 7%) is transported as dissolved carbon dioxide in blood. Recall that the solubility of carbon dioxide is approximately 20 times greater than that of oxygen, and therefore, we would anticipate that blood can carry more carbon dioxide compared with oxygen.

10.7 Compressible fluid flow*

One of the most critical differences in compressible fluid flow, compared with incompressible fluid flow, is that the physical properties of the fluid become dependent on changes in container area, frictional forces along the walls, and heat transfer phenomena that may occur. We will begin our discussion of compressible fluid flow with isentropic flows. For this type of flow, friction and heat transfer are neglected and the only independent variable is the change in the cross-sectional area of the conducting vessel. The equations for isentropic flows are derived from the basic equations developed in Chapter 3 of this textbook, for a fixed volume of interest with steady 1D flow. The properties of interest for an isentropic flow are generally the fluid's temperature, pressure, density, cross-sectional area, and velocity at any location within the flow field (Fig. 10.10).

For a steady isentropic flow, the continuity equation simplifies to

$$\rho_1 v_1 A_1 = \rho_2 v_2 A_2 = \dot{m} \quad (10.12)$$

With the same assumptions, the conservation of momentum equation will simplify to

*This section is considered advanced and can be skipped without a loss of continuity.

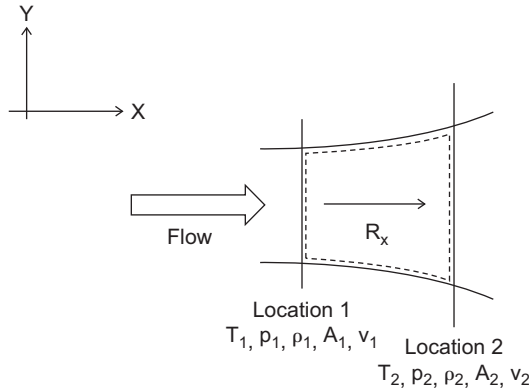


FIG. 10.10 General isentropic flow in an expanding channel. In general, we would be interested in the temperature, pressure, density, and velocity of the fluid for a given change in area. The fluid mechanics governing equations for compressible flows can be found in [Section 10.7](#).

$$R_x + p_1 A_1 - p_2 A_2 = \dot{m} v_2 - \dot{m} v_1 \quad (10.13)$$

Similarly, the first and second law of thermodynamics can be written as

$$h_1 + \frac{v_1^2}{2} = h_2 + \frac{v_2^2}{2} = h_0 \quad (10.14)$$

$$s_1 = s_2 = s \quad (10.15)$$

where $h = u + pV$ and h_0 is defined as the stagnation enthalpy (recall that u is the internal energy of the system, p is the pressure, and V is the volume of interest). The stagnation enthalpy is the enthalpy of the fluid that would be obtained when the fluid is decelerated to a zero velocity. For many compressible fluids, the enthalpy and the density are tabulated as functions of entropy and pressure. If the fluid is an ideal gas (or if it is valid to assume that the fluid is behaving as an ideal gas), the following equations can be used during problem solving

$$p = \rho RT \quad (10.16)$$

$$h_2 - h_1 = c_p(T_2 - T_1) \quad (10.17)$$

$$\frac{p}{\rho^k} = \text{constant} \quad (10.18)$$

where k is the ratio of specific heats $k = c_p/c_v$.

The Mach number (M) is defined as the ratio of the fluid velocity to the speed of sound

$$M = \frac{v}{c} \quad (10.19)$$

For most, if not all, biological applications, flow will be subsonic, in which the Mach number is less than 1. In this case a decrease in cross-sectional area causes an increase in velocity, whereas an increase in cross-sectional area causes a decrease in flow velocity. However, in supersonic flows ($M > 1$), the effects are exactly opposite. Flow accelerates in an expanding channel and decelerates in a narrowing channel.

Let us now consider the compressible flow through a channel with friction but no heat transfer. For these conditions, Eqs. (10.12) through (10.18) remain the same with the exception of Eqs. (10.13) and (10.15). This assumption is valid if the channel is relatively short. In Eq. (10.13), the reaction force in the x-direction must now include frictional forces (F_x), so that the conservation of momentum becomes

$$R_x + F_x + p_1 A_1 - p_2 A_2 = \dot{m} v_2 - \dot{m} v_1 \quad (10.20)$$

The fluid flow is no longer reversible because energy is lost to friction. Therefore, the second law of thermodynamics becomes

$$s_2 - s_1 = c_p \ln\left(\frac{T_2}{T_1}\right) - R \ln\left(\frac{p_2}{p_1}\right) \quad (10.21)$$

If the fluid can be assumed to be an ideal gas, we can also make use of the ideal gas laws, described in Eqs. (10.16) through (10.18).

If there is heat being transferred during the flow conditions but there is no friction, the equations to describe the flow field will take the following form. Continuity and conservation of momentum take the same form Eqs. (10.12) and (10.13), respectively (although there may be no surface forces acting on the flow). The first law of thermodynamics will simplify to

$$\dot{Q} = \dot{m} \left(h_2 + \frac{v_2^2}{2} - h_1 - \frac{v_1^2}{2} \right) \quad (10.22)$$

The second law of thermodynamics remains the same as Eq. (10.21).

In general, the equations just provided and discussed are all applicable to the diffusion of gas across the respiratory boundary. Under these conditions, it is possible that there is some exchange of energy during gas flow and potentially friction losses. Because the respiratory boundary is so thin, it is possible to use the more general formula for steady isentropic flows, but one may want to consider the more complete forms of the equations.

10.8 Disease conditions

10.8.1 Emphysema

Emphysema is a chronic disease that is associated with shortness of breath that prevents the patient from participating in strenuous activities. One of the most common causes of this disease is exposure to cigarette smoke, both from mainstream smoke (i.e., the smoker) and from sidestream smoke (e.g., secondhand smoke). This biological problem is associated

with the destruction of the alveolar sacs, leaving larger air pockets where several alveoli structures used to be found. This effectively reduces the surface area for oxygen and carbon dioxide exchange to occur over, which results in a reduction in the diffusion rate of each molecule. In severe cases of emphysema, alveoli merge, forming large sacs covered with fibrous tissue that ineffectively participate in gas exchange. These larger sacs are fairly rigid and also decrease the lung elasticity, making it more difficult to experience volume changes to generate the small pressure changes (i.e., Boyle's law) needed during inspiration and exhalation. Thus, there is a combination of a reduction in the surface area for exchange, a reduction in the diffusion properties of that surface, and a decrease in the ability to generate pressure differences to aid in air movement into and out of the lung cavities. Without the proper surface area for gas exchange, the body does not obtain enough oxygen to transport to tissues and not enough carbon dioxide leaves the body. The V/Q ratio is well above 0.8, under these conditions, indicating adequate blood flow (often with shunting) and/or increased ventilation (hyperventilation).

As the alveoli continue to break down, hyperventilation is unable to compensate for the decreased surface area for gas exchange. Therefore, the blood oxygen level begins to decrease and there is an overall constriction of the pulmonary blood vessels (hypoxic pulmonary vasoconstriction) to account for this lowered blood oxygen level. Unchecked, this places a large load on the right ventricle of the heart and can lead to right heart failure, making it more difficult to return venous blood to the right atria. If this continues, the entire cardiovascular system is placed under high pressure, which places a large load on the left ventricular heart muscle. To reverse this new load from the high blood pressure, the heart muscle begins to thicken, which as we have learned previously will lead to heart failure.

Emphysema is an irreversible condition. The only way to slow its progression is to have the patient stop smoking and avoid all other lung irritants. It is possible for the patient to breath bronchodilators to help increase ventilation of the lungs, but with significant destruction of alveoli, there is little that physicians can do to reverse the effects of emphysema. Patients are typically also placed on antiinflammatory agents to decrease the risk for the inflammatory system further attacking the damaged alveoli.

10.8.2 Asthma

Asthma can be a chronic condition, and/or seen acutely when influenced by environmental factors. Common environmental factors include smoke, allergens, cold air, and exercise. This biological problem occurs when the irritant causes bronchoconstriction, restricting the flow of air into the lungs. The gas exchange is compromised because of a decreased ventilation rate and diminished volume of fresh air per breath. The ventilation perfusion ratio (V/Q) is lower than 0.8 during an asthma attack, indicating that ventilation has decreased with little effect on the blood flow. Shunt is not present. Drugs that act to dilate the bronchioles are prescribed by physicians to alleviate the bronchoconstriction; these pharmaceuticals are designed to increase both blood flow and ventilation rate. Untreated asthma spirals into a proinflammatory state in which the bronchioles are inflamed and more reactive to irritants. This leads to thickening of the bronchiolar walls further and permanently restricting ventilation flow rate.

10.8.3 Tuberculosis

Tuberculosis results from an infection of the lungs by a specific bacterium. The bacteria may propagate in the conducting pathways and the alveoli. Like with most infections, the patient has a fever and general malaise, but during severe cases the lungs can begin to be destroyed. As this occurs, the patient will begin to “cough up” blood. There are some similarities between tuberculosis and any other respiratory infection. In general, the defense mechanisms in the lungs become overwhelmed by the invading pathogens. When the pathogens begin to grow within the lungs there is a large mucus buildup along the conducting pathways. This tends to increase the resistance to airflow and may disrupt gas exchange. If the pathogens destroy lung tissue, the surface area for gas exchange reduces and blood may enter the lung space in extreme conditions.

It has been estimated that one-third of the world’s population (and approximately 5% of the U.S. population) is currently infected with the bacteria that cause tuberculosis, *Mycobacterium tuberculosis*. New tuberculosis infections are occurring at a rate of approximately one person every 3 seconds, but the death rate from tuberculosis is falling. Therefore, the absolute number of people with tuberculosis is increasing. The disease is most prominent in developing countries, but more people in developed countries are contracting the tuberculosis bacteria because their immune systems are compromised by drug use or other immunosuppressant diseases such as acquired immunodeficiency (AIDS).

Tuberculosis infections manifest when *M. tuberculosis* reach the pulmonary alveoli, where they take over and replicate within alveolar macrophages. It is common for lymphatic vessels and blood vessels to transport bacteria to other locations within the body, but it is the lungs that are most susceptible to degradation from this bacteria. If the tuberculosis bacteria enter the bloodstream, patients have nearly a 100% fatality rate. In most cases of tuberculosis, a granuloma is formed within the lung tissue. The granuloma houses many immune cells that release cytokines to help destroy the bacteria and call other inflammatory cells to the infection site. However, a good portion of the *M. tuberculosis* organisms can remain dormant within the granuloma and cause an infection later.

Summary

10.1. The respiratory system provides the means for gas exchange between the atmospheric air and the cardiovascular system. It is divided into a conducting pathway (composed of the nasal cavity, the pharynx, the larynx, the trachea, and the bronchi) and a branching pathway, which eventually diverges into the alveolar sacs. The alveoli are the locations for gas exchange and provide approximately 70 m² of area for exchange. The respiratory boundary is composed of the alveoli epithelial cells, the capillary endothelial cells, and the fused laminae between these cells. Each lung is surrounded by a pleural membrane that facilitates the changes in lung volume to account for the movement of gases into and out of the lungs. This is based on Boyle’s law, which for a constant temperature system is represented as

$$P_1 V_1 = P_2 V_2$$

- 10.2.** The lungs go through an approximate 20% change in volume, which significantly affects the blood vessel area within the lungs. As a result of these large stresses, the Kirchhoff stress and the Green's strain are most applicable to relate the forces to the deformation. This is experimentally found to be represented as

$$\begin{aligned}s_{xx} &= a_1 E_{xx} + 0.6429 E_{yy} \\ s_{yy} &= a_2 E_{yy} + 0.6429 E_{xx}\end{aligned}$$

The separation distance for the respiratory boundary is also affected by the pressure of the respiratory and vascular system. This distance can be modeled as

$$h(\Delta P) = \begin{cases} 0 & \Delta P < -0.7 \text{ mmHg} \\ 0.5 \mu\text{m} + \frac{0.5 \mu\text{m}}{0.7 \text{ mmHg}} \Delta P & -0.7 \text{ mmHg} \leq \Delta P < 0 \text{ mmHg} \\ 0.5 \mu\text{m} + \frac{2 \mu\text{m}}{75 \text{ mmHg}} \Delta P & 0 \leq \Delta P < 30 \text{ mmHg} \\ 1.3 \mu\text{m} & \Delta P > 30 \text{ mmHg} \end{cases}$$

- 10.3.** The pressure and the volume of the lungs are altered based on the movement of the ribs and diaphragm. As the diaphragm moves downward and the ribs move outward, the lungs expand and experience a temporal reduction in pressure. The opposing movements of the diaphragm and lungs cause the lungs to shrink and experience a temporal increase in pressure. Under normal conditions, the tidal volume is approximately 500 mL (of which 350 mL is used for gas exchange), and there are approximately 12 to 15 breaths per minute. In extreme conditions, the lungs can move approximately 4800 mL of air per breath, which is using all of the inspiratory reserve and the expiratory reserve. There is 1200 mL of residual volume which maintains the alveolar space open.
- 10.4.** Adequate respiration requires that the ventilation rate of the lungs be matched with the blood flow rate through the pulmonary circulation. The ventilation rate (V) is a measure of the ability of the lungs to take in and exchange fresh atmospheric air, whereas the perfusion rate (Q) is a measure of the flow through the capillaries. If the V/Q ratio is low, not enough fresh air is entering the lungs. In contrast, if the V/Q ratio is high, there is not enough flow to support gas exchange. Under physiological conditions, the V/Q ratio is close to 0.8, whereas under pathological conditions the V/Q ratio can decrease (e.g., emphysema) or increase (e.g., pulmonary embolism).
- 10.5** Oxygen and carbon dioxide diffusion is based on the solubility of the gas within blood. Henry's law formulates this as

$$P = \frac{\text{Gas concentration}}{\text{Solubility coefficient}}$$

The solubility coefficients for oxygen and carbon dioxide in blood are 0.024 and 0.57, respectively. Gas diffusion also can be modeled as the movement of gases across a semipermeable boundary. In general, we would write the mass balance equations (the equations for oxygen are shown) as

$$Ru_G(C_{O_2-gas}(x + \Delta x) - C_{O_2-gas}(x)) + J\Delta x = 0$$

and

$$Ru_B(C_{O_2-blood}(x + \Delta x) - C_{O_2-blood}(x)) - J\Delta x = 0$$

assuming that the concentration of the gas remains constant within the channel.

- 10.6.** Oxygen has a very low solubility in blood, and therefore, another mechanism for oxygen transport is needed. As we know, oxygen diffuses into the red blood cell and becomes associated with the heme groups of hemoglobin. Carbon dioxide has a much more complicated transport mechanism. Approximately 70% of the carbon dioxide enters the red blood cells and interacts with carbonic anhydrase to form hydrogen and bicarbonate ions; 25% of carbon dioxide associates with free amino groups on the hemoglobin protein. The remaining carbon dioxide is transported directly in the blood.
- 10.7.** Gases are fairly compressible, and it is important to develop the relationships for compressible fluid flow. For a steady isentropic flow, the governing equations are

$$\rho_1 v_1 A_1 = \rho_2 v_2 A_2 = \dot{m}$$

$$R_x + p_1 A_1 - p_2 A_2 = \dot{m} v_2 - \dot{m} v_1$$

$$h_1 + \frac{v_1^2}{2} = h_2 + \frac{v_2^2}{2} = h_0$$

$$s_1 = s_2 = s$$

For an ideal gas, we can make use of the following relationships

$$p = \rho RT$$

$$h_2 - h_1 = c_p(T_2 - T_1)$$

$$\frac{p}{\rho^k} = \text{constant}$$

If there is friction without heat transfer, we need to consider

$$R_x + F_x + p_1 A_1 - p_2 A_2 = \dot{m} v_2 - \dot{m} v_1$$

and

$$s_2 - s_1 = c_p \ln\left(\frac{T_2}{T_1}\right) - R \ln\left(\frac{p_2}{p_1}\right)$$

If there is heat transfer without friction, we need to consider

$$\dot{Q} = \dot{m} \left(h_2 + \frac{v_2^2}{2} - h_1 - \frac{v_1^2}{2} \right)$$

- 10.8.** Emphysema, asthma, and tuberculosis are common diseases that affect the respiratory system. Emphysema is characterized as a destruction of the respiratory boundary, and therefore, there is an ineffective transport of gases between the alveolar space and the cardiovascular system. Asthma is characterized by a severe constriction of the conducting pathways that reduces the ventilation of the lungs. Tuberculosis is characterized by an infection within the lungs that can either increase the resistance to air movement or break down the respiratory boundary.

Homework problems

- 10.1.** Describe the passage of air from the nose to the alveoli and discuss some of the important structures within the respiratory system. Pay close attention to the structure–function relationship of the organs.
- 10.2.** Describe the mechanism of breathing, paying close attention to the movement of the ribs and the diaphragm.
- 10.3.** The surfactant along the alveolar wall is present to prevent the alveoli from collapsing. How does this fluid perform this function?
- 10.4.** Gas exchange along the alveolar wall occurs rapidly and efficiently because the driving forces are large, oxygen and carbon dioxide are lipid soluble, and the surface area for diffusion is large. Describe the role of each of these during exchange.
- 10.5.** The bronchioles in the respiratory system are analogous to the arterioles in the cardiovascular system. How?

Homework problems (cont'd)

- 10.6. The differences among the atmospheric, the interpulmonary, and the intrapleural pressures determine the direction of airflow within the lungs. How would this relationship change at different elevations at which the atmospheric pressure could change drastically?
- 10.7. Under a disease condition, the separation distance for the alveolar gas and the capillary gas can be described as

$$h(\Delta P) = \begin{cases} 0 & \Delta P < -0.7 \text{ mmHg} \\ 0.5 \text{ } \mu\text{m} + \frac{0.5 \text{ } \mu\text{m}}{0.5 \text{ mmHg}} \Delta P & -0.7 \text{ mmHg} \leq \Delta P < 0 \text{ mmHg} \\ 0.5 \text{ } \mu\text{m} + \frac{2 \text{ } \mu\text{m}}{50 \text{ mmHg}} \Delta P & 0 \leq \Delta P < 30 \text{ mmHg} \\ 1.7 \text{ } \mu\text{m} & \Delta P > 30 \text{ mmHg} \end{cases}$$

Plot separation distance h as a function of pressure and compare this with the normal case. What has happened under these conditions, and what are some of the possible characteristics of the disease?

- 10.8. Under exercise conditions, predict what the tidal volume would be. Why would this be necessary? Where would the extra volume needed to accommodate these changes be taken from: the inspiratory reserve volume or the expiratory reserve volume or both?
- 10.9. What would happen if there was no residual volume within the lungs?
- 10.10. The solubility coefficient for carbon dioxide is an order of magnitude larger than the solubility coefficient for oxygen. What does this suggest about gas transport within the blood, and is this accounted for by the known processes of gas transport in the blood?
- 10.11. Using [Table 10.1](#), calculate the solubility coefficients for nitrogen and carbon monoxide, assuming that the cross-sectional area and diffusion distance are the same.
- 10.12. In the upper atmosphere, the oxygen concentration drops to 15% of the total composition of air at an air temperature of 5°C. Assume that the nitrogen concentration makes up the difference in air composition. Calculate the respiratory rate needed to maintain the body oxygen requirements of 250 mL/min. Assume that the tidal volume remains the same, that 35% of the tidal volume enters the bloodstream, and that all of this would be used to meet the body's oxygen requirements. In addition, assume that the pressure reduces to 700 mmHg.

Homework problems (cont'd)

- 10.13.** Assume at particular atmospheric conditions, a person's respiratory rate increases to 25 breaths per minute because the body needs 350 mL/min of oxygen. If the oxygen concentration in the atmosphere is 21% and that percent usage of oxygen is 40%, calculate the air pressure if the temperature is 32°C.
- 10.14.** The carbon dioxide concentration in a gas at the inlet of a semipermeable oxygenator is 5 mmHg and the carbon dioxide concentration in blood within the oxygenator is 45 mmHg. Assume that the radius of the channel is 4 cm and that the thickness of the boundary is 100 μm . Calculate the change in carbon dioxide concentration with distance if the diffusion coefficient is $2 \times 10^{-4} \text{ cm}^2/\text{s}$, the gas velocity is 5 cm/s, and the blood velocity is 10 cm/s.
- 10.15.** Air is flowing from the alveoli to the trachea and is following an isentropic flow condition. Calculate the velocity at which air is leaving the alveoli if the temperature within the alveoli is 37°C and that in the trachea is 33°C. The velocity of air within the alveoli is 50 mm/s and the specific heat for air (c_p) is equal to 30.02 mJ/(kg mol K).
- 10.16.** Is there heat being transferred under the conditions in problem 10.15 if you can assume steady flow and the alveoli radius is equal to 100 μm ? What is the rate of heat transfer?
- 10.17.** What is the change in entropy under the conditions in problem 10.15, if the pressure is 1.1 atm in the trachea and 1.15 atm in the alveoli?

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Intraocular fluid flow

LEARNING OUTCOMES

- Describe the physiology of the eye
- Identify regions within the eye that are filled with fluid
- Discuss how the eye senses light intensity and the wavelength of light
- Evaluate the mechanism for aqueous humor formation
- Explain aquaporins and their function within the body
- Model the flow through aquaporin channels
- Describe the flow of aqueous humor through the eye
- Calculate the flow of aqueous humor through regions of the eye
- Evaluate intraocular pressure and describe what regulates intraocular pressure
- Model the time-dependent changes in intraocular pressure
- Identify common ways to measure intraocular pressure
- Discuss common disease conditions that affect the eye

11.1 Eye physiology

The eye is part of the specialized senses and is an extremely versatile and sensitive visual instrument. The eye is spherical, with an average diameter of 24 mm, and is located within the eye socket of the skull (also termed the *orbit*). Also within the orbit are the extrinsic eye muscles, which control the movement of the eye; the optic nerve, which transmits visual information to the brain; the blood vessels, which provide the eye with nutrients and are responsible for the removal of wastes; and fat tissue, which acts to support and cushion the eye (Fig. 11.1). The exterior wall of the eye is composed of three layers. The first layer of the eye (most exterior layer) is termed the *fibrous tunic*, and it consists of the sclera and

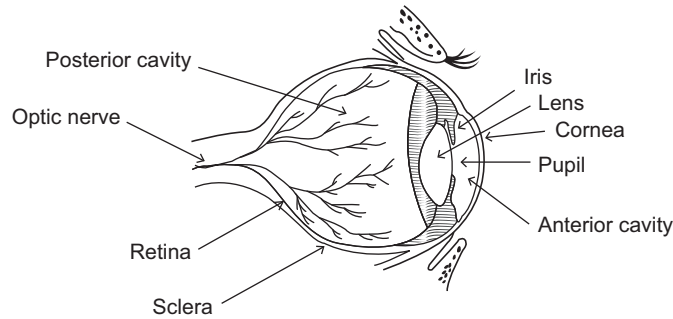


FIG. 11.1 Anatomical structures of the eye, showing the major optical and sensory components. The anterior cavity and the posterior cavity experience fluid movement. The anterior cavity is continuously forming and circulating aqueous humor, and the posterior cavity experiences a slow flow of aqueous humor.

the cornea. The primary functions of the fibrous tunic are to provide the mechanical support for the eye, to provide a location for extrinsic muscle attachment, and to provide protection for the interior structures of the eye. The sclera covers most of the eye structure and is composed of connective tissue (mostly collagen and elastin). The sclera is the white portion of the eye, and it gets this color from the high concentration of collagen fibers present within this region. Small blood vessels and nerves are located within the sclera. The cornea is continuous with the sclera and is located on the anterior side of the eye, protecting the eye from mechanical injury and/or contamination. The cornea also protects the iris and lens of the eye. Interestingly, the cornea contains no blood vessels and must obtain enough oxygen and nutrients through diffusion.

The second layer of the eye (middle layer) is termed the *vascular tunic* (or uvea), and it contains a large quantity of blood vessels and lymphatic vessels. The primary functions of the vascular tunic are to provide a pathway for blood vessels and lymphatic vessels, to secrete and absorb aqueous humor (more on this in [Sections 11.3 and 11.5](#)), to control the amount of light that enters the eye, and to control the shape of the lens. The blood and lymphatic vessels are housed with the intrinsic muscles of the eye (these are smooth muscle cells). The intrinsic muscles can partially regulate the shape of the eye through dilatory and contractile events. Also included within this layer are the iris, the ciliary bodies, and the choroid. The iris is primarily composed of smooth muscle cells, which contain blood vessels and pigment cells. When these smooth muscle cells contract, the shape and the size of the pupil change, which effectively regulates the amount of light that enters the eye. There are two types of smooth muscles cells, the constrictor muscles and the dilatory muscles; as the names imply, one constricts the pupil and the other dilates the pupil. Pigment cells, which are also termed *melanocytes*, partially provide the iris with its color. Like melanocytes in the skin, pigment cells produce melanin at a particular concentration. The concentration of melanin and the light scattering properties of the fluid surrounding the iris determines the overall pigmentation of the eye. The ciliary bodies are a specialized region of the vascular tunic that is composed of a large number of ciliary muscles. The ligaments that are associated with these muscles are attached to the lens, holding it in place to collect and focus all of the light that enters through the pupil. The choroid is the name given to the purely vascular regions of the vascular tunic.

The third layer of the eye (innermost layer) is termed the *neural tunic* or the *retina*. The inner layer of the neural tunic is termed the *neural part* and contains all of the photoreceptors of the eye. The outer layer of the neural tunic is termed the *pigmented part* and acts to absorb and not reflect light that has passed through the neural part, thus preventing the light returning into the eye structure. There are two types of photoreceptors located within the neural part of the neural tunic. The first type of receptor is termed the *rods*, which are sensitive to the intensity of light and not the wavelength (color) of the light. The rods allow us to see structures under low light conditions. The second type of photoreceptor is termed the *cones*, which enable us to distinguish between different wavelengths of light but they are not as sensitive to intensity. There are three types of cones to help determine different colors, but they require a higher-intensity light to function properly (thus under low light conditions, it is difficult for the eye to discriminate between different colors). There is a higher density of rods along the periphery of the eye, whereas there is a higher density of cones along the center of the eye.

The interior portion of the eye is hollow and is composed of two chambers: the posterior cavity and the anterior cavity, which are divided by the ciliary bodies and the lens. The posterior cavity (also known as the *vitreous chamber*) contains the vitreous body. This chamber makes up approximately 90% of the hollow portion of the eye. The vitreous body primarily helps maintain the shape of the eye. The vitreous body is a gel (which can be considered as a very viscous fluid) because cells within this cavity produce and secrete a large quantity of collagen fibers and proteoglycans. The collagen fibers and the proteoglycans are highly charged and can organize and absorb large quantities of water. This water is associated closely with the charged molecules and is not as free to move compared with water in the bulk phase. The vitreous body is produced only during fetal development and is not replaced during the remaining portion of life.

The anterior cavity is divided into an anterior chamber and a posterior chamber and is filled with the biofluid aqueous humor. The anterior chamber is bounded by the cornea and the iris, and the posterior chamber is bounded by the iris and the ciliary bodies/lens. The aqueous humor also helps maintain the shape of the eye, but it has other functions as well. The aqueous humor is continually formed and circulates through the anterior cavity and along the surface of the retina. Some aqueous humor enters the vitreous chamber, and its movement through this chamber can be described by diffusion laws better than fluid mechanics laws, because of the gel that fills the cavity. The formation of aqueous humor will be discussed extensively in [Section 11.3](#), and the flow of aqueous humor will be discussed in [Section 11.5](#).

The remaining structure of the eye that we will describe here is the lens. The lens is held in place by ligaments attached to the ciliary bodies. The function of the lens is to focus incoming light onto the photoreceptors located within the retina. To accomplish this task, the shape of the lens can be altered. Cells within the lens are organized into concentric circles, layered throughout the lens. These cells are all covered by a fibrous capsule mainly composed of elastic fibers that tend to make the lens less spherical. Elastic fibers along the periphery of the lens are associated with the ciliary body ligaments that mechanically pull on the lens to make it more spherical. Cells within the interior of the lens are termed *lens fibers*. These cells do not have a nucleus or other organelles, but instead are filled with transparent proteins called *crystallins*. Crystallins give the lens the ability to focus light onto the retina. In fact, the aqueous humor and the vitreous body also function as a liquid lens that helps further focus the light onto the retina. Light is primarily focused by changing the shape of the lens

and small changes to the shape of the eye. When viewing objects that are at a distance, the lens is flat and elongated. However, when the object that is being viewed is close, the lens becomes more spherical. This change in shape is accomplished by a contraction of the ciliary muscles, which pulls the choroid layer of the eye toward the lens, causing the associated ligaments to relax. Because of this reduced tension on the lens, the elastic lens becomes thicker and rounder, which causes the incident light to bend more rapidly.

As stated previously, the retina contains both rod cells and cone cells. There are approximately 125 million rod cells and 6 million cone cells in each eye. Combined, these cells account for more than 70% of all of the sensory receptors within the body. Rods are more sensitive to light intensity, they do not distinguish between colors, and they help us to see at night. Cones can distinguish between different wavelengths of light but are not as sensitive to intensity and therefore do not play an important visual role when it is dark (hence everything looks gray under low-intensity light). Each rod or cone cell is composed of an outer segment that is composed of highly membranous discs. These discs contain the visual pigments that consist of a light-absorbing pigment, retinal, bounded to a membrane protein, opsin. The protein opsin varies in structure based on the photoreceptor type.

The opsin that can be found in rods combines with retinal to form the visual pigment rhodopsin. As rhodopsin absorbs light, it experiences a conformational change that triggers a signal transduction pathway, which ultimately leads to the membrane potential of rod cells to decrease. In fact, when rod cells are in the dark, the cells are in a depolarized state, and because of this excited state, the cells release an inhibitory neurotransmitter to reduce electrical signal impulses. As the membrane potential of rod cells decreases during light stimulation (becomes more negative), the release of inhibitory neurotransmitters is slowed/stopped and the cells can begin to send signals through the retina to the brain. Color vision occurs through the presence of three types of cone cells within the retina. Each of these cone cells has its own type of opsin that associates with retinal to form a particular photopsin. Each type of photopsin has an optimal wavelength of light that it can absorb; either yellow (peak wavelength 430 nm), green (peak wavelength 540 nm), or blue (peak wavelength 570 nm) light. Different shades of these colors can be viewed based on the differential stimulation of each of these three types of cone cells.

11.2 Eye blood supply, circulation, and drainage

Many of the characteristic properties of other vascular beds apply to the circulation of the eyes. However, this section will focus on some unique properties. Probably the most unique thing about the circulation of the eye is that all cells must have a readily available supply of blood (e.g., generally within 50 to 100 μm from a capillary, although this is not unique, how the eye accomplishes this task is somewhat unusual) and that the blood vessels cannot interfere with the transmission of light through the eye and the sensing of light by the optic sensors. In general, the blood vessels of the eye are divided into the uveal circulation and the retinal circulation. The uveal vessels supply the choroid, the ciliary bodies, the iris, and the portion of the retina that contains photoreceptors (note that the retina receives nutrients by diffusion and the vessels do not permeate that section of the eye extensively). The retinal vessels supply all other locations of the eye with blood. Interestingly, during development, blood

vessels exist along the cornea and the lens. However, by birth, these vessels have been pruned from the vascular tree (through a process termed *rarefaction*), so that they do not interfere with light transmission through the eye. These structures, which no longer have a direct blood supply, are supplied with nutrients by the flow of aqueous humor (refer to [Sections 11.3 and 11.5](#)). Wastes are also removed by the flow of aqueous humor.

Blood is supplied to the eye and some of its surrounding tissue by the ophthalmic artery, which is a branch of the internal carotid artery. Each ophthalmic artery enters the orbit by the optic canal, in parallel with the optic nerve ([Fig. 11.2](#)). Various vessels that branch off from the ophthalmic artery along its length supply different regions of the eye with blood. Additionally, some of these branches of the ophthalmic artery end up supplying various tissues associated with the eye. For example, the dorsal nasal artery supplies the lacrimal sac with blood, and the medial and lateral palpebral arteries supply the eyelids with blood. In contrast to the one large artery that supplies the eye with blood, two large veins exist to drain blood from the eye and its surrounding structures. Blood leaves the orbit through either the superior ophthalmic vein or the inferior ophthalmic vein, which combine and drain blood into the cavernous sinus and then pass into the internal jugular vein. In general, the superior locations of the eye and the surrounding tissue are drained by the superior ophthalmic vein, whereas the inferior locations are drained by the inferior ophthalmic vein.

The small arteries of the eye play a significant role in the formation of aqueous humor, which will be discussed in the following sections. However, it is important to detail how blood is passed into these important structures. Arterioles that supply the rectus muscle group of the eye are unique in that they do not terminate in capillary beds. In the rectus muscles, the capillary beds are side branches of the small arterioles and the main feeding arterioles

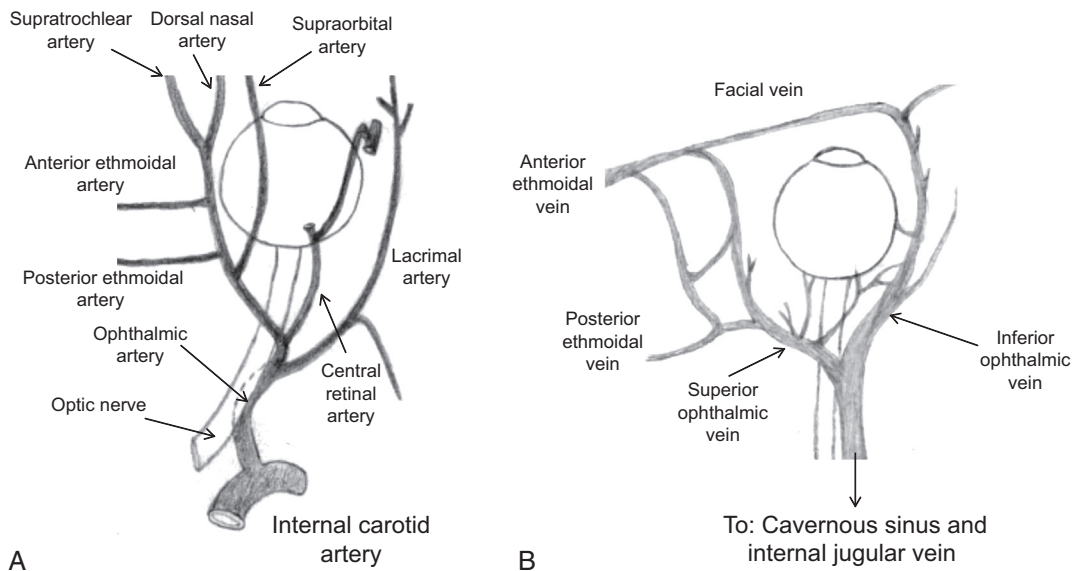


FIG. 11.2 Blood distribution within the ophthalmic artery system (A) and ophthalmic venous system (B). Some of the major tributaries of the vessels are highlighted on this schematic.

continue to penetrate the eye and emerge along the orbital surface posterior to the muscle tendons. These arteries continue to progress forward along the eye, at which point their name changes to anterior ciliary arteries. In total, there are typically seven anterior ciliary arteries, which penetrate from each of the different rectus muscles along the eye. Almost immediately distal to the rectus muscle tendons, the ciliary arteries bifurcate; one branch remains along the surface of the eye, whereas the second branch penetrates the sclera to traverse toward the ciliary body (Fig. 11.3). The branch that remains along the surface of the eye is named the episcleral artery, and it supplies the conjunctiva with blood. The branch of the anterior ciliary artery that penetrates the sclera is renamed the major perforating artery. This vessel branches a number of times as it progresses through the tissue space toward the ciliary bodies. These various branches reconnect, forming the anastomosed intramuscular arterial circle. Branches from the major intramuscular arterial circle enter the ciliary processes (Fig. 11.4), which contain a very dense intertwined aggregate of small arterioles, capillaries, and venules. This intertwined and interconnected vascular network is surrounded by a small layer (typically two cells thick) of epithelium, which separates blood from the aqueous humor and is responsible for aqueous humor formation. The capillaries of the ciliary processes are somewhat unusual in that they typically have a larger diameter than the feeding arterioles with little to no fenestrae (“windows” or openings between or through the cells). This helps increase the surface area for aqueous humor formation and helps regulate the formation of aqueous humor. The ciliary processes contain large venules that run in parallel with veins from the iris, where they converge into the choroidal veins. It is interesting to note that there are typically few episcleral arteries that supply the ciliary processes with blood, but there are significantly more veins coming from the ciliary processes. This is due to the presence of veins that do not collect blood from capillary beds, but instead collect aqueous humor back into the circulation. These veins collect aqueous humor from the canals of Schlemm, which will be discussed in later sections of this chapter.

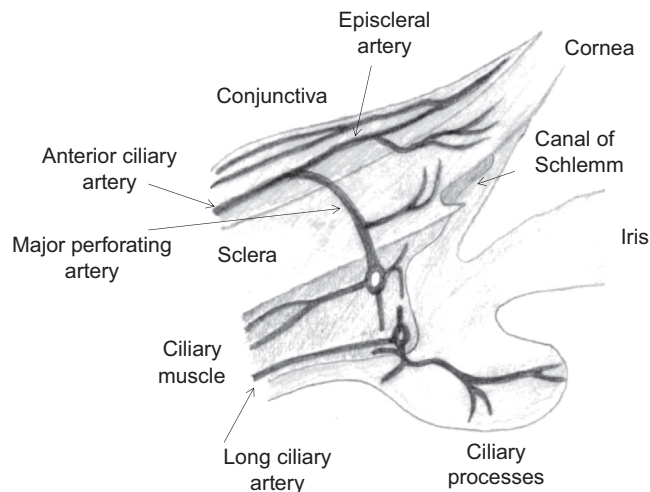


FIG. 11.3 Branches of the anterior ciliary artery that provide blood to the conjunctiva (episcleral artery) and the ciliary bodies (major perforating artery). This illustrates the redundancy within the optic circulation.

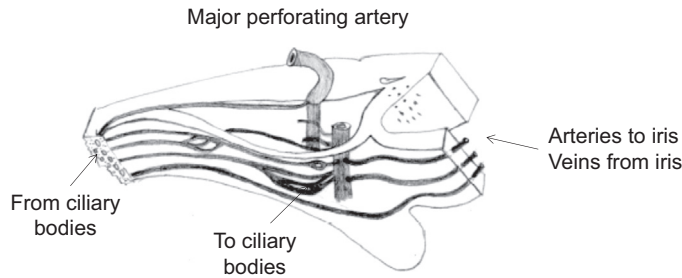


FIG. 11.4 Detailed view of the blood supply to the ciliary processes, by the major perforating artery and the major arterial circle. The venous circulation from the ciliary processes and the iris converge and drain into the vortex veins.

The blood–retinal barrier is the critical structure for the separation of blood constituents and eye constituents, and the breakdown of this barrier would cause a massive interference with vision. The blood–retinal barrier is composed of the retinal capillary endothelial cells and the epithelium of the retina. The endothelial cells are relatively thick, have extensive tight junctions along the cell–cell boundaries, and are not fenestrated. It has been shown that the presence of extensive tight junctions is what is responsible for the diffusion restriction in both directions at the blood–retinal barrier. In contrast, the endothelial cells of the choroid capillaries are highly permeable and this has been suggested to play a role in fluid uptake and diffusion of nutrients to the retina. For instance, vitamin A is necessary for retina functions and appears to be obtained by diffusion out of the choroid capillaries followed by pinocytosis by the retinal epithelium. Similarly, the colloidal tissue oncotic pressure is significantly higher than the retinal colloidal oncotic pressure, which will act to facilitate water movement out of the retina into the choroid capillaries. This water movement will then locally increase the hydrostatic pressure to aid in water movement through the sclera and eventually out of the eye. Overall, the circulation of the eye is efficiently designed to provide nutrients and collect water/wastes from the eye, while not disrupting vision.

11.3 Aqueous humor formation

Aqueous humor is continually being formed and reabsorbed within the anterior and posterior chambers of the eye. The formation and reabsorption of aqueous humor is balanced by the volume of fluid within the eye and the intraocular pressure ([Section 11.6](#)). Aqueous humor is formed at a rate of approximately $2\ \mu\text{L}/\text{min}$ within the anterior cavity. The majority of this is secreted into the posterior chamber of the anterior cavity from the ciliary processes, which are projections from the ciliary bodies. Aqueous humor can flow into the anterior chamber from the posterior chamber by passing through the pupil. In addition, some of the aqueous humor can freely diffuse into the posterior cavity to wet the retina. This provides an important route for nutrient delivery and waste removal to nonvascularized structures of the eye. The ciliary processes are located behind the iris where the ciliary muscle attaches to the eye. The ciliary processes have a very large surface area associated with them, approximately $6\ \text{cm}^2$ per eye. Secretory epithelial cells cover the ciliary processes, which are also highly vascularized.

Aqueous humor is actively secreted from the ciliary processes. The epithelial cells that line the ciliary processes regulate the composition of aqueous humor. To form aqueous humor, sodium ions are actively (through the use of adenosine triphosphate) transported out of the ciliary epithelial cells. Chloride and bicarbonate ions diffuse out of the ciliary processes to maintain the electrical neutrality of the intercellular space. The efflux of these ions into the intercellular space causes an increase in the osmotic pressure of the intercellular space. To counterbalance the increase in intercellular space osmotic pressure, water moves from the blood vessels underlining the ciliary epithelial cells into the intercellular space. As water moves into the intercellular space, it flows across the ciliary processes into the posterior chamber. Other molecules, such as glucose and amino acids, can be transported within the aqueous humor if they migrate or are transported into the intercellular space. Therefore, aqueous humor formation is induced by the active transport of sodium ions and the passive movement of water.

The composition of aqueous humor is similar to that of arterial plasma and cerebrospinal fluid. However, there is a significantly higher concentration of ascorbate in the aqueous humor than in the blood plasma, and there is a marked reduction in proteins and blood cells (no cells are found suspended in the aqueous humor). Ascorbate is an ester of vitamin C and is used to maintain the health of the lens. With a deficiency in ascorbate, it is common for cataract formation to be observed and macular degeneration to proceed. Plasma proteins cannot be filtered by the ciliary bodies, and therefore, proteins account for approximately 0.02% of the total aqueous humor composition (whereas proteins account for nearly 10% of the plasma composition). The major functions of aqueous humor include maintaining intraocular pressure, providing nutrients to the cornea and lens (which are avascular), and removing wastes from the cornea and lens.

11.4 Aquaporins

Aquaporins are transmembrane proteins that regulate the flow of water into and out of cells. For many years, it was thought that water movement into and out of the cell was (1) not regulated in any manner and (2) could be accounted for by simple diffusion across the cell membrane. However, the rapid movement of water in aqueous humor formation could not be described by simple diffusion. In the early 1990s, aquaporins were discovered, and it was found that they can selectively control water movement into and out of cells. One of the critical functions of aquaporins is that whereas they allow the passage of water they prevent the passage of ions. If aquaporins allowed ions through their channels, all ion concentration gradients across the cell membrane would approach zero (i.e., all ions would be in equilibrium with themselves) and therefore the cells would not be able to perform many of the critical functions that depend on the concentration gradient of various molecules (e.g., many transport processes that rely on an electrochemical gradient would fail). Furthermore, if ions were allowed to pass through aquaporins, the amount of energy that cells would expend on maintaining the necessary ion concentration gradients across the cell for the cell to function as we know, would exceed the amount of energy produced during cellular respiration (if the cell could even maintain a concentration gradient under these conditions).

Aquaporins are found in a high concentration in the epithelial cells that produce aqueous humor (as well as other epithelial cells that allow water to move readily across their membrane, e.g., epithelial cells in the kidney). These pores allow water molecules through in a single file. To understand how aquaporins regulate water movement into a single file and prevent the movement of other ions, it is important to understand the three-dimensional (3D) structure of the aquaporin protein. An aquaporin channel is composed of six transmembrane α -helices, with both the amino and carboxyl terminal on the cytoplasmic side of the membrane. Two of the five loops that connect the six transmembrane helices are extremely hydrophobic. One of these loops is on the intracellular side of the membrane, and the other is on the extracellular side of the membrane. The two hydrophobic loops contain a three-amino-acid sequence, termed the *asparagine–proline–alanine (NPA) motif*. The NPA motif folds back into the aquaporin channel created by the six transmembrane helices. In 3D space, the folding back of these two domains resembles an hourglass shape (or a bottle neck for flow). This hourglass constriction restricts water molecules to a single file as they are passing through the channel. In addition, the hydrophobic portion “coats” one side of the channel (the reason for this and the effect this has on ions will be discussed later). The restriction of water most likely occurs because of an electric field created by the charges on the protein structure, inducing the majority of the channel’s core to be hydrophobic. This electric field also dictates the direction of the water molecules as the flow through the channel. As water molecules enter the channel, they typically are oriented with the oxygen atom facing the entrance of the channel. As the molecules enter the NPA motif, the water molecules flip, so that the oxygen atom is facing toward the channel’s exit. It is thought that the orientation of oxygen changes as a result of a hydrogen-bonding event with the two asparagine molecules within the NPA motif. Therefore, because each water molecule must be reoriented to pass through the aquaporin channel and it can be reoriented only by interacting with the two asparagine molecules within the NPA motif, only one water molecule can flow through the channel at a time. Through these two restrictions it has been observed that the permeability of aquaporin channels toward water molecules is on the order of $6_E - 14 \text{ cm}^3/\text{s}$, which allows approximately 10^9 water molecules through each pore per second.

There is a second constriction of the aquaporin channel, usually toward the extracellular side of the cell membrane, which acts to restrict the movement of other molecules through the channel. This selectivity filter is termed the *aromatic/arginine selectivity filter* in aquaporin channels. The selectivity filter is a grouping of amino acids that interact only with water molecules and helps them through the narrowing created by this filter. Other molecules that do not interact with the selectivity filter cannot pass through this narrowing. The aromatic ring weakens the hydrogen bonds between water molecules, and then the partial negative charge on the oxygen atom interacts with the positive charge on the arginine. The interaction between the oxygen and the arginine allows water through the channels and prevents the passage of other molecules, especially protons.

All of the restrictions that were described are physically smaller than hydrated ions; remember that all ions that are in the body are hydrated (e.g., a sodium ion, which has a positive charge, will typically traverse through the biological substrates, with four water molecules associated with it; the partial negative charge on the water’s oxygen form weak hydrogen bonds to the sodium ion; a similar analysis can be made for all other ions). However, ions in solution can dehydrate and this is how ions typically pass through biological

ions channels. To dehydrate an ion, a significant amount of energy would be needed, and typically this is counterbalanced by other binding events. In the case of the aquaporin channel, the location where the ions would need to become dehydrated to pass through the pore restriction is associated with hydrophobic amino acid regions. A hydrophobic surface cannot provide a temporary bonding event for a hydrophilic ion. Thus an ion would need an energy source to break the water hydrogen bonding events and not create new hydrogen bonding events. This significant amount of energy is not readily available, which effectively prevents ions from moving through aquaporin channels.

Four aquaporin channels associate with each other in the membrane, so that in one location there are four possible passageways for water to move through the cell membrane. Each aquaporin channel can have a slightly different protein structure. There are at least 4 different aquaporins in mammals and upward of 10 aquaporin channels found in plants. The different structures between the aquaporin molecules may allow for the movement of a small quantity of ions or other solutes (such as glycerol and small sugars) through the channels, although most aquaporin channels restrict ion and solute movement. In addition, some aquaporin channels respond to stimuli from external hormones or other paracrine molecules. On stimulation, the rate of water movement (and possibly the direction of movement) can be altered.

It is important to remember that aquaporins do not actively transport water across the cell membrane; instead they facilitate the diffusion of water across the cell membrane. Because of the slow diffusion of water across the lipid bilayer, aquaporins effectively increase the overall rate of water movement across the cell membrane.

11.5 Flow of aqueous humor

Immediately after the formation of aqueous humor (which uses aquaporin channels described in the previous section) within the intercellular space of the ciliary processes, aqueous humor flows between the ciliary muscle ligaments that attach to the lens (Fig. 11.5). From here, the aqueous humor flows through the pupil into the anterior chamber of the eye. The fluid flows throughout the anterior chamber and passes through a trabeculae

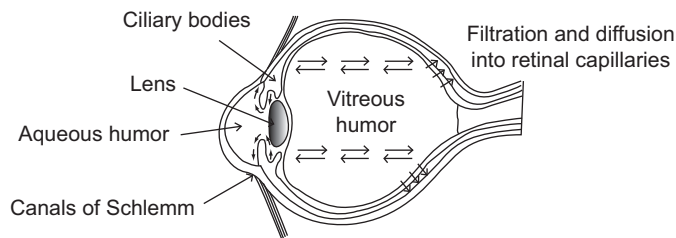


FIG. 11.5 Anatomical structures salient for the formation of aqueous humor. Aqueous humor is formed at a rate of approximately $2 \mu\text{L}/\text{min}$ within the ciliary bodies. It then flows between the lens and the iris to fill the anterior chamber. Aqueous humor can leave the anterior chamber by the canals of Schlemm or diffuse into the posterior chamber, and fluid within this chamber can leave by diffusion into the retinal capillaries. Arrows depict the movement of aqueous humor through the eye. (Modified from Guyton and Hall, *Textbook of Medical Physiology*, 10th edition, Saunders, 2000).

meshwork. The trabeculae act as a filter for the aqueous humor, removing any debris that may enter the aqueous humor. The debris may come from a bacterial infection or hemorrhaging of the vascular system within the ciliary processes. After passing through the trabeculae, the aqueous humor passes into the canals of Schlemm. Each canal of Schlemm is a thin-walled vein that connects to the extraocular veins with the vascular tunic. The canals of Schlemm extend around the entire eye, collecting aqueous humor from all locations. Each canal of Schlemm is lined by highly permeable endothelial cells that allow the passage of red blood cells (if any enter the aqueous humor) and proteins into the vascular network of the eye such that these molecules do not accumulate within the eye. Although the canal of Schlemm is a blood vessel, it is typically never filled with blood because the flow rate of aqueous humor is very high. Under normal conditions, the rate of removal of the aqueous humor is equal to the rate of formation (i.e., approximately $2 \mu\text{L}/\text{min}$). This can be quantified by a mass balance of the aqueous humor.

$$\rho v A_{in} = \rho v A_{out} \quad (11.1)$$

The flow of aqueous humor through many of the portions of the eye can be represented by a simple pressure–flow relationship. In particular, an accurate representation of flow through the canals of Schlemm can be calculated from

$$\frac{dQ}{dx} = \frac{p_{IO} - p(x)}{R} \quad (11.2)$$

where Q is the flow rate along the canals of Schlemm, p_{IO} is the intraocular pressure, $p(x)$ is the local pressure within the canal, and R is the resistance to flow primarily generated from the trabecular mesh. In this formulation, x is the distance along the canal's length. The flow through the canal can be described by low Reynolds number flow properties, and the pressure gradient can then be approximated from the flow between two parallel infinite plates, assuming a 2D uniform problem. The pressure gradient can therefore be calculated from

$$\frac{dp}{dx} = \frac{12\mu Q(x)}{zh^3(x)} \quad (11.3)$$

where μ is the aqueous humor viscosity, z is the thickness of the tissue, and $h(x)$ is the local spacing between walls in the channel. Using [Eqs. \(11.2\) and \(11.3\)](#), the flow rate or pressure gradient through the canals of Schlemm can be obtained.

Very small quantities of aqueous humor enter the posterior cavity of the eye, instead of following the pathway described previously. Typically, on the order of a few nanoliters of aqueous humor enter the posterior cavity every hour. As stated earlier, this portion of the aqueous humor does not “flow” through the posterior cavity because it is filled with the vitreous body, which is a highly charged gel. Remember that the vitreous body does not flow, although it allows for a very slow diffusion of aqueous humor through it. The aqueous humor will typically wet the retina and is eventually collected into the venous flow within the vascular tunic through diffusion processes.

11.6 Intraocular pressure

Intraocular pressure is a measure of the hydrostatic pressure within the globe (hollow cavities) of the eye. This pressure is essential to maintain the appropriate distance between the lens and the retina and is carefully regulated by the body. The intraocular pressure is slightly positive compared with the pressure of neighboring tissue to ensure that the eye-ball remains open and does not collapse. The intraocular pressure is maintained by the constant production of the aqueous humor from the ciliary processes, as described previously. Under normal conditions, the intraocular pressure is close to 15 mmHg. Interestingly, the intraocular pressure varies within an individual by about 2 to 3 mmHg each day. There is a significant difference between the intraocular pressure during the day and night (or more accurately awake versus sleeping). During extended periods of sleeping, the intraocular pressure decreases because there is a slight reduction in the formation of the aqueous humor. The intraocular pressure is also related to the episcleral venous pressure, which is the hydrostatic pressure of the veins within the sclera. Intraocular pressure is defined by

$$p_{IO} = \frac{F}{C} + p_{EV} \quad (11.4)$$

where p_{IO} is the intraocular pressure, F is the rate of formation of the aqueous humor, C is the drainage rate of the aqueous humor as a function of pressure (or the eye compliance), and p_{EV} is the episcleral venous pressure. The episcleral venous pressure is fairly constant throughout the day and averages close to 14 mmHg under normal conditions.

If the inflow rate of the aqueous humor does not balance the outflow rate of the aqueous humor, there will be changes in the volume of the eye (this typically can act for only small pressure changes). The volume of the eye is equal to the compliance of the eye multiplied by the pressure of the eye (which may be equal to the intraocular pressure).

$$V_{eye} = Cp_{eye} \quad (11.5)$$

In Eq. (11.5), C is the compliance of the eye. If the intraocular pressure is changing, the outflow rate will not balance the inflow rate, as described by Eq. (11.1). Instead, the outflow rate is equal to

$$Q_{out} = \frac{p_{eye}}{R} \quad (11.6)$$

where R is the resistance to aqueous humor flow. Using the two previous relationships to solve for the conservation of mass, we get

$$\begin{aligned} \frac{dV_{eye}}{dt} &= Q_{in} - Q_{out} \\ C \frac{dp_{eye}}{dt} &= \frac{p_{norm}}{R} - \frac{p_{eye}}{R} \\ \frac{dp_{eye}}{dt} + \frac{p_{eye} - p_{norm}}{RC} &= 0 \end{aligned} \quad (11.7)$$

where p_{norm} is the steady-state pressure that normally acts and regulates the inflow of aqueous humor.

Example 11.1

Under a disease condition in which the trabeculae become occluded, the intraocular pressure transiently increases by 5 mmHg. If the trabeculae occlusion is removed, which brings the flow resistance back to normal levels, what is the time required to bring the intraocular pressure back to within 5% of the steady-state value? Assume that C is equal to 2.8 $\mu\text{L}/\text{mmHg}$ and that R is equal to 5 mmHg min/ μL . Assume that the inflow flow rate is 2 $\mu\text{L}/\text{min}$.

Solution

To solve this problem, we will need to solve the differential equation derived for the conservation of mass of the eye

$$\begin{aligned}\frac{d(p_{eye} - p_{norm})}{dt} &= -\frac{p_{eye} - p_{norm}}{RC} \\ \int \frac{d(p_{eye} - p_{norm})}{p_{eye} - p_{norm}} &= -\int \frac{dt}{RC} \\ \ln(p_{eye} - p_{norm}) &= \frac{-t}{RC} + K\end{aligned}$$

where K is the indefinite integration constant

$$p_{eye} - p_{norm} = K_0 e^{-t/RC}$$

where K_0 is a different constant from K

$$p_{eye} = p_{norm} + K_0 e^{-t/RC}$$

To solve for K_0 , we know that the initial condition is

$$\begin{aligned}p_{eye}(t = 0) &= p_{norm} + 5 \text{ mmHg} \\ p_{norm} + 5 \text{ mmHg} &= p_{norm} + K_0 e^0 = p_{norm} + K_0 \\ K_0 &= 5 \text{ mmHg} \\ p_{eye} &= p_{norm} + 5 \text{ mmHg}(e^{-t/RC})\end{aligned}$$

To solve for the time required to return back to 5% of the steady-state normal pressure

$$\begin{aligned}1.05 p_{norm} &= p_{norm} + 5 \text{ mmHg}(e^{-t/RC}) \\ \frac{0.05 p_{norm}}{5 \text{ mmHg}} &= e^{-t/RC}\end{aligned}$$

Continued

Example 11.1 (*cont'd*)

$$\begin{aligned}
 -\frac{t}{RC} &= \ln\left(\frac{0.05 p_{norm}}{5 \text{ mmHg}}\right) = \ln\left(\frac{0.05 Q_{in}(R)}{5 \text{ mmHg}}\right) \\
 t &= -RC \ln\left(\frac{0.05 Q_{in}(R)}{5 \text{ mmHg}}\right) \\
 t &= -(5 \text{ mmHg min} / \mu\text{L}) \left(2.8 \frac{\mu\text{L}}{\text{mmHg}}\right) \ln\left(\frac{0.05 * 2 \frac{\mu\text{L}}{\text{min}} * 5 \text{ mmHg min} / \mu\text{L}}{5 \text{ mmHg}}\right) \\
 t &= 32.2 \text{ min}
 \end{aligned}$$

Tonometry is a method to directly measure the intraocular pressure. By assuming that the eye is composed of elastic tissue that forms a perfect spherical shell, the effect of increases in external pressure, which causes deformations to the eye, can be used to estimate the intraocular pressure. Increases in intraocular pressure would make it harder to deform the eye. There are two general approaches to conduct tonometry: the first is to measure the force required to deform a fixed area of the eye (Goldmann tonometry, which is the gold standard to measure intraocular pressure), and the second is to measure the area deformed by a fixed force (air-puff tonometry). In this ideal situation, the intraocular pressure can be quantified as

$$p_{IO} = \frac{F}{A} \quad (11.8)$$

where F is either the force applied or force measured and A is either the covered area or the measured deformed area. Although this formulation can be used to estimate intraocular pressure, it is important to note that the eye is not a thin-walled, homogeneous, purely elastic, spherical shell (of uniform thickness) and that the deformed area would not be the same as anticipated because the fluid that bathes the exterior portion of the eye can dissipate some of the load applied to the eye. Obviously, more accurate methods can be developed to describe the relationship between external pressure changes and deformation areas.

11.7 Disease conditions

11.7.1 Glaucoma

Glaucoma is one of the leading causes of blindness and occurs when the intraocular pressure rises significantly. Typically the intraocular pressure rises slowly during glaucoma, but any increase can eventually lead to blindness, if the force exerts itself on the eye structures for enough time. An increase in intraocular pressure to about 30 mmHg is common

during glaucoma. This level of pressure causes a significant decrease in vision and will eventually lead to blindness. However, under severe conditions, the intraocular pressure can rise to 60 mmHg, which will lead to blindness within weeks. In most cases of glaucoma, the rise in intraocular pressure is caused by a decrease in aqueous humor draining. Commonly, the decrease in drainage is due to a blockage of the trabeculae, and thus, the aqueous humor either does not enter the canals of Schlemm or there is an overall increase in the resistance to flow through the anterior cavity. The intraocular pressure rises because the production of aqueous humor is continuous and the sclera is fairly rigid and cannot accommodate large changes in fluid volume through a distention of its walls. Although not discussed in previous sections, there is one weak point within the sclera. Along the posterior section of the eye, the optic nerve and the central retinal artery and vein pass through the three layers of the eye. This location is termed the *optic disc*. As the intraocular pressure increases, the optic nerve is forced outward because of the increased pressure forces. This induces irreversible damage to the nerve fiber. When the intraocular pressure increases to twice the normal intraocular pressure, the damage to the optic nerve interferes with action potential signal transmittance. Therefore, as the action potential becomes blocked, vision is lost.

Glaucoma is common, affecting over 2% of people over the age of 35. In the United States alone, this is over 2 million people. If caught early enough, glaucoma can be treated with a topical drug, but it may eventually need corrective surgery. There have been a number of studies conducted on the cause of glaucoma. According to Eq. (11.2), there can be changes in either the episcleral venous pressure or the inflow/outflow rate of the aqueous humor. In multiple species, it has been shown that the episcleral venous pressure and the inflow rate of the aqueous humor remain relatively constant under glaucoma conditions compared with normal conditions. Therefore, as discussed earlier, glaucoma is more than likely caused by changes in the outflow rate of the aqueous humor. These changes can be induced by multiple pathological events.

11.7.2 Cataracts

The transparency of the lens depends on the exact balance between structural characteristics of the lens proteins and the biochemical interactions of the proteins. Once this balance is disturbed, the lens will tend to lose its transparency. Cataract is the condition that is associated with this process. There are many causes of cataracts, including aging, exposure to radiation, and drug reactions, but it is most commonly found in the elderly. A cataract is defined as a cloudy or opaque region within the lens. During the early stages of cataract formation, some of the lens proteins become denatured. In later stages, the proteins aggregate, forming the opaque regions.

Over time, it is natural for the lens to become yellow and lose its transparency. It is then typical for the patient to require brighter lights to read and to have “night blindness.” When the lens becomes completely opaque, the patient is functionally blind and will require removal of the lens. The patient is only functionally blind because the photoreceptors within the retina function properly when stimulated with light. After lens removal, an artificial substitute can be put in its place, and eyeglasses can be used to focus light onto the retina properly to allow for vision.

Summary

- 11.1.** The eye is a specialized sensing organ that is sensitive to both the intensity and the wavelength of light. The wall of the eye is composed of three layers, which provides mechanical support for the eye (the fibrous tunic), provides blood to the eye (the vascular tunic), or is composed of sensing cells (the neural tunic). The eye can also be divided into two chambers, each filled with fluids. The vitreous cavity maintains the shape of the eye and is filled with a gel that is composed of many proteins and proteoglycans. The anterior cavity is filled with aqueous humor that wets the cornea and lens, providing these structures with the nutrients it needs to function. The lens is made up of the protein crystallin, which helps focus light on the retina. The retina is composed of two sensing cell types, the rods and the cones, which can be stimulated by changes in the incident light and transmit those changes to the brain.
- 11.2.** The blood supply to the eye is unique in that all cells need to have a readily available blood supply but the blood vessels cannot interfere with the transmission of light through the eye. The blood vessels of the eye are divided into the uveal vessels, which supply the choroid, ciliary bodies, the iris, and parts of the retina, and the retinal circulation, which supplies all other locations of the eye. Small arteries of the eye play a significant role in the formation of aqueous humor. Arterioles that supply the rectus muscle branch into both capillaries, which feed the muscle, and arterioles, which continue to penetrate the eye tissue. These arteries divide and penetrate the ciliary bodies. These capillaries have a unique structure that helps in the formation of aqueous humor in the ciliary processes. The blood–retinal barrier prevents the mixing of blood constituents with the eye constituents.
- 11.3.** Aqueous humor is formed at a rate of approximately 2 $\mu\text{L}/\text{min}$ within the anterior chamber. It is secreted by the ciliary bodies, which are located behind the iris and are composed of secretory epithelial cells. Sodium ions are actively transported out of the ciliary bodies, which causes chloride and bicarbonate ions to diffuse out of the ciliary bodies. The efflux of these ions causes an increase in the osmotic pressure of the fluid, and therefore, water moves out of the ciliary bodies to balance this increase in osmotic pressure.
- 11.4.** Aquaporins are transmembrane proteins that facilitate the movement of water across the cell membrane wall. Under normal conditions, water ions can diffuse across the cell membrane freely; however, this is a relatively slow process. Through the addition of aquaporin channels to the cell membrane, water movement occurs significantly faster. Interestingly, aquaporins contain structures that can regulate the movement of water through the channels. A structure termed the *NPA motif* forms a bottleneck within the aquaporin channel. This constriction causes water ions to move through the channel in a single file. This is likely caused by an electric field that is generated within the channel. A second filter, termed the *aromatic/arginine selectivity filter*, interacts with water molecules to facilitate their transport through the channel. Other compounds cannot interact with this filter and cannot pass through the channel.

- 11.5.** Aqueous humor flows from the ciliary processes, between the ciliary ligaments into the anterior chamber. Within the anterior chamber, aqueous humor can either pass through the pupil to wet the lens or remain in the anterior chamber to wet the cornea. After passing through the anterior chamber, aqueous humor passes through the trabeculae that act as a filter for the aqueous humor and then enters the canals of Schlemm. The canals of Schlemm connect back to the vascular tunic so that aqueous humor is reabsorbed into the cardiovascular system. A small portion of aqueous humor diffuses into the posterior chamber. In general, the flow of aqueous humor can be quantified through a mass balance equation

$$\rho v A_{in} = \rho v A_{out}$$

- 11.6.** Intraocular pressure maintains the proper shape of the eye, helps aqueous humor flow, and is a measure of the hydrostatic pressure within the eye. Intraocular pressure can be calculated from

$$p_{IO} = \frac{F}{C} + p_{EV}$$

which is a function of the formation/drainage rate of the aqueous humor and the cardiovascular venous pressure. When the inflow rate of aqueous humor and the outflow flow of aqueous humor are not balanced, the volume of the eye can increase and the outflow rate depends on the resistance to outflow (this usually increases because of a blockage). This can be quantified with

$$\frac{dV_{eye}}{dt} = Q_{in} - Q_{out}$$

which would measure the time rate of change of the eye volume. There are two typical ways to measure the intraocular pressure, the first with a constant area and the second with a constant force. Each of these methods assumes that the eye is a perfect spherical shell with uniform elastic properties.

- 11.7.** Glaucoma and cataracts are two common pathological conditions that affect the eye. Glaucoma is one of the leading causes of blindness and is caused by a slow increase in intraocular pressure. Intraocular pressure normally increases as a result of a blockage of the canals of Schlemm. Cataracts are caused by an imbalance of the biochemical interactions of the lens proteins. Because of this imbalance, the lens proteins either experience a structural change or do not organize properly. Either way, the lens tends to lose its transparency and light cannot be focused on the retina properly. The retina is not normally damaged during cataracts, but it is damaged during glaucoma.

Homework problems

- 11.1. Describe the three layers of the eye, with respect to the structure–function relationship.
- 11.2. There is a blind spot along the retinal wall where the optic nerve attaches to the retina. Why does this not impair vision?
- 11.3. Aqueous humor circulates at a constant inflow rate of $2\ \mu\text{L}/\text{min}$ and at steady-state drains from the eye at the same flow rate. This flow rate depends on the pressure–volume relationship of the eye, which can be described by $V = Cp$, where C is the compliance of the eye and the outflow rate is equal to p/R , where R is the resistance to outflow. Calculate the compliance of the eye at steady state, knowing that the resistance to outflow is $4.2\ \text{mmHg min}/\mu\text{L}$ and the volume of the eye is $7\ \text{cm}^3$. If the pressure is increased by $10\ \text{mmHg}$ because of a compression of the eye that reduces the overall volume to $5.5\ \text{cm}^3$, what is the outflow flow rate in these conditions?
- 11.4. Approximate how many aquaporin channels are required to maintain an inflow rate of $2\ \mu\text{L}/\text{min}$, assuming that the permeability of each aquaporin channel is $6_E - 14\ \text{cm}^3/\text{s}$ and that each channel allows one water molecule to pass at a time.
- 11.5. Discuss in detail the restrictions of water movement through the aquaporin channels. Is this an effective way to move water into and out of cells?
- 11.6. Assume that there are 10,000 aquaporin channels that, when combined, can form aqueous humor at a rate of $2\ \mu\text{L}/\text{min}$. Assume that the diameter of each aquaporin channel is $0.25\ \text{nm}$. Under disease conditions, the aqueous humor drains at a rate of $1.95\ \mu\text{L}/\text{min}$. Assuming that there are 2000 canals of Schlemm present, calculate the average diameter of one canal.
- 11.7. Calculate the intraocular pressure knowing that the episcleral venous pressure is $14\ \text{mmHg}$ and the compliance of the eye is $2.5\ \mu\text{L}/\text{mmHg min}$. What is the absolute pressure of the eye under these conditions?
- 11.8. If the pressure of the eye is decreased transiently by $10\ \text{mmHg}$, calculate the time required to return to within 10% of the steady-state pressure value, if the eye compliance is equal to $2.7\ \mu\text{L}/\text{mmHg}$, the resistance to outflow is $5\ \text{mmHg min}/\mu\text{L}$, and the inflow rate is $2\ \mu\text{L}/\text{min}$ (all under normal conditions).
- 11.9. Discuss some of the reasons why glaucoma can cause an increase in intraocular pressure. How can this be represented mathematically with the inflow rate, eye compliance, and so on?
- 11.10. Conduct a parameter analysis for the effects of the rate of formation of the aqueous humor, the eye compliance, and the episcleral venous pressure on intraocular pressure. Assume that the normal value for the compliance of the eye is $2.8\ \mu\text{L}/\text{mmHg}/\text{min}$, the formation rate of aqueous humor is $2\ \mu\text{L}/\text{min}$ and the episcleral venous pressure is $14\ \text{mmHg}$. Which of these parameters alters the intraocular pressure most significantly?
- 11.11. Considering what you know about the central dogma of molecular biology (e.g., how long it takes to make, transport, and/or activate a protein), would it be more effective to produce more aquaporin channels or increase the permeability of channels, when cells need to move larger quantities of water. If you choose increase the permeability, how do you propose that this would happen?

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Lubrication of joints and transport in bone

LEARNING OUTCOMES

- Explain the structure of bones
- Describe the molecular composition of bones
- Differentiate between the four bone cell types and identify the function of each type of bone cell
- Model the Haversian canal system within long bones
- Classify different types of joints found within the skeletal system
- Discuss the function of cartilage
- Describe the special circulation found within bone
- Describe the function and formation of synovial fluid
- Model the flow of synovial fluid through a joint
- Construct a restricted diffusion coefficient based on the molecular weight of a polymer within solution
- Calculate the flux of species through the synovial membrane
- Solve for the forces acting on bones and within joints under particular loading conditions
- Examine the stress and strain bones can experience under loading conditions
- Relate loading conditions to the formation of synovial fluid within joints
- Discuss transport of salient molecules to bone and throughout bone
- Describe disease conditions that are related to the skeletal system

12.1 Skeletal physiology

In this section, we will briefly describe the structure of bones and then move quickly into the structure of common joints, which use a biological fluid as a lubricant to facilitate motion at the joints. The discussion of the blood vessels that perfuse bone will be highlighted in the following section, although some minor discussion will appear here. All of the bones in the

body are divided into two groups. The first group is the axial skeleton, consisting of 80 bones that compose the skull, the rib cage, and the vertebral column. The second group is the appendicular skeleton, which consists of the remaining 126 bones within the body. The bones of the appendicular skeleton are found in the pectoral girdle, the pelvic girdle, the upper limbs, and the lower limbs. All 206 bones in the human body function to support and protect the body, store minerals, produce blood cells, and act as levers for motion.

In this textbook, we will restrict ourselves to a discussion of the long bones, which are typically elongated and thin and are located in the limbs of the body (Fig. 12.1). All long bones have a tubular shaft that extends for the majority of the length of the bone. This shaft is termed the *diaphysis of the bone*. The wall of the diaphysis is composed of compact bone, which is very solid and stiff and provides much of the mechanical stiffness of bone. The diaphysis also forms a protective layer that surrounds a central open space termed the *medullary cavity* (or the marrow cavity). At the longitudinal ends of the diaphysis, the bone expands to a region termed the *epiphysis*. The epiphysis is composed mostly of spongy bone (or trabecular bone). In contrast with compact bone, spongy bone is an open mesh of bone tissue surrounded by a thin covering of compact bone. This thin layer of compact bone is termed *cortical bone*. Spongy bone acts to transmit stresses that are applied to the ends of bone from multiple different directions and reorient these stresses into a more uniform direction toward the stiffer compact bone. In fact, the stiffer compact bone can normally withstand significant stresses in only one direction, typically the longitudinal direction. Between the diaphysis and the epiphysis is a small region termed the *metaphysis*. The metaphysis is composed of both compact bone and spongy bone, with about 50% of each. The metaphysis is the region of bone that transitions from mainly compact bone in a tube structure to mostly spongy bone and also helps reorient the applied stresses into the longitudinal direction of the tubular shaft.

Bone is a connective tissue that is composed of specialized cells and a stiff matrix that consists of extracellular proteins and a hardened ground substance. The bone matrix is especially

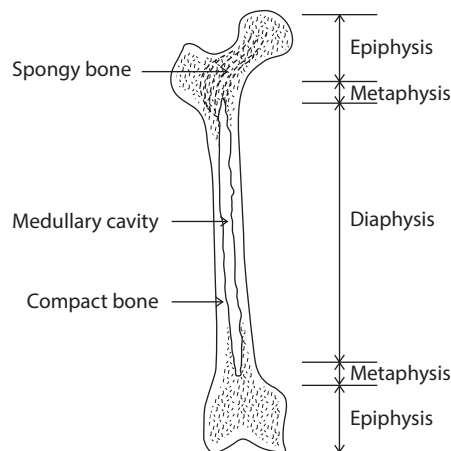
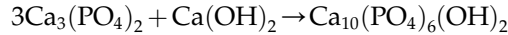


FIG. 12.1 A representative long bone, showing the various regions within the bone. Long bones are composed of both compact bone and spongy bone. Regions of the bone are classified both by the bone type that composes the majority of the section and by the load direction that the bone normally experiences in that region. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, Pearson, New York, 2018).

stiff because of the deposition of calcium salts within the protein fibers. The major component of bone, by weight, is calcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$, which accounts for nearly 65% of the total bone mass. In bone tissue, three calcium phosphates interact with one calcium hydroxide to form hydroxyapatite crystals. The molecular formula for hydroxyapatite is $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, and the chemical reaction for hydroxyapatite formation can be described by



As hydroxyapatite forms, other ions (such as sodium and fluoride) and other calcium compounds (e.g., calcium carbonate) incorporate into the crystal lattice structure of hydroxyapatite. Through the incorporation of these secondary components, these crystals become very stiff but remain quite brittle. Similar to ceramic materials, these crystalline compounds can withstand intense compressive forces (typically in one direction) but cannot withstand significant torsion, bending, or forces in tension.

Roughly 33% of bone mass is accounted for by collagen fibers. Different types of collagen can be found in the bone matrix, and each collagen type forms into a different three-dimensional (3D) structure. For instance, collagen type I forms into fibers, whereas collagen type IV forms a more mesh-like structure. Most collagen fibers are long, unbranched proteins and are composed of individual protein subunits that are wound together. Collagen fibers are very strong, especially when subjected to forces in tension. Structurally, collagen resembles a rope and does not withstand any significant forces in compression. Collagen can withstand some pure torsional and bending stresses, but if there is any compressive loading on the collagen fiber, it will tend to fail.

Ground substance fills the spaces between the extracellular proteins, collagen, and cells within bone tissue. Ground substance is typically clear and viscous because of the presence of proteoglycans. Ground substance is so viscous that most cells have a difficult time traveling through the fluid. Therefore, it is uncommon to see a significant amount of cellular transport occurring within this portion of bone. However, if a foreign cell or a foreign particle enters the ground substance, the highly viscous fluid aids in the inflammatory response by increasing the amount of time the foreign cell/particle is visible to white blood cells. In addition, the amount of time needed to enter the vascular system is increased; therefore, the likelihood of the infectious agent to spread to other regions of the body is diminished. The danger of inflammation arises when foreign cells or particles overwhelm the body's defenses in the bone. Since it is also difficult for inflammatory cells to migrate through the ground substance, sufficient numbers of innate inflammatory cells may not be able to make it to the site of infection. New inflammatory cells can slowly migrate into the ground substance to combat the infection, which may have become very strong and stable.

The remaining 2% of bone mass is accounted for by the cells within the bone matrix. Bone cells are divided into four cell types, which are classified based on their function and appearance. The first type of bone cells are the osteocytes. These are mature cells that make up the vast majority of all of the bone cells. Osteocytes can be found within void spaces throughout the bone matrix. These void spaces are termed *lacunae*. Each lacuna is occupied by one osteocyte that remains in this location during that particular cells entire life span (unless the bone is broken down to such an extent that the lacunae open to the surrounding interstitial space). Lacunae are connected to each other via narrow channels that infiltrate the entire

bone matrix. These channels are termed *canaliculi*, and their primary function is to provide nutrients to osteocytes as well as to allow osteocytes to communicate with each other. In fact, osteocyte cellular extensions fill the canaliculi, and these cellular extensions directly connect to neighboring osteocytes by gap junctions among other junctional proteins. Similar to endothelial cell gap junctions, osteocyte gap junctions allow for the transfer of ions and other signaling molecules to facilitate cell–cell communications.

Osteocytes perform two major functions for bone tissue. The first function is to maintain the mineral content and protein composition of the bone matrix. Bone formation is a process that occurs continually depending on the particular loading conditions to which the bone is subjected. This is interesting because if a person starts to run daily as an exercise (for example), this will be accompanied by an increased bone density (among other physiological adaptations). After bed rest or space travel (reduced gravity and/or reduced mechanical loading on cells) the bone density decreases (again among other physiological adaptations). Therefore, bone is a very adaptive tissue. Osteocytes can release compounds to degrade the surrounding matrix, or they can aid in the deposition of new hydroxyapatite. Osteocytes also have a critical function in bone repair. If osteocytes are released from a lacuna, they have the ability to differentiate into osteoblasts or osteoprogenitor cells that function to build new bone.

The second type of bone cell is the osteoblast. Osteoblasts are typically found on the exterior surfaces of bone and function to produce new bone matrix. To produce new bone matrix, osteoblasts secrete the proteins that constitute the bone matrix. Osteoblasts also release calcium phosphate to help calcify the proteins within the matrix, effectively increasing the stiffness of the newly formed matrix. The compounds that osteoblasts release do not become true bone until the calcium salts interact with calcium hydroxide to form hydroxyapatite. Before this reaction, the organic matrix is termed *osteoid*. If an osteoblast becomes completely surrounded by bone matrix, the osteoblast differentiates into an osteocyte and will stay within that particular lacuna, as described previously.

The third type of bone cell is the osteoclast. Osteoclasts are also typically found on the exterior surfaces of the bone tissue. Osteoclasts degrade and recycle the bone matrix. Osteoclasts are multinucleated cells (typically approximately 50 nuclei per cell) derived from the same stem cells that produce macrophages. Osteocytes secrete proteolytic enzymes to dissolve the bone matrix in a process termed *osteolysis* (or resorption). This process is critical in the regulation of free calcium and phosphate within the body.

Bone is continually being formed and degraded through the actions of osteoblasts and osteoclasts. The balance between these two processes is very critical to the normal function of the particular bone as a tissue. Under normal conditions, when osteoblasts are depositing more matrix than the osteoclasts are removing, the bone itself will become stiffer in compression and larger. The downside of this reaction is that the bone typically becomes more brittle than it should be, and it might exceed the work capacity of the muscles because the bone mass increases. Therefore, the effort needed and the tension that must be generated to move the bones might be too much for the other organ systems to handle. On the other hand, if osteoclasts remove more bone matrix than is being produced by the osteoblasts, the bone becomes weaker and thinner. The downside of this process is that the bone cannot typically withstand the normal loading condition that it would be subjected to, and it would more than likely fail during normal activities. Under normal loading conditions, these

processes can occur in everyday life, but they are typically coupled to changes in other systems. For example, individuals who do a lot of strength training increase their muscle mass as well as their bone mass and increase the number of blood vessels perfusing these systems. Therefore, under these conditions, all of the physiological systems have adapted, which should allow the muscles to generate the required tension. For someone on bed rest, the loading conditions on their bones have decreased, and in parallel the muscles begin to atrophy. Thus, the bone mass and muscle mass decrease, and the loads that the bones typically withstand are diminished; however, under these conditions, if the bones are subjected to more significant loads, they may fracture.

The last bone cell is the osteoprogenitor cells. These are mesenchymal cells that can divide and differentiate into osteoblasts. The primary function of osteoprogenitor cells is to maintain the quantity of osteoblasts within bone tissue. These cells play a very important role in fracture healing when it would be necessary to rapidly increase the number of osteoblasts within the bone to repair and produce new bone matrix.

We will now briefly describe the structure of compact and trabecular bone. The most basic structural unit of compact bone is termed the *Haversian system* (Fig. 12.2). In each Haversian system, concentric lamellae surround a central canal termed the *Haversian canal*. Lamellae are individual layers of bone matrix that are similar to the concentric circles found within a tree trunk. Lacunae are found between individual lamellae and not within one lamella, because the bone cells that form and degrade bone are found on only the exterior regions of the bone. Within each Haversian canal are the blood vessels that supply the bone with nutrients. Typically, there is one capillary (or arteriole) and one venule within each canal. Canaliculi run perpendicular to the Haversian canal and connect the lacunae to the blood supply and other lacunae. The canaliculi can penetrate through lamellae to connect bone cells, on neighboring

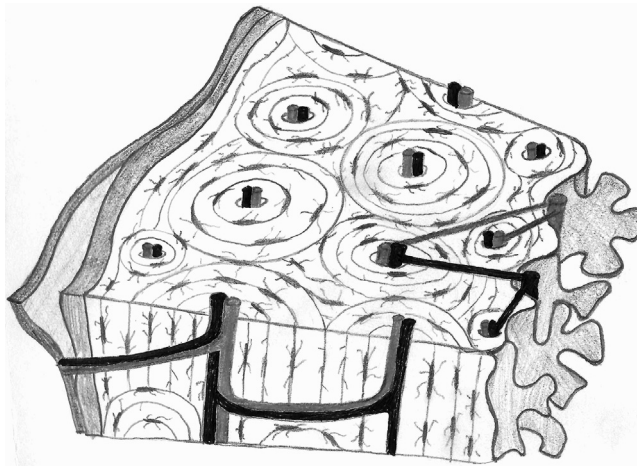


FIG. 12.2 Schematic of the structure of compact bone. Compact bone is formed from multiple Haversian canal systems that are composed of concentric lamellae. Each Haversian canal has its own venule and capillary (possible arteriole) to provide the osteocytes with nutrients and oxygen. On the interior surface of the compact bone, trabeculae can be found to form a spongy bone marrow within long bones. Osteocytes can be found between the lamellae (black ovals on figure), within a lacuna. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, Pearson, New York, 2018.)

concentric circles, and to aid in nutrient transport. Because the Haversian system is fairly circular, neighboring systems do not align perfectly with one another. This open space is filled with interstitial lamellae, which is leftover bone matrix from older Haversian systems that have been partially degraded and replaced by the newer systems.

The outer surface of bone is covered by a structure called the *periosteum*, and the inner surface of bone is covered by the endosteum. The periosteum is a fibrous membrane that isolates bone from other tissue. Within joints, the periosteum is continuous with the surrounding joint connective tissue. The endosteum is a cellular layer that lines the marrow cavity of bone. This layer participates in bone growth and repair and consists of osteoprogenitor cells. In some locations, the endosteum layer is not complete. Here the bone matrix is exposed, and osteoblasts and/or osteoclasts can be found that are actively forming or degrading bone.

In trabecular bone, lamellae do not form a structural unit similar to the Haversian canal system seen in compact bone. Instead the bone is composed of many thin tubes termed *trabeculae* that resemble a branching network. There is no direct blood supply to the cells within these trabeculae. Nutrients must be transported through the canaliculi system that is connected to a different blood supply that can be far from the bone cells. Trabecular bone is adapted to withstand stresses in many orientations, but the majority of the trabeculae are oriented along the major and normal stress-loading directions. The trabeculae are branched and interconnected to distribute and transmit the loads and to be able to withstand stresses in nonmajor directions. Trabecular bone is lighter than compact bone and therefore reduces the overall weight of the bone. In addition, some trabecular bone houses the red and the yellow marrow. Red marrow produces blood cells, and the yellow marrow is a store of adipose tissue for future energy needs.

Bone is relatively inflexible, and the only way that movement can occur is at the joints between the bones. There are three types of joints in the body that are each classified based on the range of movement they permit. The first type of joints allow no movement between the neighboring bones and are termed *synarthroses joints*. The bones do not rotate about each other because the edges are typically in contact and may even be fused together. These joints are very strong and can be considered an extension of the bone itself. This type of joint is commonly found between the bones that compose the skull. In some sense, the bones are not individual anymore because they fuse to one another. The second type of joint, the *amphiarthroses joint*, allows some movement between the neighboring bones. These joints are still relatively strong and are typically connected by collagen fibers or cartilage. This type of joint can be found between the radius and the ulna or the tibia and the fibula within the limbs. These bones rotate slightly around each other but do not have a great deal of free motion.

The third type of joint, the *diarthroses joint*, allows for a wide range of motion depending on the structure of the joint. This type of joint is surrounded by an articular capsule and a synovial membrane. The synovial membrane runs along the interior portion of the articular capsule. Synovial fluid (which will be discussed in [Sections 12.3 and 12.4](#)) fills the space between the bones that compose the joint. There are six types of diarthroses joints, depending on the exact nature of the movement that the joint allows. The first joint type is the gliding joint, which typically allows translation in one or more directions. The bones that are in contact with each other are typically flat or slightly rounded, allowing for translational motion without rotation. Movement within these joints (as well as rotation) is restricted by

the ligaments that anchor the bones. An example of this type of joint is the joint that is formed from the connection between the clavicle and the manubrium. The second type of joint is the pivot joint, which typically allows rotation about only one axis. It is normal for the bones in these joints to be touching each other and for a small piece of ligament connected to the first bone to wrap around the second bone. An example of this type of joint is between the atlas and the axis within the neck. The last joint that allows motion in one direction is a hinge joint. This joint also allows rotation about the joint that connects the bones but not translation. The elbow and the knee are two examples of a hinge joint.

The remaining types of diarthroses joints allow more degrees of freedom in their movement than the first three described. The first of these joints is the ellipsoid joint, which allows rotation in two planes. Typically, one bone has a convex protrusion that fits within a concave depression of a second bone. An example of this type of joint is found between the metacarpal and phalanges bones within the hand (i.e., finger joints). The next type of joint, the saddle joint, also allows rotation within two planes. One of the bones is shaped like a saddle and the second bone is shaped like a rider's lower body surrounding a saddle. This is also a concave surface facing a convex surface. This type of joint allows for the movement of the thumb about the trapezium. The last type of joint is the ball-and-socket joint, which allows for 3D rotation about the joint. In this type of joint, the end of one bone is shaped as a ball and the other bone is concave. The ball fits within the concave depression and is held in place by ligaments. The shoulder and hip joints are examples of ball-and-socket joints.

The surface of bone is rough, and the coefficient of friction between two bones is very high. If bones were able to come into contact with each other, to rotate about a joint, the bone itself would become damaged as a result of the high frictional forces. To prevent bone from coming into contact with another bone, a thin layer of cartilage is present on the ends of the bone. This cartilage is termed *articular cartilage*, and it partially acts to reduce the coefficient of friction between two bones. Under normal conditions, the two cartilage surfaces do not come into contact with each other either. Instead, there is a small fluid layer between the cartilage surfaces. The fluid is termed *synovial fluid*, and we will discuss this fluid and how it forms in [Sections 12.3 and 12.4](#). The cartilage acts as a safety mechanism for bone–bone contact, but it also helps maintain a layer of synovial fluid within the joint by absorbing and releasing this fluid when needed.

Ligaments provide support and strength to joints by helping to restrict bone movement and to directly connect the bones to one another. Ligaments are typically made of collagen fibers. It takes a great deal of force to tear a ligament because typically they are stiffer than the bones. Therefore, the bone will fracture before the ligament ruptures. However, in a sprain some damage occurs to collagen fibers within the ligament. Tendons are not part of the joints themselves but rather pass over the joint. Tendons connect bone and muscle together. In relation to the joint, tendons help hold the joint in place but may restrict the joint motion. However, tendons do provide mechanical support for the joints by connecting bones to other muscles. For instance, many of the muscles that move the humerus are located within the torso and are connected to the axial skeleton. Therefore, the shoulder joint maintains the appropriate orientation because of these connections among the axial skeleton, the muscles, and the humerus.

12.2 Bone vascular anatomy and fluid phases

Bone is perfused by a sparse capillary network that allows for the exchange of nutrients and wastes between blood and the bone cells. As mentioned earlier, the net movement of calcium ions (Ca^{2+}) to and from bone is critical for the proper functioning of nearly every organ, because calcium ions are necessary for many cellular and enzymatic reactions to occur (e.g., contraction of muscle, release of neurotransmitters, coagulation reactions). The vascular tree that is specific to bone can be subdivided into four general categories that are classified based on their size and function. These categories include the conduit vessels, the capillaries of bone, the lacunar–canalicular system, and finally the microcanalicular system. Again for this discussion we will restrict ourselves to a discussion on long bone vasculature.

In the vast majority of long bones, a single main artery enters the bone at the region of the diaphysis. This large artery bifurcates, and one branch ascends while the other descends along the marrow cavity (Fig. 12.3). Along the entire length of this artery we can observe lateral branches that pass into the bone cortex. As with other tissues, small afferent arteries supply the capillary beds of the cortex with blood and regulate the perfusion of these capillary beds. These afferent arteries and each of the feeding arteries are considered part of the conducting or conduit vascular system, which feeds the second level of the bone vasculature, the bone capillaries. Although much work has been conducted on the vascular anatomy of bone, it has become apparent that each bone has a slightly different vascular plexus, and even the arrangement within analogous bones can vary. For instance, the canine tibial artery has been shown to supply capillary beds using a parallel blood vessel arrangement, whereas the analogous artery in rodents uses a series blood vessel arrangement. In cortical bone, the arrangement of blood vessels is slightly different; the afferent vessels penetrate along the entire tissue ending with small capillary loops beneath the cartilage layer. The venous drainage system in bones is typical of most vascular beds. Small venules exist that penetrate through the cortex of bone, eventually converging to the periosteal vein. Large emissary veins also exist that penetrate and drain blood from the cortex.

As described previously, the Haversian canal system is the location where nutrient exchange occurs between the blood and the bone tissue. Within each Haversian canal system, a small arteriole (which is capable of exchange) or a capillary is present. These small blood vessels are lined first by cells that form the endosteum of bone and then by a continuous basement membrane. It has been observed that the endothelial cell wall that forms bone capillaries restricts the movement of many molecules into bone and the majority of transport

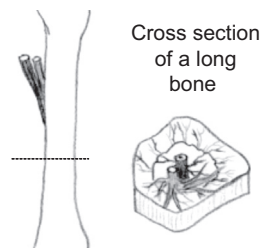


FIG. 12.3 Blood supply of a long bone, illustrating that an artery and vein are paired along the medullary cavity. Branches of these vessels penetrate into the bone at various levels (see Fig. 12.8).

occurs through pinocytosis and vesicle transport mechanisms. Some passive diffusion around the endothelial cell junctions and active transport also can occur. It appears that molecular sieving is a property of bone capillaries. The intercellular clefts of bone capillaries appear to be in the range of 20 nm, whereas endothelial transport vesicles appear to be in the range of 100 nm in diameter. Although these transport mechanisms are very effective for molecules, the transport of cells through this endothelial cell layer would not be able to occur. In the bone marrow, the endothelial cell layer appears to be discontinuous to allow for the passage of forming blood cells (note that this is a second specialty circulation that is found in bone that will not be discussed in detail here).

The percentage of water found within bone has been shown to be related to the extent of bone mineralization. Higher bone mineralization values are accompanied by lower percentages of water. This can be quantified by an increase in bone density. Bone mineralization increases primarily because there is a higher quantity of hydroxyapatite, which fills the water space in forming bone. Under these conditions, the water is displaced from pores formed by protein fibers to the extracellular fluid, lymphatics, or blood. Although it has proven difficult to quantify the water percentage within different sections of bones, the values of water do not appear to vary significantly for different types of bone. However, the vast majority of water in bone is not found within the bone, per say; instead it is found in the blood and the extravascular spaces.

12.3 Formation of synovial fluid

As discussed in [Section 12.1](#), synovial fluid fills the space between joints to reduce the coefficient of friction between the articular cartilage adhered to the ends of the bones that compose the joint. Synovial fluid is produced by the synovial membrane, which is located on the interior side of the fibrous capsule within the joint. The synovial membrane is composed of many interwoven matrix proteins, especially proteoglycans and collagens. Within the joints, this membrane also includes macrophages and fibroblasts to prevent foreign cellular matter entering the joint space. The combined actions of the woven matrix fibers and the inflammatory cells within the membrane regulate the composition of synovial fluid.

Synovial fluid is produced as a filtrate of interstitial fluid. The composition of synovial fluid is very similar to that of interstitial fluid, except that there is a significantly higher concentration of proteoglycans within synovial fluid. The proteoglycans are secreted by fibroblasts within the synovial membrane, and thus these molecules are not found within plasma or the interstitial space. The purpose of the proteoglycans is to increase the organization of water within synovial fluid, so that it can withstand forces better than unorganized water (i.e., the zeta potential and the electric double layer increase, as discussed in Chapter 8). The water becomes organized as a result of hydrogen bonding between water molecules and the charged amino acids that make up the protein portion of the proteoglycans. Because of this increased arrangement between the protein structures and water, there are more bonds present within the fluid phase (compared with normal conditions), which strengthens the fluid. The other major function of the proteoglycans is to increase the overall viscosity of the synovial fluid, again the result of increased molecular actions. A fluid with a higher

viscosity requires more force to cause the same displacement. Thus, under severe loading conditions, bone and cartilage will not come into contact, because the fluid will remain in the joint space.

The formation of synovial fluid can be described by a sieving coefficient of the synovial membrane. In general, the sieving coefficient is a dimensionless number that quantifies the equilibration potential between a receiving system and a donating system. In the case of the synovial membrane, the sieving coefficient can be defined as

$$S = \frac{C_J}{C_I} \quad (12.1)$$

where S is the sieving coefficient, C_J is the mean concentration of a solute in the joint space, and C_I is the mean concentration of a solute in the interstitial space. The mean concentration for the different spaces is quantified immediately before and after solute transfer; thus, this coefficient may be a variable with time. A sieving coefficient with a numeric value of 1 would suggest that the solute concentration within the two compartments equilibrates. In most instances the sieving coefficient is less than 1, which would suggest that the compartments have not equilibrated because (1) there has not been a sufficient time for exchange, (2) there are other physical considerations affecting the equilibrium concentrations (e.g., an electrochemical gradient does not reach chemical equilibrium only), or (3) the products are continually consumed, produced, used, or modified so that chemical equilibrium cannot be reached. It is theoretically possible for a sieving coefficient to be greater than 1; this would suggest that there are some external forces affecting transport or the solutes are being produced on only one side of the membrane. In the case of the synovial membrane, the sieving coefficient of molecules obtained from the interstitial space would be less than 1 whereas the sieving coefficient for proteoglycans would be greater than 1.

As we briefly discussed earlier, one of the major functions of synovial fluid is the lubrication of the joint. The articular cartilage becomes filled with synovial fluid and the cartilage helps hold the fluid in place. When the joint is under compression, the two articular cartilage surfaces come into contact with each other, compress each other, and force some of the synovial fluid out of the cartilage into the joint space. The “free” synovial fluid lubricates the two articular cartilage surfaces and significantly reduces the coefficient of friction between these surfaces. When the compressive forces are removed from the joint, the articular cartilage expands again to its normal size. At this point, there is some “free space” within the cartilage and some of the synovial fluid that was forced out of this space may reenter the cartilage. Therefore, the cartilage effectively holds the synovial fluid within the joint and releases it as needed. It is very devastating when cartilage is torn from the bone or degenerates significantly. When this occurs, the joint can no longer hold significant quantities of synovial fluid, and therefore, there is no added lubrication and no added buffering system for applied forces. Also, the coefficient of friction increases significantly because the contact surfaces become bone–bone or bone–cartilage. Cartilage can repair itself naturally, albeit this repair occurs at a very slow pace. Additionally, as the cartilage is repairing itself, more damage may occur as a result of the increased coefficient of friction experienced and decreased ability to absorb the loading conditions on bone. Thus, it appears that cartilage has very low (or no) healing or repair properties. Chondrocytes, which are the cells responsible for forming and

maintaining cartilage, are bound within lacunae, and thus these cells do not necessarily have access to the damaged regions. Additionally, most cartilage does not have a significant blood supply, so supporting cells, growth factors, etc. may not be able to diffuse into the damaged region. New techniques are being developed to repair cartilage, which include regenerative medicine procedures or injection of juvenile cartilage.

Another mechanical property of the synovial fluid is that it acts as a shock absorber during loading. Because synovial fluid is highly viscous, during compressive loading there is a time-dependent strain that tends to distribute the load over a larger surface area and to diminish the overall stress within the joint. Synovial fluid is also a dilatant fluid, meaning that as the strain increases on the fluid (e.g., the amount that the fluid has displaced), the amount of stress/force required to move the fluid also increases. This is beneficial in the cartilage system because it helps prevent an overloading condition on the bone that would effectively damage the cartilage and possibly the bone itself. One of the major proteins that is responsible for these functions is lubricin (proteoglycan 4), which is a fairly large protein produced by both chondrocytes and synovial membrane lining cells.

The last major function of synovial fluid is to bring nutrients into the joint space. The joint spaces are avascular but require nutrients so that chondrocytes and the other cells that make up the joint space can maintain their proper functions. To perform this task, the synovial fluid must continually circulate around the joint space. This provides nutrients to all of the cells and removes the cellular wastes. During each joint compression, the synovial fluid is circulated throughout the joint space. As the fluid comes into contact with the synovial membrane, wastes are removed and fresh nutrients diffuse into the fluid from the interstitial fluid. The removed wastes enter the interstitial joint space and then diffuse into capillaries that are located outside of the joint capsule. From these three functions, it should be apparent that synovial fluid is critical for the proper functioning of movable joints.

12.4 Synovial fluid flow

To enter the joint space, synovial fluid traverses a fairly complex path starting from blood vessels and ending with reentry into the vascular system. Water, ions, and other small solutes have the ability to cross the endothelial cell boundary that comprises capillaries, as described in Chapter 7. For most diarthrodial joints, the blood vessels that directly supply the joint form an anastomosis around the joint space. This helps provide redundant circulation to the joint space, which is critical because the nutrient exchange depends entirely on diffusion. Capillary exchange through these blood vessels forms the interstitial fluid, which has a slightly different composition depending on the particular tissue within which it is formed. Synovial fluid is then formed as a filtrate of the interstitial fluid within the joint capsule space (refer to the discussion on the sieving coefficient for some details regarding the formation of synovial fluid). As described previously, the synovial membrane is the tissue that performs the filtering function. This membrane is composed of two layers, the synovium, which is approximately 50 μm thick and the subsynovium, which is approximately 100 μm thick. The synovium is the tissue structure that is composed of an incomplete layer of macrophages and fibroblasts. The function of this layer is to prevent foreign particles from entering the joint space, and it produces some of the molecules that make up synovial fluid. The subsynovium

is composed of extracellular fibers that filter the interstitial fluid. The primary extracellular fibers within this layer are various collagens, fibronectin, hyaluronan, and various proteoglycans. What is interesting about the subsynovium is that it is permeable enough to allow fluid to enter the joint space but exhibits a high enough resistance to prevent fluid from exiting the joint space (i.e., it acts as a unidirectional valve). Once the synovial fluid enters the joint space, it is associated with the charged proteins within the cartilage and only “flows” under a compressive load of the joint. The modeling of this flow is quite complex and will be described in the remainder of this section.

The synovial membrane must be modeled as a semipermeable membrane that has a different permeability toward different molecules within the synovial fluid. In some cases, the sieving coefficient can be used as a means to characterize the different permeabilities. In addition, cartilage would need to be modeled as a store for the lubricant and molecules, which may become available during loading conditions. Under these conditions, the time rate of change of molecule i within the synovial fluid would be represented as

$$\frac{\partial(Vc)_i}{\partial t} = (r_s A_s + r_c A_c - d - J)_i \quad (12.2)$$

where V is the volume of the synovial fluid, c is the concentration of molecule i , r is the formation rate of i by the synovial membrane (denoted with a subscript s) or the cartilage (denoted with a subscript c), d is the degradation rate of molecule i , and J is the flux of i into and out of the joint space. The degradation rate typically depends on the concentration and kinetic rate constants of degradation enzymes within the synovial fluid. The flux of molecules within the joint space typically depends on the synovial membrane, the permeability of the membrane, the concentration gradient, the cross-sectional area of the membrane, and the ratio of restricted diffusion to free diffusion. For this type of diffusion, we would need to develop a restricted diffusion coefficient, because of the interaction of the molecules with the charged proteins within synovial fluid and the cartilage. The restricted diffusion coefficient can be defined as

$$D_i = D e^{(-\sqrt{\theta}) \left(1 + \frac{a_i}{a}\right)} \quad (12.3)$$

where D is the free diffusion coefficient of species i , θ is the volume fraction of the protein molecules (e.g., proteoglycans), a_i is the effective radius of the molecule i , and a is the effective radius of the protein. The effective radii can be calculated from the Stokes–Einstein formulation, which is a formulation valid for any molecule and approximates the radius of a molecule based on the molecular weight and overall density as

$$a_x = \left(\frac{3MW}{4\pi\rho N_A} \right)^{\frac{1}{3}} \quad (12.4)$$

where MW is the molecular weight, ρ is the density, and N_A is Avogadro’s number. From Eqs. (12.2) to (12.4), it is possible to model the changes in the concentration of various

species over time. As we have stated before, this is not a typical biofluid flow problem, but instead it relies more on convection and diffusion of species out of a particular compartment.

Example 12.1

Calculate the time rate of change of proteoglycans within the synovial fluid if their diffusion is restricted only by the presence of glycosaminoglycans (GAGs) within the synovial space. Assume that the molecular weight for the proteoglycan of interest is 300 kDa and its density is 1.45 g/mL. The effective radius for the GAGs is 0.5 nm and the volume fraction is 0.008. The free diffusion of proteoglycan in water is $1.1_E - 7 \text{ cm}^2/\text{s}$. The permeability of the proteoglycans through the synovial membrane is $1_E - 6 \text{ cm/s}$. Assume that the degradation of the proteoglycan is negligible. The formation rate of proteoglycans within the synovial membrane and the cartilage are $6_E - 9 \text{ mg}/(\text{cm}^2\text{s})$ and $3_E - 7 \text{ mg}/(\text{cm}^2\text{s})$, respectively. The cross-sectional areas of the synovial membrane and the cartilage are 29.5 mm^2 and 13.5 mm^2 , respectively. The concentration gradient of the proteoglycans is 0.13 mg/mL .

Solution

First it will be necessary to calculate the effective radius of the proteoglycan

$$a = \left(\frac{3 * 300 \text{ kDa}}{4\pi * \left(1.45 \frac{\text{g}}{\text{mL}}\right) (6.02_E 23)} \right)^{\frac{1}{3}} = 4.35 \text{ nm}$$

As a side note, Avogadro's constant is used to convert between units of Daltons and units of grams. Now we can calculate the restricted diffusion coefficient

$$D_i = \left(1.1_E - 7 \frac{\text{cm}^2}{\text{s}} \right) e^{(-\sqrt{0.008}) \left(1 + \frac{4.35 \text{ nm}}{0.5 \text{ nm}} \right)} = 4.62_E - 8 \frac{\text{cm}^2}{\text{s}}$$

To calculate the time rate of change of the proteoglycan, we need to know the flux of the proteoglycans out of the synovial membrane. The flux can be formulated from

$$J = p \Delta c A \frac{D_i}{D} = \left(1_E - 6 \frac{\text{cm}}{\text{s}} \right) \left(0.13 \frac{\text{mg}}{\text{mL}} \right) (29.5 \text{ mm}^2) \left(\frac{4.62_E - 8 \frac{\text{cm}^2}{\text{s}}}{1.1_E - 7 \frac{\text{cm}^2}{\text{s}}} \right) = 0.000058 \frac{\text{mg}}{\text{h}}$$

which quantifies the permeation of the proteoglycans as a function of the area of exchange, the concentration gradient, and the percent reduction in diffusion.

Therefore, the time rate of change of proteoglycans within the synovial fluid can be calculated

Continued

Example 12.1 (*cont'd*)

$$\begin{aligned}\frac{\partial(Vc)}{\partial t} &= r_s A_s + r_c A_c - d - J = \left(6_E - 9 \frac{mg}{cm^2 s}\right)(29.5 \text{ mm}^2) + \left(3_E - 7 \frac{mg}{cm^2 s}\right)(13.5 \text{ mm}^2) - 0 - 0.000058 \frac{mg}{h} \\ &= 0.000094 \frac{mg}{h}\end{aligned}$$

Note that the flux is negative because the concentration gradient for the proteoglycans would act to remove the proteoglycans from synovial fluid.

12.5 Mechanical forces within joints

For this section, we will briefly review how to calculate the mechanical forces that may arise in joints, because as we have discussed, under different types of mechanical loading conditions the formation rate of particular molecular species may increase or decrease within cartilage. The discussed material may be familiar from a biosolid mechanics course or the more traditional engineering statics, dynamics, or solid mechanics course sequence (e.g., engineering mechanics). To start this discussion, we will first restrict ourselves to the standard statics/dynamics assumption that there are no changes in the orientation of the internal molecules that make up the joint (i.e., there are no deformations that alter that chemical bonding arrangement). Furthermore, we will assume that there is no change in mass as a function of time (by degradation, removal, consumption, or addition). When these assumptions are made, the governing equations for engineering mechanics become

$$\sum \vec{F} = m \vec{a} \quad (12.5)$$

and

$$\sum \vec{M} = I \vec{\alpha} \quad (12.6)$$

where $\vec{F}$ is the external forces acting on a body, m is the mass of the body, $\vec{a}$ is the acceleration of the body, $\vec{M}$ is the external moments acting on a body, I is the mass moment of inertia of the body, and $\vec{\alpha}$ is the angular acceleration of the body (remember that the moments and the mass moment of inertia were typically calculated about the body's center of mass but that there are many ways to apply Eq. (12.6) to a rigid body; some of these ways may increase the difficulty of the problem, but you can typically arrive at a solution as long as all of the variables are accounted for in the equation). You may recall from a previous engineering statics course that $\vec{a}$ and $\vec{\alpha}$ were always assumed to be zero (e.g., that the rigid body is in equilibrium), allowing you to simplify Eqs. (12.5) and (12.6) to the summation of the forces is equal to zero and the summation of the moments is equal to zero, respectively.

In engineering dynamics courses, we generally include the acceleration (both linear and angular) of the rigid body, which is assumed to no longer be in equilibrium. Recall from either class that these equations could be represented in component form (e.g., Cartesian directions, cylindrical directions, etc.) to solve more relevant and fully described scenarios. Using Eqs. (12.5) and (12.6), one can calculate the forces required to maintain a joint in place during physiological and pathological physical activities.

Example 12.2

Calculate the force on the shoulder joint for an athlete who is holding a weight with the arm perfectly horizontal (Fig. 12.4). To calculate the reaction forces within the shoulder joint, consider that the weight of the arm is equal to 10 lb and is located at a distance 1 ft from the shoulder joint. The weight that the athlete is holding is equal to 30 lb, and it is held at a distance of 2.1 ft from the shoulder joint. To simplify the problem, let us consider that the deltoid muscle is the primary muscle holding the arm in place and that it attaches to the humerus at a distance of 0.45 ft from the shoulder joint at an angle of 17 degrees.

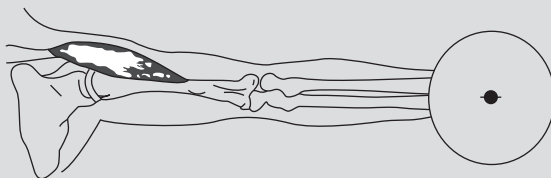


FIG. 12.4 Diagram of a shoulder joint for the in-text Example 12.2. (Modified from N. Ozkaya, M. Nordin, *Fundamentals of Biomechanics: Equilibrium, Motion, and Deformation*, Springer, New York, NY, 1999.)

Solution

First, let us draw a free-body diagram of the arm.

In Fig. 12.5, W_A is the weight of the arm, W is the weight that is being held, F_D is the force of the deltoid muscle, and F_S is the force exerted by the shoulder joint.

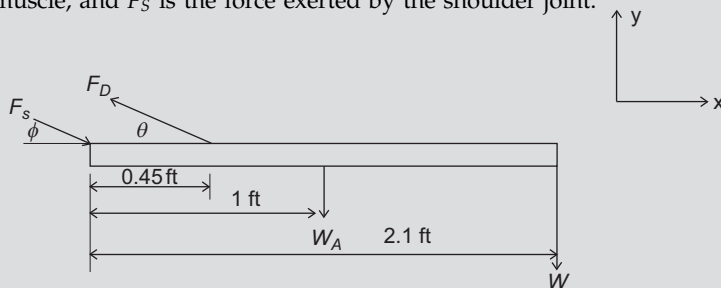


FIG. 12.5 Free-body diagram of a shoulder joint.

Continued

Example 12.2 (*cont'd*)

Writing the equations of motion in vector form, we have

$$\begin{aligned}\sum F_x &= 0 = F_s \cos(\phi) - F_D \cos(\theta) \\ \sum F_y &= 0 = -F_s \sin(\phi) + F_D \sin(\theta) - W_A - W \\ \sum M_D &= 0 = (0.45 \text{ ft}) F_D \sin(\theta) - (1 \text{ ft}) W_A - (2.1 \text{ ft}) W\end{aligned}$$

if we assume that there is no accelerated motion associated with this joint, meaning that the joint is assumed to be in equilibrium. Solving the third equation for F_D , we can obtain the force the deltoid must generate as

$$F_D = \frac{(1 \text{ ft})(10 \text{ lbf}) + (2.1 \text{ ft})(30 \text{ lbf})}{(0.45 \text{ ft}) \sin(17^\circ)} = 555 \text{ lbf}$$

Solving the first and second equations with the new information, we can obtain

$$\begin{aligned}F_s \cos(\phi) &= F_D \cos(\theta) = (555 \text{ lbf}) \cos(17^\circ) = 530 \text{ lbf} \\ F_s \sin(\phi) &= F_D \sin(\theta) - W_A - W = (555 \text{ lbf}) \sin(17^\circ) - 10 \text{ lbf} - 30 \text{ lbf} = 122 \text{ lbf}\end{aligned}$$

Solving for F_s ,

$$F_s = \sqrt{(F_s \cos(\phi))^2 + (F_s \sin(\phi))^2} = \sqrt{(530 \text{ lbf})^2 + (122 \text{ lbf})^2} = 545 \text{ lbf}$$

To solve for ϕ ,

$$\phi = \tan^{-1} \left(\frac{F_s \sin(\phi)}{F_s \cos(\phi)} \right) = \tan^{-1} \left(\frac{122 \text{ lbf}}{530 \text{ lbf}} \right) = 13^\circ$$

The force that is generated in the deltoid muscle is very large, which suggests that this is not a stable position for the arm or that other muscles are needed to accommodate for holding this load in this particular position. Only considering the load that is being held (and not the weight of the arm), there is an approximate 20-fold amplification of the loading conditions in the deltoid muscle.

Example 12.3

During normal motion (walking, jogging, or running), for some instant in time, all of our body weight is supported by one leg (Fig. 12.6). Typically, the bones are not completely vertical because of the way in which the femur connects to the other bones of the leg, especially the hip joint (Fig. 12.7, free-body diagram). Using the following values, calculate the reaction forces that act in the hip joint during running at the instant when the body is supported by one leg. The angle between the femoral head and the horizontal plane is 40 degrees. The angle between the distal extremity of the femur and a horizontal plane is 75 degrees. The hip abductor muscle attaches at the junction of the femoral head and the femur at an angle of 75 degrees. Assume that the weight of the leg is 15% of the total body weight and the reaction force at the floor is 340% of the body weight (because of running). Assume that the direct length between the point O (refer to the free-body diagram) and the femoral head is 9 cm. Assume that the weight of the leg acts a distance of 35 cm from point O and that the reaction force acts at a distance of 88 cm from point O . The person has a weight of 800 N.

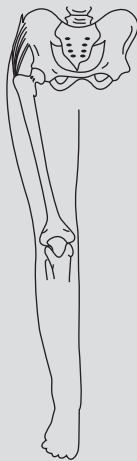


FIG. 12.6 Diagram of a hip joint during running. (Modified from N. Ozkaya, M. Nordin, *Fundamentals of Biomechanics: Equilibrium, Motion, and Deformation*, Springer, New York, NY, 1999.)

Solution

First, let us draw a free-body diagram of the leg.

In Fig. 12.7, W_L is the weight of the leg, W is the reaction force from the floor, F_A is the force of the abductor muscle (at an angle of 75 degrees off the horizontal direction), and F_H is the force exerted by the hip joint (at an unknown angle, ϕ). The angles that are related to the leg geometry and orientation are not shown in this figure.

Continued

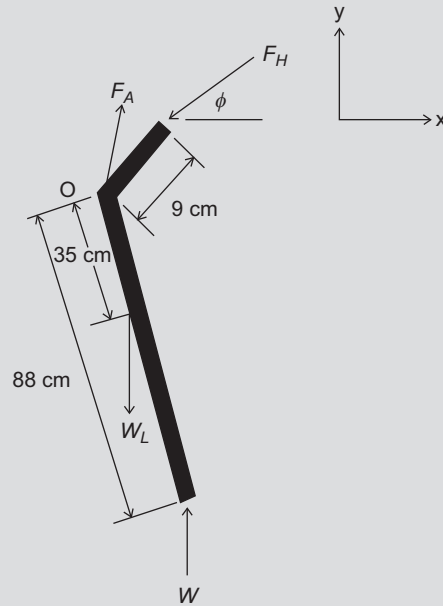
Example 12.3 (cont'd)

FIG. 12.7 Free-body diagram for a hip joint.

Writing the equations of motion in vector form, we have

$$\begin{aligned}\sum F_x &= 0 = F_A \cos(75^\circ) - F_H \cos(\phi) \\ \sum F_y &= 0 = -F_H \sin(\phi) + F_A \sin(75^\circ) - W_L + W \\ \sum M_0 &= 0 = ((9 \text{ cm}) \sin(40^\circ))(F_H \cos(\phi)) - ((9 \text{ cm}) \cos(40^\circ))(F_H \sin(\phi)) \\ &\quad - ((35 \text{ cm}) \cos(75^\circ))W_L + ((88 \text{ cm}) \cos(75^\circ))W\end{aligned}$$

if we assume that there is no acceleration under these conditions. Using the third equation,

$$\begin{aligned}(5.785 \text{ cm})F_H \cos(\phi) - (6.89 \text{ cm})F_H \sin(\phi) &= 9.059 \text{ cm}(0.15 * 800\text{N}) - 22.77 \text{ cm}(3.4 * 800\text{N}) \\ &= -60,864\text{N cm}\end{aligned}$$

From the first and second equations,

$$\begin{aligned}F_H \cos(\phi) &= 0.259F_A \\ F_H \sin(\phi) &= 0.966F_A - 0.15 * 800\text{N} + 3.4 * 800\text{N} = 0.966F_A + 2600\text{N}\end{aligned}$$

Substituting these two relationships into the third equation,

Example 12.3 (*cont'd*)

$$\begin{aligned}
(5.785 \text{ cm})F_H \cos(\phi) - (6.89 \text{ cm})F_H \sin(\phi) &= -60,864 \text{ N cm} \\
5.785 \text{ cm}(0.259F_A) - 6.89 \text{ cm}(0.966F_A + 2600 \text{ N}) &= -60,864 \text{ N cm} \\
(1.5 \text{ cm})F_A - (6.566 \text{ cm})F_A - 17,914 \text{ N cm} &= -60,864 \text{ N cm} \\
(-5.066 \text{ cm})F_A &= -42,949 \text{ N cm} \\
F_A &= 8478 \text{ N} \\
F_H \cos(\phi) &= 0.259(8478 \text{ N}) = 2196 \text{ N} \\
F_H \sin(\phi) &= 0.966(8478 \text{ N}) + 2600 \text{ N} = 10,790 \text{ N} \\
F_H &= \sqrt{(F_H \cos(\phi))^2 + (F_H \sin(\phi))^2} = \sqrt{(2196 \text{ N})^2 + (10,790 \text{ N})^2} = 11,011 \text{ N} \\
\phi &= \tan^{-1}\left(\frac{10,790 \text{ N}}{2196 \text{ N}}\right) = 78.5^\circ
\end{aligned}$$

We show this analysis here because by using some simple assumptions, it becomes relatively easy to calculate the forces that arise within a joint. From force, we can calculate the stress that acts on the cartilage and the strain of the cartilage. This is useful because the rate of synovial fluid formation from the cartilage during loading conditions can be assumed to depend on the compression of the cartilage. With a higher compression, more synovial fluid will be released from the cartilage and vice versa. This information can be built into a relationship for the formation rate of cartilage used in [Eq. \(12.2\)](#). For reference, stress and strain are defined as

$$\sigma = \frac{F}{A} \quad (12.7)$$

and

$$\varepsilon = \frac{\sigma}{E} = \frac{\Delta l}{l} \quad (12.8)$$

respectively.

Example 12.4

Using the results obtained from the in-text Example 12.3, calculate the cartilage stress and the change in length of cartilage on the femoral head. Assume that the cross-sectional area of the cartilage is 150 cm^2 , that the elastic modulus for cartilage is 25 MPa , and that the cartilage thickness is 1.5 mm . Also assume that all of the forces acting on the femoral head are transmitted through the cartilage.

Continued

Example 12.4 (cont'd)**Solution**

$$\sigma = \frac{F}{A} = \frac{11,011\text{N}}{150\text{ cm}^2} = 0.734\text{ MPa}$$

$$\epsilon = \frac{\sigma}{E} = \frac{0.734\text{ MPa}}{25\text{MPa}} = 0.029$$

$$\Delta l = \epsilon l = 0.029(1.5\text{ mm}) = 0.044\text{ mm}$$

This suggests that the thickness of the cartilage changes from 1.5 to 1.456 mm in thickness.

12.6 Transport of molecules in bone

Fluid transport within the lacunar–canalicular system is key for the passage of nutrients, ions, and wastes to and from the cells that make up bone tissue. As we have discussed earlier, osteoblasts reside on the surfaces of bone tissue. These cells can produce bone matrix and can become embedded within the calcified matrix. Cells that become embedded within the formed bone matrix are termed *osteocytes*, are located within individual lacunae, and are highly connected to each other via canalicular passages (Fig. 12.8). The lacunar–canalicular passage system provides a rapid pathway for movement of solutes throughout calcified bone tissue. Previous work has shown that within 30 minutes of an intravenous injection of a solute with a molecular weight in the range of 40,000 Da, the same solute was found

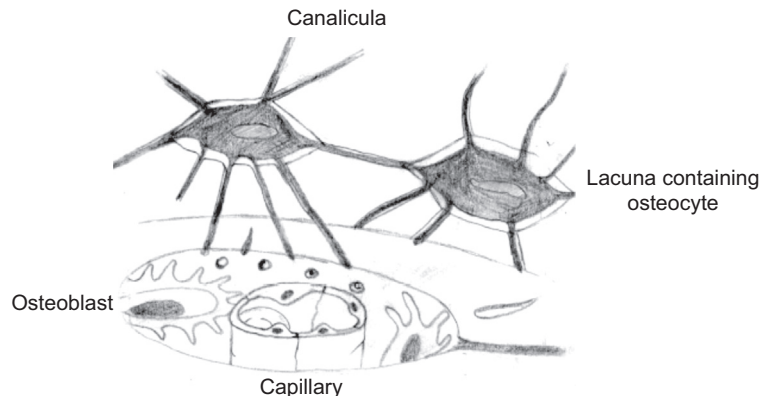


FIG. 12.8 Relationship between capillaries and the osteoblasts/osteocytes within a lacunae. As illustrated in this figure, canaliculi penetrate toward the central canal and help nutrient delivery throughout the entire bone. (Modified from *Handbook of Physiology: Section 2. The cardiovascular system. Vol. 3. Peripheral circulation and organ blood flow, parts 1 and 2.* Edited by J. T. Shephard and F. M. Abboud. American Physiological Society. Waverly Press, Baltimore, MD)

throughout the canalicular system and within the lacunae of bone tissue. This suggests that transport through this system is highly efficient and quick.

Many groups have worked on identifying the mode of transport from capillaries within the Haversian canal system to cells on the periphery of bone tissue. These groups have shown that first, molecules are transported across the endothelial cell barrier using typical methods previously described in this textbook (e.g., hydrophilic molecules diffuse through the intercellular cleft, lipophilic molecules are transported with a vesicle transport mechanism). Once these nutrients enter the interstitial fluid, the fluid flows through the lacunar–canalicular complex, primarily using a diffusion-based process. Through similar transport processes, nutrients can enter cells that have entered the canalicular system and wastes can enter the interstitial fluid. However, this transport system suggests the necessity of a lymphatics system (or an analogous system), since the fluid flow is largely unidirectional within the lacunar–canalicular complex. It appears that the lymphatic system does not enter the lacunar–canalicular complex, but instead resides on the periosteal surface (outer surface of bone), in close proximity to the periosteal capillaries and the peripheral lacunae. The presence of lymphatics at this one location also supports the notion of unidirectional fluid flow through the lacunar–canalicular system, because the reuptake of interstitial fluid within the venous portion of the Haversian canal system cannot accommodate all of the fluid that is lost along the arterial portion of the Haversian canal system (recall the discussion of Starling's relationship).

This leads to some important generalizations regarding the movement of solutes from the capillary fluid into the interstitial fluid of bone. The three broad categories of substances that can be transported across the capillary wall are (1) small hydrophilic molecules, (2) small lipophilic molecules, and (3) large molecules (such as plasma proteins). As we have learned previously, the majority of large molecules do not cross the capillary wall and thus they establish an osmotic gradient between plasma and interstitial fluid. There are some instances in which these molecules are transported, primarily in pathological conditions such as an inflammatory reaction, but they can be transported under physiological conditions using vesicular trafficking methods across the endothelial cell wall. In bone, it appears that these large proteins are transported at a higher rate than most systemic vascular beds, and it appears that these proteins play three important roles within bone tissue. First, plasma proteins that enter the interstitial space of bone appear to act as carrier molecules for hormones and vitamins. Thus, the transport of proteins into the bone interstitial space acts to regulate bone cell activity. Second, the transport of plasma proteins into bone interstitial space appears to dictate the osmotic pressure of bone interstitial fluid and thus the transport of all molecules into bone interstitial space. Compared with other interstitial fluids, the concentration of solutes seems to be highly variable, and thus this movement may provide a mechanism to stabilize the osmotic pressure. A third effect of transport of plasma proteins in bone interstitial fluid is that they can help buffer the pH of the fluid that is transported through the lacunar–canalicular system. Because there is reduced availability of a direct blood supply, the fluid within the lacunar–canalicular system would be very highly susceptible to changes in any solute concentration based on the actions of cells within a localized region. Plasma proteins may help reduce this susceptibility to changes in pH. Remember, however, that any changes to the bone interstitial fluid compartment may have significant implications for bone

homeostasis because the clearance of these changes occurs over a very large length scale (e.g., the bone lymphatic system is present only on the periosteal surface).

The transport of hydrophilic and lipophilic molecules through bone is less complex and appears to be under less control than the transport of large plasma proteins. It is typical for small hydrophilic solutes to diffuse out of the capillary through the intercellular cleft and become evenly distributed throughout bone tissue. Local concentration gradients would account for the movement of solutes into or out of the osteocytes and toward the lymphatic system, which always acts as a sink for dissolved solutes. The transport of lipophilic solutes would follow an analogous path, except that this type of molecule would be transported through endothelial cells, which make up the vascular wall. These molecules would be transported through the bone interstitial space with varying mechanisms that depend on the molecular structure and whether specific transport mechanisms exist for that molecule.

This leads us to the question of how efflux of nutrients from the bone interstitial space into the periosteal capillaries or periosteal lymphatics is regulated. We can imagine two scenarios for efflux of nutrients. The first is the case in which the movement of solutes is limited by the flow of bone interstitial fluid, and the second is when the movement of solutes is limited by a barrier. For most solutes that have been studied it appears that the efflux of solutes out of the lacunar–canalicular system is limited by the transport through a barrier and cannot be completely described by clearance relationships. It is currently thought that in these cases, efflux occurs because of an energy-dependent mechanism that functions based on ligand binding relationships. The efflux of potassium and calcium from the bone interstitial fluid follows these barrier-limited relationships.

12.7 Disease conditions

12.7.1 Synovitis

Synovitis is a condition characterized by an inflammation of the synovial membrane. As discussed earlier, synovial fluid is secreted by the synovial membrane, and it is this process that is disrupted during inflammation of the synovial membrane. During synovitis, the permeability of the synovial membrane increases, allowing white blood cells into the joint space to defend against the infection. Under most instances of synovitis, an increase occurs in the number of polymorphonuclear leukocytes, and these are the principle cells observed in a higher concentration within the synovial fluid. White blood cells in the joint space release enzymes that can degrade the cartilage and the proteoglycan core if the condition persists for an extended period. This will cause a great deal of pain, and the overall lubrication of the joint will be reduced because (1) the cartilage will not store as much synovial fluid as normal, (2) the shock-absorbing function of the cartilage/synovial fluid will be reduced, and (3) bone may come into contact with bone. A secondary effect associated with synovial membrane breakdown is an increase in interstitial fluid movement into the joint space. Increases in interstitial fluid within the joint space will decrease the viscosity of the synovial fluid and increase the hydrostatic pressure within the joint space. A decreased synovial fluid viscosity will reduce the ability of synovial fluid to protect the joint during compressive loading. Furthermore, an increased hydrostatic pressure within the joint space acts to decrease the mobility of

the joint and can increase the forces exerted within the joint space. Combined, the overall effects of synovitis are a loss of the synovial fluid properties, a possible degradation of the cartilage, and a decreased joint mobility. Synovitis can be recognized by a swelling of the joints and is diagnosed by taking a sample of the synovial fluid from the patient. Minor synovitis is common during arthritis and is generally treated with antiinflammatory medications.

In severe cases of synovitis, inflammatory cells and/or the products these cells' release can burrow beneath the articular cartilage layer. In these cases, a significant increase in the presence of collagenase and elastase proteins has been observed. In most instances, the subchondral bone density decreases through an enhancement of resorption processes. If the inflammatory processes are quelled, it is possible for the damage to bone to be repaired, given sufficient time. Again, however, any damage to the articular cartilage persists because of the limited capability of chondrocytes to reform the specific proteins needed to maintain cartilage.

12.7.2 Bursitis and tenosynovitis

Bursitis and tenosynovitis are forms of nonarticular rheumatism that result from the inflammation of the bursa or tendons that surround the joint capsule. In these cases, impairment to the joint and some of the fluid properties can be observed.

Bursae are closed sacs that are filled with synovial-like fluid. These sacs can be found at sites of interaction between skin, ligaments, tendons, bone, and muscles. Inflammatory cells and/or mediators found during synovitis can migrate to the bursa, inducing secondary inflammatory sites. It is also possible for bursitis to form under direct trauma to the bursa. In general, as the bursa becomes inflamed, its size will increase. This makes the bursa more susceptible to wear by friction and can induce a tear in the lining of the bursa. In most instances, bursitis is treated with mild antiinflammatory mediators, either systemically or locally.

Tenosynovitis is an inflammation of the sheath that surrounds the tendons. These linings, much like bursa, are composed of synovial linings and can experience inflammation similar to synovitis. When this sheath becomes inflamed, it is common for the joint to "lock up" and cause significant pain and decreases in locomotion. In some instances, the inflammation of the tendon is so severe that the tendon sheath must be removed surgically.

Summary

- 12.1** There are 206 bones in the human body that are divided into bones that compose the axial skeleton and those that compose the appendicular skeleton. All bones have the function to support and protect the body, store minerals, produce blood cells, and act as levers for motion. Long bones are divided into three major sections: the epiphysis, the metaphysis, and the diaphysis. The epiphysis is composed of spongy bone and can withstand loads from many different directions. The diaphysis is composed of compact bone and can withstand loads in one main direction. The metaphysis is the interface of these two regions, where the bone type transitions. The bone extracellular matrix is composed of a hardened ground substance that is stiff because of the deposition of calcium salts. Hydroxyapatite crystals are a major component of the ground substance. Thirty-three percent of bone mass is accounted for by collagen fibers. There are four

types of bone cells that can be identified. These are the osteocytes, the osteoblasts, the osteoclasts, and the osteoprogenitor cells. The action and balance in actions of these four cell types determines the chemical makeup of bone. Bone is composed of a Haversian canal system structural unit. Each of these units has a central canal that is filled by an artery and vein. Concentric circles of bone surround this canal and are termed *lamellae*. Canaliculi run perpendicular to the Haversian canal and function to connect bone cells to each other. The junctions between bones form joints where bones can move around each other. The coefficient of friction between bones is relatively high, and in fact bones can wear on each other. The coefficient of friction is lowered through the presence of cartilage and synovial fluid.

- 12.2. Bone is perfused by a sparse capillary network that allows for the exchange of nutrients/wastes between blood and the bone cells. The vascular tree that is specific to bone can be subdivided into four general categories: the conduit vessels, the capillaries of bone, the lacunar–canalicular system, and finally the microcanalicular system. Within each Haversian canal system a small arteriole (which is capable of exchange) or a capillary is present. The percentage of water found within bone has been shown to be related to the extent of bone mineralization. Higher bone mineralization values are accompanied by lower percentages of water. This can be quantified by an increase in bone density. Bone mineralization increases primarily because there is a higher quantity of hydroxyapatite, which fills the water space in forming bone. The vast majority of water in bone is not found within the bone, per say, but rather in the blood and the extravascular spaces.
- 12.3. Synovial fluid fills the space between joints and is produced as an ultrafiltrate of interstitial fluid. The interstitial fluid is filtered by the synovial membrane and is very similar in composition to interstitial fluid, except that there is a significantly higher concentration of proteoglycans. These proteoglycans act to organize water (because they are highly charged) so that the overall synovial fluid can withstand a higher load. Cartilage also has a property of organizing and holding synovial fluid within the joint.
- 12.4. Synovial fluid enters the joint space as a filtrate through the synovial membrane. This membrane is composed of two layers: the synovium and the subsynovium. The synovium functions to prevent foreign particles from entering the joint space, while the subsynovium is composed of an extensive extracellular fiber mesh that acts to filter the interstitial fluid. The synovial membrane is actually a unidirectional valve because fluid can enter the joint space through the membrane, but the fluid does not exit the joint space through the synovial membrane. To model flow through the synovial membrane, we use a modified flux equation that accounts for the degradation rate and formation rate of species within synovial fluid. This can be represented as

$$\frac{\partial(Vc)_i}{\partial t} = (r_s A_s + r_c A_c - d - J)_i$$

The flow of species through the synovial space must also take into account a restricted diffusion coefficient that is based on the restricted movement of ions through the joint space

$$D_i = De^{(-\sqrt{\theta})\left(1+\frac{a_i}{a}\right)}$$

- 12.5. Using material developed in standard engineering statics and dynamics courses, the forces within joints can be solved by a direct summation of the forces that act within the joint and a summation of the moments about a certain location within the joint

$$\sum \vec{F} = m \vec{a}$$

and

$$\sum \vec{M} = I \vec{\alpha}$$

Recall from a mechanics of materials course that the deformation of a material can be described by the stress, strain, and elastic modulus. This is formulated as

$$\sigma = \frac{F}{A}$$

and

$$\varepsilon = \frac{\sigma}{E} = \frac{\Delta l}{l}$$

- 12.6. Fluid transport within the lacunar–canalicular system is key for the passage of nutrients, ions, and wastes to and from the cells that comprise bone tissue. Molecules are first transported across the endothelial cell barrier using typical methods. Once these nutrients enter the interstitial fluid, the fluid flows through the lacunar–canalicular complex, primarily using a diffusion-based process. It appears that the lymphatic system does not enter the lacunar–canalicular complex, but instead resides on the periosteal surface, in close proximity to the periosteal capillaries and the peripheral lacunae. Large proteins are transported through bone capillaries at a higher rate than most systemic vascular beds. Small hydrophilic solutes diffuse out of the capillary through the intercellular cleft and become evenly distributed throughout bone tissue.
- 12.7. Synovitis is a condition that is characterized by an inflammation within the synovial membrane. This process alters the formation of synovial fluid, and therefore, the overall lubrication of the joint space will be diminished. This would eventually lead to an abrasive wear of the cartilage and possibly the bone itself. A second possible outcome of synovitis is that the quantity of synovial fluid that is produced remains

the same but the composition of the fluid changes. Typically, there would be a decrease in the viscosity of the synovial fluid, which would tend to decrease its lubricating efficiency (and the fluid would not withstand the same amount of load as under normal conditions). Bursitis and tenosynovitis are similar pathological conditions that effect the bursa and tendon sheaths, respectively.

Homework problems

- 12.1. The formation of blood cells occurs within what component of the bones?
- 12.2. There are four critical functions of bones: protection of internal organs, support of the body, blood cell production, and regulation of internal calcium concentration. Discuss how bones conduct each of these four tasks.
- 12.3. What are the structural and functional differences between the diaphysis and the epiphysis locations within long bones?
- 12.4. Spongy bone can withstand stresses that arrive from multiple directions, whereas compact bone can normally withstand stresses in only one direction. Why is there this difference and what structures account for this difference?
- 12.5. What are the functions of the four types of bone cells?
- 12.6. We discussed some of the differences that are observed in the microvasculature (e.g., feeding arterioles and capillary beds) found in different bones and even within different regions of bone. Why do you suppose these differences are found? Does the anatomical organization of the bone and/or blood vessels solely account for these differences.
- 12.7. If the synovial fluid is not formed properly, there is the possibility for the cartilage at the ends of the bone to come into contact with each other. How can synovial flow be reestablished and what would happen if it were not reestablished?
- 12.8. Calculate the change in molecular volume of the synovial fluid if the formation rate of synovial fluid by the synovial membrane is $6.5 \mu\text{g}/\text{h}/\text{cm}^2$ and by the cartilage is $73 \text{ ng}/\text{h}/\text{cm}^2$. Assume that the synovial membrane area is 15 mm^2 and that of the cartilage is 25 mm^2 . The degradation rate of the synovial fluid is $23 \text{ ng}/\text{h}$, and the flux of synovial fluid out of the membrane is $0.97 \mu\text{g}/\text{h}$.
- 12.9. Calculate the restricted diffusion coefficient for proteoglycans within the synovial fluid if the time rate of change of proteoglycans within synovial fluid is $0.095 \text{ mg}/\text{h}$. The free diffusion for proteoglycans in water is $1.25_E - 7 \text{ cm}^2/\text{s}$. Assume that the degradation rate for proteoglycans is negligible and that the formation rate for proteoglycans within the synovial membrane and the cartilage is $2.2 \mu\text{g}/\text{h}/\text{cm}^2$ and $31 \text{ ng}/\text{h}/\text{cm}^2$, respectively. The area of the synovial membrane is 15 mm^2 and that of the cartilage is 25 mm^2 . The permeability of this proteoglycan through the synovial membrane is $1.23_E - 6 \text{ cm}/\text{s}$, and the concentration gradient for this proteoglycan is $0.07 \text{ mg}/\text{mL}$.
- 12.10. Consider a person who is standing on tiptoes on one foot. The forces acting on this joint are the person's weight (175 lb), the force of the muscle (F_M) acting through the Achilles tendon, and the joint reaction force (F_J) [Fig. 12.9](#) depicts the location and directions that the forces act on the ankle joint. The angle that the Achilles tendon

Homework problems (cont'd)

- makes in this position is 40 degrees, and the angle that the joint reaction force acts on the ankle is 75 degrees. Calculate the muscle force and the joint reaction force needed to maintain this position. Ignore the weight of the foot itself and geometrical considerations.
- 12.11. Calculate the stress on the cartilage and the change in length of cartilage, assuming that the force on the cartilage is 9875 N and that the diameter of the cartilage is 2 cm (assume that the cartilage has a circular area). The cartilage has a thickness of 1.5 mm and an elastic modulus of 250 MPa.
 - 12.12. Using the results from Homework Problem 12.11, calculate the change in molecular volume of synovial fluid if all of the criteria are the same as in Homework Problem 12.7, except that the formation of synovial fluid from cartilage now includes 142 ng/h/mm from compression.
 - 12.13. Discuss the movement of solutes within and to bone cells. Why is a robust lymphatic system missing from the Haversian canal system? What do you think is the primary mode of delivery and reuptake of solutes in bone?
 - 12.14. We described some of the mechanical properties of bone using elastic deformation principles. In your opinion, do these calculations suitably account for the mechanical deformations and loading conditions that bone experiences. If so, why? If not, propose some other variables that should be considered when quantifying loading dynamics on bones and discuss why you think these parameters are important.

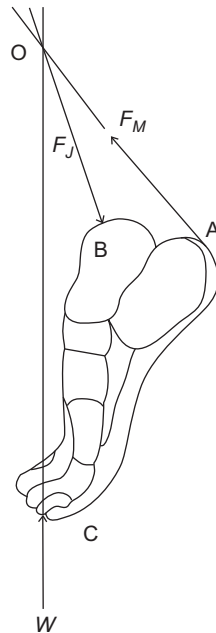


FIG. 12.9 Diagram of a foot for Homework Problem 12.10. (Modified from N. Ozkaya, M. Nordin, *Fundamentals of Biomechanics: Equilibrium, Motion, and Deformation*, Springer, New York, NY, 1999.)

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Flow through the kidney

LEARNING OUTCOMES

- Describe the physiology and anatomy of the kidneys
- Explain the unique characteristics of the renal circulation
- Identify the functional unit of the kidney
- Detail the flow of blood and its distribution throughout the kidney and to the nephron
- Evaluate the flow through a nephron
- Model the forces that alter glomerular filtration
- Examine the feedback mechanisms within glomerular filtration
- Calculate the filtered load for various metabolically important compounds
- Distinguish between tubule reabsorption and secretion
- Examine the mechanisms for tubule reabsorption
- Formulate a function for the amount of a particular substance excreted
- Describe the filtration rate of a single nephron and how this relates to the overall kidney function
- Explain the flow of blood through the peritubular capillary system
- Compare feedback mechanisms for sodium absorption
- Discuss the autoregulation of blood flow and urine formation within the kidney
- Use compartmental analysis to describe the movement of solutes throughout the nephron
- Model multicompartiment systems
- Describe extracorporeal flows
- Discuss disease conditions that commonly affect the kidney

13.1 Kidney physiology

The kidneys perform two critical functions for the body. The first is the removal of metabolic waste products, foreign particles, and metabolites from the body. If the kidneys are functioning properly, the removal of these waste products should occur as fast as the wastes are being generated through cellular metabolism, such that there is essentially no buildup of toxins within the body. Under normal conditions, the processes that occur within

the kidneys occur at about this rate. The second critical function that the kidneys perform is the maintenance of the blood volume within the body and in parallel the regulation of the concentration of physiologically important molecules within blood. This is maintained as a balance between which molecules and fluids are ingested versus which compounds are excreted from the body (e.g., after a person eats a bunch of bananas, there may be a large excess of potassium ions within the body, and this excess would normally be removed by the kidneys; however, if a person does not eat a significant amount of bananas, the amount of potassium removed by the kidneys would likely be significantly less). The first function occurs through a filtration of the blood plasma. The second function occurs through the reabsorption of molecules from the filtrate at a rate that depends on the need of the body combined with an added secretion of unnecessary compounds from blood into the filtrate of blood. Following the banana example, when potassium ions are in excess, the reabsorption of potassium will be low; however, if the potassium ion concentration is depleted within the blood plasma, then the reabsorption of potassium will be higher. At the same time, the secretion of potassium may be altered to dictate the potassium ion concentration.

The kidneys are located along the posterior wall of the abdomen and are approximately the size of a clenched fist. Each kidney is indented at its interior medial location, and this location is termed the *hilum* (Fig. 13.1). At the hilum, the renal artery, which branches directly from the abdominal aorta, and the renal nerve enter the kidney. Also at this location, the renal vein, which converges with the inferior vena cava, the renal lymphatic vessels, and the ureter, leaves the kidney. The kidney itself has been divided into two main sections, which are related to the functions that occur within those sections: the outer cortex and the medulla. The outer cortex is the location where plasma is filtered, and reabsorption and excretion generally occur within the medulla (note that there are two main types of nephrons, the cortical nephron and the juxtamedullary nephron, which filter and secrete nutrients and wastes in slightly different locations and with slightly different mechanisms, but we will discuss these differences later). Each renal artery enters the kidney at the hilum and branches to form smaller arteries until they penetrate throughout the entire outer cortex of the kidney (the kidney has a unique blood supply and perfusion mechanism that will be described in Section 13.2). At this point, the vessels are the size of arterioles. The smallest arterial blood

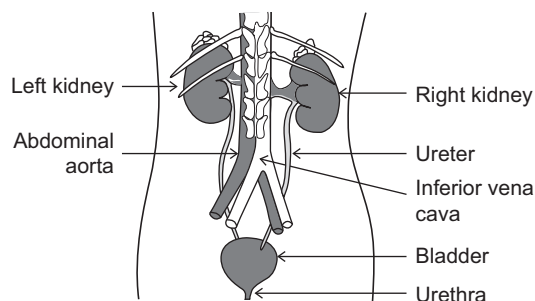


FIG. 13.1 Anatomical location (posterior view) of the kidneys, showing their location in relation to other structures in the abdomen. The kidneys are protected by the 11th and 12th ribs (both shown). Urine formed in the kidneys passes through the left and right ureter into the bladder. As the bladder fills, urine can be removed from the body by the urethra. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, Pearson, New York, 2018.)

vessel within the kidney circulation is termed the *afferent arteriole*, which supplies each nephron (the functional unit of the kidney) with blood. The afferent arterioles branch into the glomerular capillaries, which then converge to an efferent arteriole. A second capillary network, termed the *peritubular capillaries* (surrounding the cortical nephrons) or vasa recta (surrounding the juxtamedullary nephrons), surrounds the nephron, and then these capillary beds converge to renal venules. These venules converge to larger veins and eventually the renal vein, which exits the kidney at the hilum. Interestingly, slightly more than 20% of the cardiac output is directed to both kidneys under normal resting conditions. This supports the important role for the kidneys in maintaining homeostasis.

A unique characteristic of the renal circulation is that it has two capillary beds, which are separated by an arteriole. Interestingly, the efferent arteriole primarily regulates the pressure in both capillary beds and hence the flow rate throughout each capillary network. The afferent arteriole, to a lesser extent, regulates the pressure and flow throughout both capillary networks. Unlike the systemic and respiratory circulatory systems, the hydrostatic pressure within the glomerular capillaries (the first capillary bed) is very high, around 60 mmHg. This allows for a rapid filtration of fluid and small molecules from plasma (termed the plasma filtrate), because there is a very high hydrostatic pressure gradient between the blood and the filtrate in the nephrons (this filtration can be described by Starling's law, as we have discussed in a previous chapter). The pressure within the peritubular capillaries (the second capillary bed) is much lower; under normal conditions the pressure is in the range of 15 mmHg (which is similar to previously discussed systemic capillary beds), which allows for rapid absorption of any filtered molecules. Changes within the cross-sectional area of the afferent arteriole and the efferent arteriole can drastically alter the pressure within both of the kidney capillary beds, acting as a regulator for the filtration and absorption rates.

The nephrons are located within the cortex and medulla of the kidney (Fig. 13.2). There are nearly 2 million nephrons within the adult body, and each one can form urine. Nephrons do not regenerate after birth; therefore, with injury, disease, and aging there is a loss of the quantity of nephrons within the body (to about 50% of the total quantity at the age of 80). The kidneys and the remaining functioning nephrons can adapt to this decrease in functional unit quantity and still produce enough urine properly to remove wastes and toxins without any adverse side effects. If the kidneys do not function properly and wastes begin to accumulate in the body, dialysis or surgical procedures may be recommended depending on the severity of the case (see Sections 13.10 and 13.11). Each nephron is composed of two major parts. The first is the glomerulus, which consists of the glomerular capillaries and Bowman's capsule. The glomerulus functions to filter fluid and compounds from blood. The second major component of the nephrons is a tortuous tube that modifies the filtered fluid into urine through differential reabsorption and secretion of metabolically important molecules.

The glomerular capillaries are very similar to all other capillaries within the body, except that they are under a very high hydrostatic pressure (approximately 60 mmHg). In addition, unlike other capillary beds, the glomerular capillaries are surrounded by epithelial cells (termed podocytes). In one sense, these capillaries are not only composed of a single endothelial cell wall, but they also have a second layer composed of epithelial cells. However, the epithelial layer does not affect the flow within the blood vessel but functions to partially regulate the blood filtration (see Section 13.3). The glomerular capillary epithelial cells are surrounded by Bowman's capsule, which is connected to the nephron tubule system. All fluid

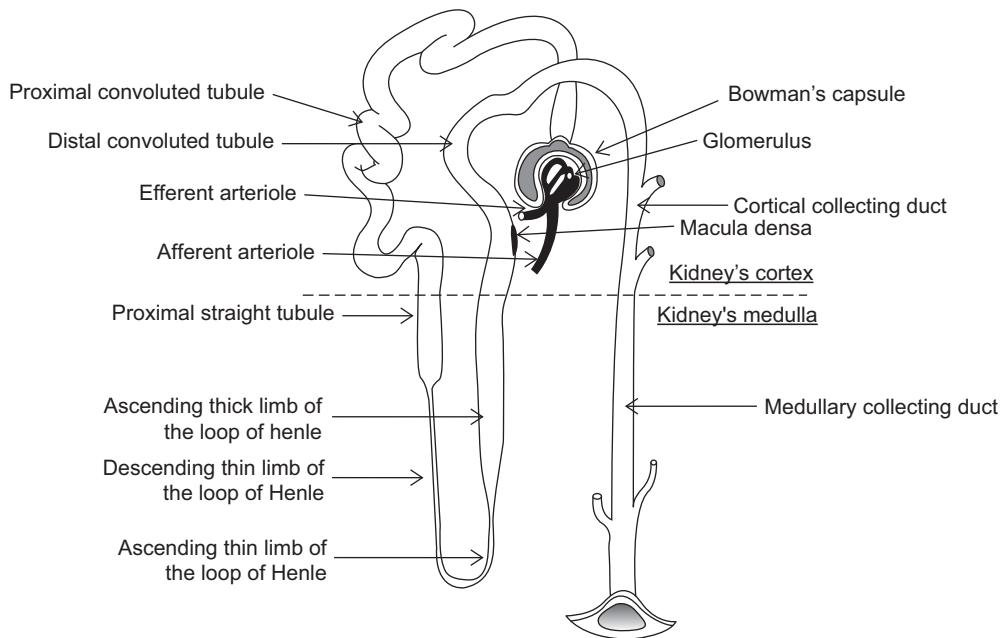


FIG. 13.2 Schematic of the functional unit of a kidney: the nephron. This figure illustrates the anatomical arrangement of the nephron. Note that the macula densa is a grouping of cells and not a particular region of the kidney. Blood is filtered in the glomerulus and the filtrate passes through the nephron (proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct) to form urine. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, Pearson, New York, 2018.)

and compounds that are filtered from the glomerular capillaries must pass through the endothelial cell barrier and the epithelial cell barrier that make up the glomerular capillaries before entering Bowman's capsule. The entire glomerulus structure lies within the cortex of the kidney. A term given to the glomerulus and Bowman's capsule is the renal corpuscle.

Any fluid that enters Bowman's capsule passes directly into the continuous renal tubule. The renal tubule is a narrow-diameter hollow cylinder that is composed of a single layer of epithelial cells, which are attached to a basement membrane. There are 10 different types of epithelial cells found within the nephron. Each of these epithelial cell types form a continuous segment of the nephron, each with a slightly different function during urine formation. These 10 segments are typically grouped into 5 tubule systems, each with their own common function. The first epithelial cell type is found within Bowman's capsule (the first tubule system) and functions to shunt the plasma filtrate into the proximal tubule. These epithelial cells have little to no role in reabsorption or secretion. The proximal tubule (the second tubule system) is divided into two segments, each with its own specific epithelial cell composition. The first segment is the proximal convoluted tubule, and the second segment is the proximal straight tubule. The third tubule system is termed the *loop of Henle* and forms a 180-degree turn within the nephron. The loop of Henle is divided into the thin descending limb, the thin ascending limb, and the thick ascending limb. Very specialized cells, termed the *macula densa cells*, are located within the thick ascending limb of the loop of Henle (more details regarding this specialized location will be discussed later). The fourth tubule system is termed the *distal*

convoluted tubule, which is composed of only one segment given the same name. The last tubule system is termed the *collecting duct system* and is composed of the connecting tubule, the cortical collecting tubule, and the medullary collecting tubule. As the reader can imagine, each epithelial cell type has a different permeability toward compounds within the plasma filtrate, which is termed the *glomerular filtrate* once the fluid is within the nephron tubule system. As one can imagine, the different functions of the nephron based on the location within the nephron structure are dictated by the epithelial cell type that is present in the location. Therefore, the function of these locations can be distinguished from the segment's preceding and following segment based on the type and characteristics of the particular epithelial cell present.

In subsequent discussions, it will become apparent that there are important differences in nephron function based on the regional location within the kidney. For reference, the renal corpuscle, the proximal convoluted tubule, the distal portion of the thick ascending loop of Henle, the distal convoluted tubule, the connecting tubule, and the cortical collecting tubule are all generally located within the kidney's cortex. The proximal convoluted tubule, the thin descending limb, the thin ascending limb, the proximal portion of the thick ascending loop of Henle, and the medullary collecting tubule are all located within the kidney's medulla. It is also important to note that the entire tubule system is surrounded by the peritubular capillaries or the vasa recta (although these are not shown in Fig. 13.2). For reference, in humans approximately 85% of the nephrons are cortical nephrons surrounded by the peritubular capillary system and 15% of the nephrons are juxtamedullary nephrons surrounded by the vasa recta.

One of the most unique locations within the nephron unit is termed the *juxtaglomerular apparatus* (Fig. 13.3). At this location, the thick ascending loop of Henle passes directly between the afferent arteriole and the efferent arteriole, which feeds the glomerular capillaries and the peritubular capillaries of the same nephron. In the thick ascending loop of Henle, there are specialized epithelial cells termed the *macula densa cells*, which are in direct contact with specialized cells present within the afferent arteriole. The afferent arteriole specialized cells are termed the *juxtaglomerular cells*. This location provides a feedback mechanism within each nephron to control the filtration rate of the glomerular capillaries of that nephron.

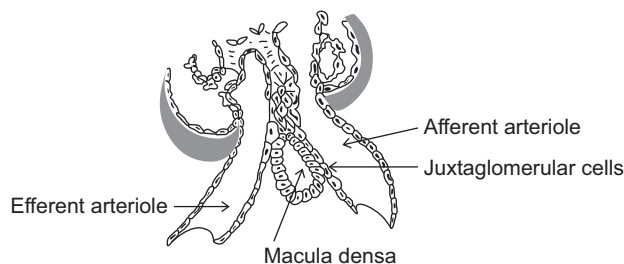


FIG. 13.3 Anatomical arrangement of the juxtaglomerular apparatus, which can monitor and regulate the glomerular filtration rate, through the production of renin. The thick ascending loop of Henle passes between the afferent and efferent arterioles of the same nephron to form the juxtaglomerular apparatus. Depending on the concentration of sodium ions and chloride ions, the macula densa cells can either increase or decrease the production of renin. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath, and Bartholomew, Pearson, New York, 2018.)

The exact details of the feedback mechanism are currently unknown, but there is significant work being conducted on identifying the exact mechanisms, but what is clear is that when the flow decreases within the loop of Henle, there is an increased reabsorption of sodium and chloride ions into the peritubular capillaries (more details regarding reabsorption can be found in [Section 13.4](#)). An increased reabsorption of these ions within the early tubule sections decreases the concentration of these ions within the plasma filtrate passing through the ascending loop of Henle. The macula densa cells are sensitive to the sodium and chloride concentrations, and when either concentration reduces, a signal is sent from the macula densa cells that has two effects on nephron function. The first effect is that the resistance of the afferent arteriole increases (e.g., the diameter is reduced), thereby decreasing the amount of filtrate within the tubule system. The second effect is the production of renin from the juxtaglomerular cells. Renin is an enzyme that causes an increased production of angiotensin I, from angiotensinogen, which is then rapidly converted to angiotensin II in the kidney and/or lung tissue. Angiotensin II formation is mediated by the angiotensin-converting enzyme (ACE), which is a common target for cardiovascular disease drugs. Angiotensin II constricts the systemic arterioles, which increases the total peripheral resistance and thus decreases blood flow throughout the systemic circulation. The net effect of this is to decrease the filtration of sodium into the kidney and, thus, increase the retention of sodium in plasma. Angiotensin II has other functions throughout the body, such as an increased release of aldosterone from the adrenal glands. If the processes that control the flow through the glomerular capillaries are functioning properly, the glomerular filtration rate changes marginally with large changes in systemic arterial pressure, and therefore, the kidneys continue to produce urine at a normal rate. Molecular concentrations, which partially dictate osmotic pressure, are the more important contributor to glomerular filtration rate.

13.2 Distribution of blood in the kidney

As we briefly mentioned in the previous section, the renal artery brings a direct supply of blood into the kidneys. This major artery branches directly from the aorta and receives close to 20% of the cardiac output under normal resting physiological conditions. Immediately after the renal artery passes through the hilum, the artery branches into interlobar arteries, which pass between the lobes of the kidney ([Fig. 13.4](#)). The interlobar arteries pass through the kidney and approximately at the border between the medulla and the cortex, these arteries bifurcate and bend, connecting to neighboring bifurcated and bent interlobar arteries. The vessels, which are now termed *arcuate arteries*, follow the boundary between the medulla and cortex of the kidney. Many small arteries branch from the arcuate arteries, which bring blood toward the outer cortex of the kidney. These small arteries branch perpendicularly from the arcuate arteries and are now termed *radial arteries*. The afferent arterioles that enter the nephron units are direct branches from the arcuate arteries.

The venous circulation through the kidney follows a similar path, but in reverse to the described arterial path. The venous portion of the peritubular capillaries and the vasa recta converge into radial veins, which converge into one larger arcuate vein. The arcuate veins run parallel to the arcuate arteries and converge in between the renal lobules into the

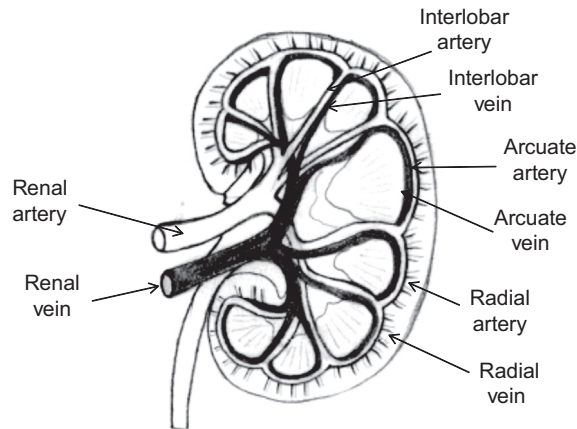


FIG. 13.4 Schematic of the renal vasculature, which makes up one renal artery that bifurcates into the interlobar arteries. The interlobar arteries bend over the renal pyramids to form the arcuate arteries, which then have the radial arteries branching off of these vessels. The afferent arterioles to each glomerulus form from the radial arteries. The venous system follows a path similar to that of the arterial system.

interlobar veins. Near the hilum of the kidney, the interlobar veins converge into the renal vein. These vessels can be seen on [Fig. 13.4](#) as well.

We highlighted briefly the difference between cortical nephrons and juxtamedullary nephrons. One of the principle differences is that the peritubular capillaries of the cortical nephrons do not penetrate as deep into the medulla as the vasa recta capillaries do for the juxtamedullary nephrons (the peritubular capillaries and the vasa recta capillaries are the second capillary network for the different nephron types). For cortical nephrons, the efferent arteriole diverges into an anastomosing capillary network. This network, termed the *peritubular capillaries*, is primarily used as a source of exchange for nutrients and wastes through reabsorption and secretion processes. To a lesser extent these capillaries supply nutrients to the renal tissue. In contrast, the vasa recta of juxtamedullary nephrons are primarily used to supply deep renal tissue with nutrients and maintain the osmotic concentration gradients necessary for reabsorption and secretion of all the nephrons. Note that these are critical important functions and that they are accomplished by approximately 15% of the nephrons, reserving most of the nephrons for blood filtration, absorption of metabolically important nutrients, and removal of wastes and toxins. This uneven distribution of blood flow within the kidneys has been observed experimentally, and some have suggested that during pathological events the distribution of blood between the cortex and the medulla is altered. It is perhaps even more important to recognize that not all nephrons, even those defined as cortical nephrons or juxtamedullary nephrons, function the same and part of this functional difference is possibly due to the difference in blood flow distribution to each of the nephrons.

Originally, researchers speculated that blood flow to different nephrons was determined based on the size of the glomerular capillaries; the glomerular capillary beds of juxtamedullary cortex nephrons are larger than the glomerular capillaries of the cortical nephrons. In parallel with this, it had been observed that the nephron filtration rates are significantly

greater for the juxtaglomerular nephrons compared with the cortical nephrons. It has been speculated that part of this uneven distribution of blood flow is due to the longer length of the tubule system that is accompanied by a longer length of capillaries (e.g., the vasa recta tend to have a longer length compared with the peritubular capillaries). However, this has been difficult to observe under physiological conditions. A second factor that may play a role in this uneven distribution is that the preglomerular vessels (e.g., afferent arterioles) have different size distributions under resting conditions between the various nephrons. As we have learned in previous sections, the diameter of the blood vessels is the most effective way for the cardiovascular system to control the perfusion rate through that same vessel; therefore, it follows that vascular beds with different perfusion rates should have different resting diameter values. This also has been somewhat difficult to observe, although some groups have used various-sized microspheres (in the range of 15 to 50 μm in diameter) to observe where the spheres get trapped/stuck within the renal circulation.

The blood flow through the medulla of the kidney has some added functions that were not considered for cortical blood flow. Not only does medullary blood flow provide nutrients and remove wastes from the kidney tissue source, medullary blood flow must remove excess water that has been reabsorbed along the collecting duct length and it must accomplish this task without disturbing the osmotic pressure gradient of the medulla interstitial space. Recall that the osmotic pressure gradient is used to maintain the countercurrent exchange gradient to absorb and secrete materials from each nephron. These apparently contradictory roles of absorbing water and maintaining the osmotic gradient, are primarily completed by the vastly different vasculature of the outer medulla compared with the inner medulla. To orient yourself to the anatomical arrangement of the nephron within the medulla, the outer medulla primarily consists of the thick ascending limb of the loop of Henle, the proximal straight tubule, and portions of the medullary collecting duct, whereas the inner medulla primarily consists of the thin descending and thin ascending limbs of the loop of Henle and the distal portions of the medullary collecting duct (see [Fig. 13.2](#)). All of the medullary vasculature arises from the efferent arteriole (primarily from the juxtamedullary nephrons). In the outer medulla these capillary beds form extensive anastomosing networks that surround the nephron tubule system. These vessels converge into larger veins that ascend along the tubular section that joins with the venous system of peritubular capillaries within the cortex to form the radial veins. In contrast, the vasculature of the inner medulla is composed of a few small vascular plexuses that surround the different levels of the thin limb sections of the loop of Henle and the distal medullary collecting duct. These vessels arise from the vessels distal to the efferent arteriole, but have a very different organization, hence the differentiation between the peritubular capillaries (which are more extensive, more branching, and surround a large section of the nephron tubule) and the vasa recta (which are less branching, less extensive, and surround well-defined sections of the tubule system, in well-defined arrangements; note that vasa recta is a Latin phrase that when translated to English means straight vessel). The venous flow from the vasa recta converges directly with arcuate veins.

Many groups have investigated the hydrostatic and oncotic pressure differences between the descending and ascending sections of the vasa recta. The hydrostatic pressure difference between the descending and ascending vasa recta is in the range of 2 to 4 mmHg and is in the range of 10 to 15 mmHg. The oncotic pressure difference is typically in the range of 10 mmHg and varies from 20 to 30 mmHg under normal conditions. The large difference in oncotic

pressure has been attributed to the reabsorption of water in the vasa recta along the ascending limb. As described earlier, there is also a large difference in flow between the vasa recta (and hence the medulla) and the peritubular capillaries (the cortex). This has experimentally been shown to be caused by the many parallel branches of capillaries that arise from one efferent vessel; it is typical for more than 20 vessels to diverge from the efferent arteriole. Recall though that the total perfusion of the kidney is quite high, and we are making the point that the medullary blood flow is slow compared with the cortical blood flow. The cortical blood flow rate is in the range of $0.5 \text{ mL} \cdot \text{min}^{-1}$ (per gram of tissue), which is similar to brain perfusion rates and considerably higher than most tissues under resting conditions. The transit time for a single red blood cell through the vasa recta is on the order of 30 to 40 seconds, whereas the transit time for a single red blood cell in the peritubular capillaries is on the order of 1 to 2 seconds. This slow transit times allows for the equilibration of materials within the descending and ascending limbs of the vasa recta, preventing the loss of the osmotic gradient within the kidney interstitial space. Thus, the microcirculation of the kidney is highly specialized for the salient functions that the kidney accomplishes.

13.3 Glomerular filtration and dynamics

The basic function of the nephron can be divided into three processes: filtration, reabsorption, and secretion. Filtration occurs within the glomerulus of all nephrons and will be the focus of this section. Reabsorption and secretion occur within the tubule section of the nephron and will be discussed in [Section 13.4](#). Filtration is the process by which some components of plasma enter the nephron tubule system. Reabsorption is when compounds are removed from the filtrate and reenter the peritubular capillaries or vasa recta capillary system. Secretion is when compounds are again removed from plasma of the peritubular or vasa recta capillary system and then enter the tubule system of the nephron. It is important to note that for each substance in the blood (except for cells and proteins), there is a particular combination of filtration, tubule reabsorption, and tubule secretion that occurs to remove the compound from the body, maintain the compound at a particular concentration in the body or retain all of the compound within the body ([Fig. 13.5](#)). Under normal conditions, cells and proteins should not enter the nephron tubule system from the glomerular filtrate and thus are excluded from this discussion.

Furthermore, the glomerulus acts as a filter for all of the remaining substances within plasma. The glomerular filtrate contains all of the noncellular compounds in plasma, except for proteins, at nearly the same concentration as found in plasma. Glomerular filtration is a bulk flow process, where water and all of the dissolved components can move freely between the vascular space and Bowman's capsule. Proteins do not move with this filtrate process because most of the pores within the glomerular capillaries are negatively charged and most of the plasma proteins also have a partial negative charge. In addition, most high-molecular-weight compounds cannot move through the pore space themselves because of a size restriction. As stated earlier, the majority of low-molecular-weight compounds can move freely into Bowman's capsule, except for those molecules that are associated with plasma proteins. For instance, most plasma calcium ions are associated with plasma proteins and are therefore not generally filtered by the glomerulus. Calcium ions can be actively secreted into the nephron along the peritubular capillary system, if necessary.

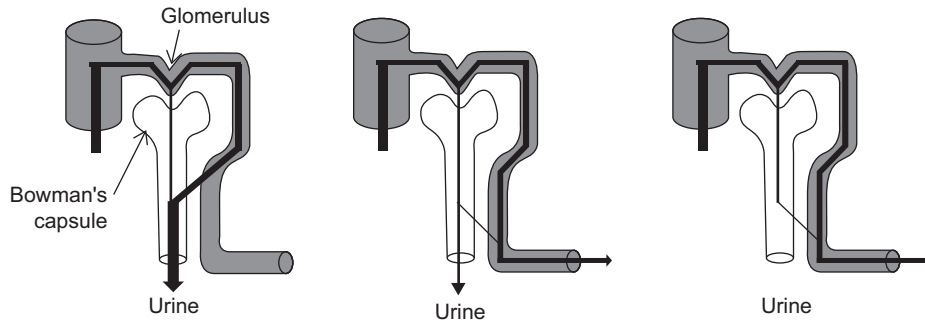


FIG. 13.5 Three possible scenarios for glomerular filtration, tubule secretion, and tubule reabsorption. In the first case, a small amount of substance is filtered and a large amount is secreted, so that there is a minimal concentration left in the peritubular capillaries. In the second scenario, some of the substance is filtered and reabsorbed. Urea would fall under the first case (although it is not completely secreted), bicarbonate would be an example for the second case, and glucose would be an example for the third case. (Modified from Widmaier et al., 2007.)

The effective flow rate of blood into the glomerular capillaries from the afferent arteriole is in the range of 600 mL/min. The effective glomerular filtration rate is on the order of 120 mL/min; thus, approximately 20% of the plasma is removed within the glomerulus to form the glomerular filtrate that enters the nephron tubule system. The efferent arteriole flow rate is in the range of 480 mL/min. Questions remain on how the glomerular capillaries accomplish this task and how they restrict the movement of species into the filtrate. The barrier to diffusion out of the glomerular capillaries consists of three layers: the endothelial cells that make up the capillaries, a basement membrane that surrounds the capillaries, and podocytes that surround the basement membrane (Fig. 13.6).

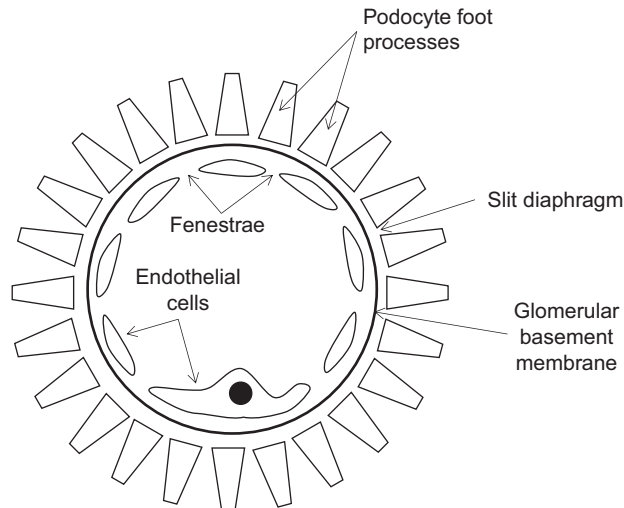


FIG. 13.6 Cross-section of a glomerular capillary surrounded by a basement membrane and foot processes of podocytes. The integrity of this barrier is critical to the processing of plasma and the production of the glomerular filtrate. For each particular molecule, a sieving coefficient can be defined that can be used to describe the filtration of that compound. The sieving coefficient is directly related to the integrity of this barrier.

Endothelial cells that make up the glomerular capillaries are fenestrated capillaries, which are capillaries that have pores throughout the entire cell. These pores are designed to have negligible resistance to fluid flow and solute movement, but because of the pore size they restrict the movement of all cellular matter. The diameter of the pores is generally in the range of 100 nm, which allows the passage of all plasma constituents, including plasma proteins, and the fenestrae cover nearly 20% to 25% of the entire capillary surface area (fenestrae translates to English as window). The basement membrane is primarily composed of collagen, laminin, and proteoglycans (heparin sulfate in the case of the kidney basement membrane), forming a layer that is approximately 200 nm thick. The net negative charge of the proteins that compose the basement membrane restricts the movement of main proteins further through the filtration barrier.

Podocytes make up the remaining portion of the filtration barrier. Podocytes extend projections, termed *foot processes*, onto the glomerular basement membrane. The space between neighboring foot processes forms specialized pore structures termed *slit diaphragms*, which contain a variety of proteins, such as podocin and nephrin. The diameter of these pore structures is in the range of 30 nm. The net charge on these proteins is negative, restricting the motion of negatively charged molecules through the slit diaphragm. Additionally, the density of these proteins within the slit diaphragm is relatively high, which allows this barrier to also restrict molecules based on their size. The sieving coefficient is one method to quantify the effectiveness of a filtration barrier against particular solutes. In the case of the glomerular filtration barrier, the sieving coefficient can be defined as

$$S = \frac{C_{\text{Bowman's space}}}{C_{\text{Glomerular capillaries}}} \quad (13.1)$$

where S is the sieving coefficient and C is the concentration of a particular species within either Bowman's space or the glomerular capillaries. Note that when defining a sieving coefficient the denominator always represents the source term and the numerator always represents the sink term. For all molecule types, the sieving coefficient of the glomerular filtration barrier decreases as the size of the molecule increases.

The glomerular filtrate is formed as a balance between the hydrostatic pressure within the glomerular capillary, the hydrostatic pressure within Bowman's capsule, and the osmotic pressure within the glomerular capillary. The glomerular capillary hydrostatic pressure favors filtration and the hydrostatic pressure of Bowman's capsule and the osmotic pressure of the glomerular capillaries resist filtration. Under normal conditions, the glomerular capillary hydrostatic pressure is approximately 60 mmHg, the Bowman's space hydrostatic pressure is approximately 15 mmHg, and the capillary osmotic pressure is approximately 30 mmHg; therefore, there is a net movement of fluid from the glomerular capillaries into Bowman's capsule. Under normal conditions, the net filtration pressure (approximately 15 mmHg into Bowman's capsule) is always positive, and this initiates urine formation by forcing the filtrate into and through the tubule system.

As briefly mentioned earlier, this barrier effectively restricts how much plasma moves from the glomerular capillaries into Bowman's space. One way to quantify the glomerulus function is through the glomerular filtration rate. This is the amount of fluid that passes from the glomerular capillaries into Bowman's space per unit time. The glomerular filtration

rate is determined by the net filtration pressure (which is on average 10 mmHg), the permeability of the glomerular capillary endothelial cell membrane, and the area available for filtration. In an average person, the glomerular filtration rate is nearly 120 mL/min or approximately 180 L/day. This is nearly 50 times more fluid being filtered out of the glomerular capillaries than across all other capillaries within the systemic circulation. Furthermore, remember that in an average adult, the total blood volume is 5 L and that the plasma composes approximately 60% of this volume, or approximately 3 L. That suggests that the kidneys filter the entire plasma volume approximately 60 times per day. This allows the kidneys to very tightly and accurately regulate the composition of plasma constituents. It also allows the kidneys to rapidly respond to changes within the blood constituents and should further suggest and support the notion that the kidneys are responsible for immensely important functions within the body.

As discussed previously the glomerular filtration rate is not constant with respect to time (e.g., the positive feedback from the juxtaglomerular system). In fact, neural and hormonal input on the kidneys can affect the filtration rate (we will discuss this more in [Section 13.8](#)). It is important to also recall that the glomerulus is located in between two arterioles, the afferent arteriole and the efferent arteriole, which both can regulate the blood flow through the glomerulus. Constriction of the afferent arteriole reduces the hydrostatic pressure of the glomerulus and thus reduces the glomerular filtration rate. This occurs because there is an increase in the resistance to flow through the afferent arteriole into the glomerular capillaries and thus a reduction in the flow (and possibly fluid volume) throughout the glomerular capillaries. Constriction of the efferent arteriole increases the hydrostatic pressure of the glomerulus, and this increases the glomerular filtration rate. This occurs because there is an increase in the resistance to flow through the efferent arteriole, and thus there is a build-up of fluid volume and pressure within the glomerulus. A third case is a constriction of both the afferent arteriole and efferent arteriole, which tends to have a limited effect on the glomerular filtration rate. This occurs because of the opposing effects of the increase in flow resistance. Dilation of the two arterioles (either in concert or individually) has the reverse effect of those described here.

It is possible to quantify the amount of a plasma molecule that enters the nephron each day. This quantity is termed the *filtered load* and is obtained by multiplying the plasma concentration of a molecule by the glomerular filtration rate. For instance, the plasma concentration of sodium is approximately 3.5 g/L of blood. This makes the filtered load for sodium equal to $3.5 \text{ g/L} \times 180 \text{ L/day} = 630 \text{ g}$ of sodium filtered per day (this assumes that there is no restriction or active transport mechanisms within the glomerular capillaries). By comparing this value to the concentration of the same molecule within urine, one can determine whether that molecule experiences a net reabsorption or a net secretion within the nephron. If the urine concentration of a molecule is lower than the filtered load, this suggests that there was a net reabsorption of the molecule into the peritubular capillaries. However, if the urine concentration of a molecule is higher than the filtered load, this suggests that there was a net secretion of the molecule into the nephron. An example of a molecule that experiences net reabsorption is glucose, whereas a molecule that experiences net secretion is para-amino hippuric acid. Therefore, urine is not only a function of the glomerular filtration properties but is also a function of the tubule reabsorption and secretion properties.

The dynamics of the glomerular capillaries determines the net filtration pressure, which helps drive fluid into the nephron tubule. Using Starling's relationship, the net filtration pressure is the difference in the hydrostatic pressure of the glomerular capillaries (which averages to approximately 60 mmHg but varies from approximately 62 mmHg at the afferent arteriole end to approximately 58 mmHg at the efferent arteriole end), the hydrostatic pressure of Bowman's space (which is relatively constant with a value of approximately 20 mmHg) and the glomerular capillary oncotic pressure (which averages to approximately 30 mmHg but varies from approximately 25 mmHg at the afferent arteriole end to approximately 35 mmHg at the efferent arteriole end) (Fig. 13.7). The oncotic pressure of Bowman's space is approximately zero, because negligible proteins enter Bowman's space. Although we highlighted the dependency of filtration pressure on the diameter of the afferent and efferent arteriole in a previous discussion, the flow of fluid through the nephron also alters the glomerular filtration pressure. As the renal flow increases, the hydrostatic pressure of Bowman's space decreases, and thus, the net driving force into the nephron tubule system also increases. Similar effects would be observed when the flow into the afferent arteriole increases.

A significant amount of work has been conducted on the overall hydraulic conductivity of the glomerular capillaries. Note that these values would take into account the sieving coefficient. What has been observed is that as the surface area for exchange increases, there is a nearly linear decrease in the hydraulic conductivity. Although these values are relatively stable across different species, they are altered as a result of vasoactive compounds that are released upon various stimuli. For instance, exposure to histamine or various prostaglandins will decrease the overall permeability of glomerular capillaries.

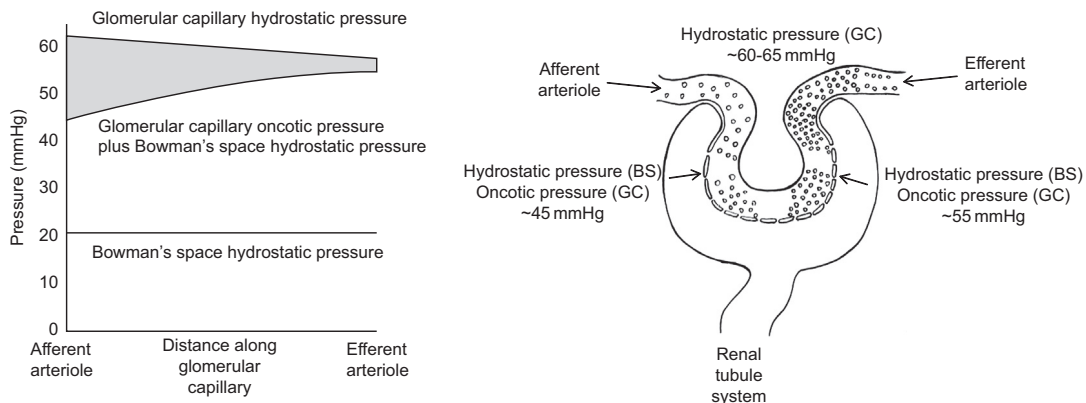


FIG. 13.7 Variation in the hydrostatic pressure of the glomerular capillaries (GCs) and Bowman's space (BS) and the GC oncotic pressure as a function of distance along the GC. There is a subtle drop in GC hydrostatic pressure and an increase in the GC oncotic pressure along the length of the GCs. The oncotic pressure of the GCs increases as a result of a net movement of protein-free materials out of the GCs into the nephron tubule system. The hydrostatic pressure of BS is relatively constant over this length. Notice that the net filtration (the gray-shaded region) always favors movement of materials out of the GCs. This is in contrast to "normal" systemic capillaries, where materials move back into the capillary along the venous end. Note that this variation is a function of distance along the GC.

13.4 Tubule reabsorption and secretion

Tubule reabsorption is the process by which molecules from the glomerular filtrate are returned to the plasma. This occurs along the entire nephron tubule unit. Metabolically important molecules are nearly completely reabsorbed, whereas wastes are typically reabsorbed to some extent, with most waste molecules making it into the urine. By looking at the relative percent reabsorbed of various molecules, it is possible to draw some conclusions about tubule reabsorption (Table 13.1). Metabolically important molecules (water, ions, and organic molecules) are completely reabsorbed so that there is no need to constantly ingest (or produce) these molecules. Waste products are not fully reabsorbed so that they can be removed from the body and do not build up a concentration into a toxic level. It is important to note that the reabsorption of most organic compounds (e.g., glucose) is not regulated and is typically very high. Therefore, under normal conditions, none of these compounds are found within the urine. For these compounds, it can be considered that the kidneys do not exist, because the kidneys have little to no effect on their plasma concentration. However, the reabsorption of most nonorganic metabolically important molecules (e.g., water and ions) is tightly regulated but is also very high under normal conditions. You can prove this by drinking a few 64-oz double-big sodas from your local gas station in under 10 minutes (hopefully this is not a normal activity that you participate in). It is guaranteed that you will be visiting the bathroom soon to remove the excess fluid from your system. However, if you eat a few candy bars with a lot of sugars in them, the amount of sugar in your urine does not increase but rather is stored for later use.

Two main processes account for the reabsorption of compounds into the peritubular capillaries. Some substances can be reabsorbed by diffusion, and others involve some receptor-mediated transport. Diffusion typically occurs across the tight junctions of the tubule epithelial cells or through specific channels, whereas the receptor-mediated transport processes occur through the epithelial cells. For example, the reabsorption of urea occurs by diffusion. However, because the composition of the glomerular filtrate is the same as the plasma composition, there should be little to no concentration gradient driving force for the movement of urea into or out of the plasma or urine. Early on within the proximal tubule system, water is removed from the filtrate (by receptor-mediated transport). With the removal of water, the effective concentration of urea increases within the tubule lumen,

TABLE 13.1 Average reabsorption values for various metabolically important compounds

Compound	Filtered load	Quantity excreted	Percent reabsorbed (%)
Water	180 L/day	1.5 L/day	99
Glucose	180 g/day	0 g/day	100
Lipids	1080 g/day	3.6 mg/day	99.99
Sodium	630 g/day	3.3 g/day	99.5
Bicarbonate	110 g/day	8.5 g/day	92.3
Urea	55 g/day	35 g/day	36

and therefore, a concentration gradient is formed between the fluid within the nephron and the plasma within the peritubular capillaries. Urea can then diffuse down its concentration gradient from the filtrate into the plasma at a distal location along the nephron. The reabsorption of most lipid-soluble compounds occurs in this manner and, therefore, depends on the early reabsorption of water, to effectively increase the molecular concentration within the nephron.

For a material to be reabsorbed by receptor-mediated transport, the molecule must first diffuse to the wall of the nephron tubule. The molecule must then cross the luminal wall into the tubule epithelial cells. The molecule could then diffuse across the tubule epithelial cell to the basolateral cell membrane. The molecule then crosses this portion of the cell membrane into the peritubular capillaries. It is not necessary for the molecule to be actively transported across both cell membranes, and typically the molecule would move down its concentration gradient only when crossing one of the barriers. For example, sodium can diffuse into the tubule epithelial cells across the apical membrane, but it is then actively transported across the epithelial cell basolateral membrane to enter the bloodstream. If the transport of a molecule is active across at least one barrier, it falls into the category of receptor-mediated transport.

It is interesting to note that the reabsorption of many molecules is coupled to sodium movement across the tubule epithelial cells (after the initial reabsorption of water). This type of movement is mediated by a cotransporter, which in this case uses the energy derived from the movement of sodium in the direction of its electrochemical gradient to drive the movement of another molecule (e.g., glucose, many organic compounds, and some inorganic ions) against its electrochemical gradient. The activity of cotransporters is classified by the number of molecules that can be transported in a unit time. Under most normal conditions, the maximum rate of transport is never reached by the cotransporters. However, if the nephron concentration of a particular compound becomes so large that all of the binding sites on every transporter are occupied, the maximum transportation rate is reached (i.e., the transporters are saturated) and this compound may enter the urine (note that we are assuming that the concentration of the transporters remains the same). As an example, under diabetic conditions, it is possible for the glomerular filtrate glucose concentration to exceed the maximum glucose transportation rate, and then glucose enters the urine and is excreted. At this point, the glucose concentration in the nephron fluid has saturated all of the transport mechanisms and the “extra” glucose cannot be reabsorbed into the blood. There is an old legend that before the age of modern medicine, diabetes mellitus would be diagnosed by determining how “sweet” a patient’s urine was. How much truth is in this legend is up for debate, but regardless, patients with diabetes can excrete glucose in urine, whereas under normal nonpathological conditions, all of the glucose within the glomerular filtrate is reabsorbed into the plasma.

Tubule secretion is the process by which molecules from the peritubular capillaries move into the nephron tubule lumen. Similar to reabsorption, secretion can occur by diffusion or receptor-mediated transport. You may be wondering why the peritubular capillaries secrete compounds into the lumen. There are a variety of reasons based on the compound. Many toxins or foreign compounds are secreted to be fully removed from the plasma. Hydrogen ions are secreted to regulate the pH of the blood. Secretion mediated by diffusion occurs similarly to the diffusion associated with tubule reabsorption, except that it occurs in the

opposite direction (i.e., from the vasculature into the nephron tubule system). Interestingly, the receptor-mediated secretion of molecules is typically coupled to sodium reabsorption, in a process similar to those described for the reabsorption of molecules. Therefore, the electrochemical gradient of sodium drives the movement of many other compounds against their electrochemical gradients. For the case of secretion, these types of transports are typically called *antiporters* because the two molecules move in opposite directions. Hydrogen ion secretion makes use of an antiporter coupled to sodium.

It is important to note before we discuss specific examples of reabsorption and secretion, which components of the nephron perform which functions during urine formation. The primary function of the proximal tubule is to reabsorb large quantities of water and other solutes within the glomerular filtrate. This helps form the concentration gradient, which will be used in later segments of the nephron to drive the reabsorption and/or secretion of particular compounds. The loop of Henle also functions to reabsorb large quantities of solutes and small quantities of water. The proximal tubule system is also responsible for the secretion of most compounds, except for potassium. This early movement of solutes and water within the proximal tubule and the loop of Henle are by bulk processes, in which the major goal of these processes is to return the plasma and urine solute concentration close to its acceptable level. The distal convoluted tubule and the collecting duct system are primarily responsible for fine-tuning the concentrations of the solutes and determining the final excreted concentration and the final plasma concentration. Therefore, it should be intuitive that most of the mechanisms that exert control over nephron reabsorption and secretion (e.g., hormones) to control the final urine concentration of a molecule act on the distal convoluted tubule and the collecting duct. As a summary, the amount of a compound that is excreted can be calculated by measuring the amount filtered, secreted, and reabsorbed, as follows

$$\text{Amount excreted} = \text{Amount filtered} + \text{Amount secreted} - \text{Amount reabsorbed} \quad (13.2)$$

It is possible to quantify the difference between the amount of a solute that is reabsorbed versus the amount of a solute that is secreted, by modifying Eq. (13.2). The filtered load is a measure of the amount of solute that enters the nephron tubule system. In general, the filtered load is defined as

$$FL_x = GFR \cdot S_x \cdot [x]_{\text{plasma}} \quad (13.3)$$

where FL represents the filtered load for solute x , GFR is the glomerular filtration rate (which is approximately 120 mL/min, but can vary based on other conditions), S is the sieving coefficient for solute x , and $[x]_{\text{plasma}}$ is the plasma concentration for x . The filtered load of a compound represents the rate of filtration for that particular molecule and is used in a modified version of Eq. (13.2), which looks at the rates of the various motions

$$\text{Rate of excretion} = \text{Rate of filtration} + \text{Rate of secretion} - \text{Rate of reabsorption} \quad (13.4)$$

The rate of excretion is typically represented as the urine flow rate multiplied by the urine concentration of the particular species. The kidney reabsorption and secretion kinetics would need to be investigated to determine the functions that represent these quantities. In the case of glucose, it is known that there is no mechanism for glucose secretion to occur; thus, the rate

of glucose secretion is equal to zero. Following this analysis, the rate of reabsorption for glucose can be represented as

$$\text{Rate of reabsorption}_{\text{glucose}} = GFR \cdot S_{\text{glucose}} \cdot [\text{glucose}]_{\text{plasma}} - Q_{\text{urine}}[\text{glucose}]_{\text{urine}}$$

One way that this is observed *in vivo* is to quantify the clearance of the particular solute over some time period. The clearance of a molecule provides a measure of how effective the kidney is clearing plasma of that solute. Clearance is defined as

$$C_x = \frac{Q_{\text{urine}}[x]_{\text{urine}}}{[x]_{\text{plasma}}} \quad (13.5)$$

Under normal plasma glucose concentrations (e.g., when the transport mechanisms are not saturated) the clearance of glucose is zero, and therefore, the kidneys do not alter the plasma glucose concentration. However, if the saturation limits are met for glucose transport, the clearance can exceed a value of zero. It was mentioned earlier that para-amino hippuric acid (PAH) is secreted by the peritubular capillaries into the nephron. Under these cases, saturation can limit the transport of PAH into the nephron; however, the clearance of PAH is very high for low plasma concentrations (because the dominator in Eq. (13.5) is very low) and decreases as the plasma concentration increases. A second way to quantify how effective the tubule sections of the nephron are reabsorbing or secreting a compound is to quantify the double ratio. The double ratio relates the relative concentration of a species in the tubule fluid versus the concentration of the same species in plasma and then relates this to the same concentrations of inulin. The double ratio is defined as

$$\text{Double ratio} = \frac{\left(\frac{[x]_{\text{tubule fluid}}}{[x]_{\text{plasma}}} \right)}{\left(\frac{[\text{inulin}]_{\text{tubule fluid}}}{[\text{inulin}]_{\text{plasma}}} \right)} \quad (13.6)$$

The denominator of the double ratio determines where and how much water has been removed or added to the tubule fluid because the nephron can filter but cannot reabsorb or secrete inulin. Therefore, the quantity of inulin remains the same along the entire tubule length but the concentration of inulin may be altered based on the movement of water into or out of the nephron tubule system. The numerator of the double ratio provides similar information about a species x and can be measured at specific locations within the tubule structure. This allows the experimentalist to obtain very detailed and location-specific information about the movement of particular solutes. The issue is that if the ratio that makes up the numerator is 1, this can suggest that either species x and water did not move across the epithelial barrier or that species x and water both moved at a value that maintained the ratio as 1. Therefore, the double ratio relates this somewhat ambiguous information to the ratio of inulin that cannot be secreted or reabsorbed and thus inulin concentration changes are dictated by water movement only.

13.5 Single nephron filtration rate

Single nephron filtration rates are similar to the total glomerular filtration rates that were discussed earlier. In general, the glomerular filtration rate (*GFR*) can be defined as

$$GFR = Q_{\text{urine}} \left(\frac{[\text{inulin}]_{\text{urine}}}{[\text{inulin}]_{\text{plasma}}} \right) \quad (13.7)$$

In a similar fashion the single nephron filtration rate (*SNFR*) can be defined as

$$SNFR = Q_{\text{tubule fluid}} \left(\frac{[\text{inulin}]_{\text{tubule fluid}}}{[\text{inulin}]_{\text{plasma}}} \right) \quad (13.8)$$

Tubule fluid information would be obtained by periodic measurements of the tubule fluid contents and flow rate using micropuncture techniques. In fact, many of the data points and localization information that we have discussed previously were obtained from these types of experiments. In general, under physiological conditions, single nephron filtration rates average to approximately 100 nL/min, but can range from as low as 20 nL/min to as high as 200 nL/min. Using the single nephron filtration rate and the glomerular filtration rate, one can approximate the number of nephrons as 1.2 million.

Many groups have investigated the effects of glomerular capillary pressure on single nephron filtration rates. By applying a negative pressure within the glomerular capillaries, a decrease in the overall pressure within Bowman's space was observed, however, the pressure within the proximal convoluted tubule was not altered, suggesting that this location partially acts as a nonlinear resistor to prevent the transmission of altered pressure from the glomerular capillaries throughout the nephron tubule system. Under these reduced pressure conditions, single nephron filtration rates were not altered significantly, suggesting the presence of regulatory mechanisms that aim to maintain the overall function of the kidneys (Section 13.8 will discuss some of these mechanisms in more detail). The single nephron filtration rate varies somewhat depending on where the values are recorded along the nephron tubule system. In general, the values vary by no more than 5 to 10 nL/min along a single nephron tubule length. As mentioned in an earlier section, the flow through cortical nephrons varies compared with the flow through the juxtamedullary nephrons. In general, the difference is on the order of 20 to 30 nL/min, with the juxtamedullary nephrons having a higher flow rate compared with the cortical nephrons. If one is comparing the single nephron filtration rates over a long time interval (e.g., years), the number of glomeruli is an important factor to consider. In general, with the loss of function of nephrons as one ages (or damage to the kidney, among other mechanisms that may damage the kidneys), the glomerular filtration rate does not decrease, but instead remains relatively constant. To accommodate this, the single nephron filtration rates increase with age, but if these filtration values are normalized by the number of active nephron units, the overall normalized single nephron filtration rate remains relatively constant with time.

There has been a significant amount of work that aimed to mathematically model the resistance of the renal microvasculature at various locations throughout the vascular network.

The resistance of the afferent arteriole is an important value that can regulate the flow through the entire glomerular capillary bed and the peritubular capillary bed (or vasa recta capillaries). The resistance of the afferent arteriole (R_{AA}) has been shown to be a function of the mean arterial pressure (P_{MA}), glomerular capillary pressure (P_{GC}), and glomerular blood flow rate (Q_G), as follows.

$$R_{AA} = \frac{P_{MA} - P_{GC}}{Q_G} \quad (13.9)$$

The glomerular blood flow rate is a function of the hematocrit of the afferent arteriole, which should be equivalent to (or at least within the range of) the systemic arteriole hematocrit, the single nephron filtration rate and the single nephron filtration fraction ($SNFF$), as follows.

$$Q_G = \frac{SNFR}{SNFF(1 - Hct_{AA})} \quad (13.10)$$

The single nephron filtration fraction is a means to quantify the ability of the glomerular capillaries to filter the blood and is calculated from the proportional difference between the efferent arteriole protein concentration and efferent arteriole hematocrit compared with the systolic protein concentration and hematocrit.

Using a similar approach, the resistance of each efferent arteriole can be approximated by the following formulation

$$R_{EA} = \frac{P_{GC} - P_{PC}}{Q_{EA}} \quad (13.11)$$

where P_{PC} is the hydrostatic pressure within the peritubular capillaries (or vasa recta) and Q_{EA} is the efferent arteriole flow rate, which can be defined as

$$Q_{EA} = Q_G - SNFR \quad (13.12)$$

The total arteriolar resistance of the preglomerular to postglomerular vascular tree can be defined as

$$R_T = R_{AA} + R_{EA} \quad (13.13)$$

In most animals the resistance of the afferent arteriole accounts for approximately 60% of the total arteriole resistance of the renal circulation, whereas the efferent arteriole accounts for approximately 40% of the total renal arteriolar resistance. Combining the arteriolar and venule resistance in a global renal vascular resistance term, the arteriolar side of the vascular tree accounts for approximately 90% of the vascular resistance, whereas the venous side accounts for approximately 10% of the vascular resistance. As with all vascular beds, changes to vascular resistance can occur as a function of changes to other fluid parameters. For instance, with an increase in the blood volume, the resistance of the afferent arteriole and

the efferent arteriole reduces at a similar rate, allowing the glomerular capillary hydrostatic pressure to remain the same. A reduction in the mean arterial pressure tends to decrease the afferent arteriole pressure; however, this is accompanied by an increase in the efferent arteriole pressure, which acts to maintain the glomerular capillary hydrostatic pressure. Increases in hematocrit tend to increase the afferent and efferent arteriole resistance, again at a similar rate to maintain the glomerular capillary pressure. With a decrease in hematocrit, the resistances of the afferent and the efferent arteriole tend to reduce at similar rates. It is important to observe that although these changes can have a net effect on the flow through the glomerulus and the peritubular capillaries, there tends to be no net effect on the filtration, reabsorption, and secretion of materials from the glomerular capillaries, the peritubular capillaries, or the nephron tubule system.

13.6 Peritubular capillary flow

As we highlighted earlier, the reabsorption of filtrate into the peritubular capillaries is accounted for by two major processes; the transport of solutes through the nephron epithelial tissue (passive or active transport mechanisms) and the uptake of solutes into the peritubular capillaries. Many groups have investigated whether the hydrostatic pressure gradient or the osmotic pressure gradient is the driving force for this motion (e.g., which forces in the Starling equation dictate the motion of the solutes out of the nephron system). Early work has shown that only approximately 5% of the net reabsorption within the proximal tubule system can be accounted for by the hydrostatic and osmotic pressure gradients that exist between that tubule system and the peritubular capillaries. Similar work has also attributed the vast majority of this 5% to the hydrostatic pressure gradient; this work has shown that by disrupting the oncotic pressure gradient one can observe no changes to the net movement of materials that are reabsorbed within the proximal tubule system. Starling's equation only holds for the passive movement of solutes through the nephron system; thus, it appears that the active transport of materials across the tubule wall is the more important transport mechanism and accounts for the vast majority of solute movement. Many studies have shown that the flow of sodium (and other ions) induces a net movement of water out of the proximal tubule system. This is accompanied by an increase in the hydrostatic pressure of the interstitial space that surrounds the nephron tubule epithelial cells and the peritubular capillary endothelial cells. The increase in hydrostatic pressure aids in movement of solutes into the peritubular capillaries; however, if the permeability of the peritubular capillaries increases, this driving force may force materials back into the proximal tubule system. This suggests that the uptake of materials by the peritubular capillaries is the rate-limiting step in the reabsorption processes that occurs within the nephron tubule system.

The uptake of material from the capillaries is equal to the single nephron filtration rate minus the rate of fluid flow within the nephron segment of interest. When quantifying these variables, one must take care to accurately assess the location of the peritubular capillary network in relation to the nephron tubule system, so the fluid transport is accounted for at the appropriate level. Additionally, the peritubular capillary network does not surround the entire nephron unit and there are some locations that have extensive lymph flow.

These variables should be accounted for within the mathematical approximation. The reabsorptive coefficient for fluid materials within the nephron unit has been represented as

$$K_r = \frac{SNFR - Q_{TS}}{\Pi_{PC} - \Pi_{IS} - P_{PC} - P_{IS}} \quad (13.14)$$

where $SNFR$ is the single nephron filtration rate, Q_{TS} is the flow rate through the nephron tubule segment of interest, Π is the oncotic pressure of the peritubular capillaries (PC) or the interstitial space (IS), and P is the hydrostatic pressure of the peritubular capillaries or the interstitial space. Capillary uptake in these instances averages to approximately 50 nL/min under physiological conditions. The Starling forces vary based on a number of parameters, as discussed in previous chapters. The oncotic pressure of the peritubular capillary is approximately 30 mmHg, the oncotic pressure of the interstitial space is approximately 7 mmHg, the hydrostatic pressure of the capillary is approximately 15 mmHg, and the hydrostatic pressure of the interstitial space is approximately 6 mmHg. Using these values, one can calculate the reabsorptive coefficient and obtain a value of approximately 400 nL mmHg/s.

A number of mathematical models exist that describe the movement of solutes through the nephron unit as a function of distance along the nephron tubule. Because the net pressure for reabsorption to occur is relatively low (e.g., the summation of the Starling forces), small changes in any of these values may have drastic effects on the solute transport. These models have shown that small changes in the protein concentration (either in the interstitial space or the peritubular capillaries) have a drastic effect on the movement of solutes, whereas large changes within the flow properties (e.g., the flow through the nephron unit or the flow through the peritubular capillaries) have a much lower effect on the transport of materials. These findings suggest that even though much of the early transport occurs through receptor-mediated processes the reuptake of solutes from the interstitial space is very highly dependent on the maintenance of the pressures across the peritubular capillaries.

The lymphatic system plays an important role in the reuptake of solutes from the interstitial space between the nephron epithelial cells and the peritubular endothelial cells. In the kidney, as we discussed previously, significant changes in the flow properties within the vascular system or the nephron tubule system have very small effects on flow of lymph. In fact, the flow of lymph appears to be unaltered under most pathological conditions and this has been attributed to the overall small changes to the flow within the nephron unit, with changes to the vascular flow conditions. With that said, because the kidney obtains and filters a relatively large percentage of blood, the lymph flow of the kidney is greater than the lymph flow of many other organs but remains relatively stable throughout all possible altered conditions.

13.7 Sodium balance and transport of important molecules

As discussed in previous sections, sodium is reabsorbed throughout most of the nephron tubule system. Recall that the concentration of sodium is high in both the tubule lumen and the interstitial fluid surrounding the nephron, but importantly the movement of sodium appears to drive the movement of many of the salient molecules through the nephron system.

The movement of sodium initiates from the passive diffusion of sodium, through a sodium channel, from the tubule lumen, into the epithelial cells lining the tubule. To maintain the electrochemical neutrality of luminal epithelial cells, potassium efflux (from the epithelial cell into the tubule lumen) is generally coupled to the process of sodium movement. This movement of potassium is by bulk diffusion, similar to the sodium movement. The movement of sodium out of the epithelial cell into the interstitial fluid is achieved by an active mechanism: the sodium–potassium ATPase pump. This pump moves three sodium ions out of the epithelial cell and two potassium ions into the epithelial cell for every ATP that is hydrolyzed into ADP. Sodium then can freely move into the peritubular capillaries.

Sodium reabsorption is regulated by the amount and type of channels present on the luminal surface of the epithelial cell. The entry of sodium into the epithelial cells that compose the cortical collecting duct is by diffusion through sodium channels. Along the proximal collecting tubule, the movement of sodium into the epithelial cells is typically by cotransport with organic molecules such as glucose or by countertransport with hydrogen ions. Therefore, the movement of sodium down its electrochemical gradient provides the energy for the reabsorption of glucose and the secretion of hydrogen ions. The transport of sodium across the basolateral membrane, by the sodium–potassium ATPase pump, is typically constant along the entire length of the tubule lumen. The quantity of these pumps present can be regulated by other mechanisms (that we will not discuss here) to determine the amount of sodium reabsorbed into the peritubular capillaries, although this does not normally occur.

Many cotransporters and countertransporters are present along the proximal convoluted tubule. For instance, nearly all glucose is reabsorbed within the proximal convoluted tubule system by a sodium–glucose cotransporter (SGLT). There are two main types of these transporters, the SGLT1 moves two sodium molecules down its electrochemical gradient to drive the motion of one glucose molecule up its concentration gradient, whereas the SGLT2 moves one sodium molecule down its electrochemical gradient to drive the motion of one glucose molecule into the tubule epithelial cell. These transporters reside on the apical membrane of the epithelial cell membrane. On the basolateral membrane a glucose transporter (normally GLUT1 or GLUT2) is present to facilitate the diffusion of glucose out of the epithelial cell into the peritubular capillaries. Amino acids are reabsorbed within the proximal convoluted tubule using specific transport proteins, many of which require sodium to be cotransported along with the amino acid (some transporters do not require any molecule to be transported in parallel to the amino acid). On the basolateral side of the epithelial cell, many of these same transporters exist to facilitate the movement of the amino acids into the peritubular capillaries.

Urea is an example of a molecule that does not need sodium present to transport into the tubule epithelial cell. Urea can passively cross through biological membranes; however, the permeability of biological membranes to urea is relatively low. Urea transporters are present that can facilitate the motion of urea through both the apical and basolateral sides of the epithelial membrane. Water movement is similar to urea movement, in that it typically moves by passive diffusion through aquaporin channels on the apical and basolateral membrane of the epithelial cells. Various aquaporin channels are found in the kidney, but all of them have the same overall function. We will discuss more details regarding water movement at the end of this section.

It is interesting to point out that some proteins can enter the filtrate because the sieving coefficient is not zero for proteins. The proximal tubule has pit regions that attract proteins, and then the cells present in this location can engulf the proteins by endocytosis mechanisms. Interestingly, most of the proteins that are reabsorbed in this way are digested into their amino acid components and not transported/maintained as the protein. This is due to specialized processes in these cells in which the engulfing endosome with the protein typically fuses with a lysosome. The amino acids are then transported into the peritubular capillaries by specific transporters using methods similar to those discussed earlier. This typically occurs very early within the proximal tubule system.

We will now move our discussion to the control of sodium reabsorption. In essence, no sodium is secreted into the nephron. Therefore, the total amount of sodium that is excreted is equal to the amount reabsorbed subtracted from the amount filtered. Changes in the glomerular filtration rate or the reabsorption rate of sodium will affect the excretion rate of sodium, but how are changes in sodium concentration sensed in the body? Currently, there are no known sensors in the body for sodium concentration. Instead, sodium concentration is regulated by changes in plasma volume (e.g., water volume) that will directly change the arterial blood pressure. Baroreceptors, located in various places throughout the body, can sense changes in blood pressure, and they have both direct and indirect effects on the kidneys. The direct effect of a reduction in systemic blood pressure is that the glomerular filtration rate will reduce because the hydrostatic pressure balance across the glomerular capillaries and Bowman's capsule decreases (see [Section 13.3](#)). The indirect effect of a decreased arterial blood pressure on sodium excretion is by activation of a sympathetic nervous signaling pathway. The renal sympathetic nerve directly innervates the juxtaglomerular cells and induces these cells to increase the production and secretion of renin. Renin enters the bloodstream and converts angiotensinogen into angiotensin I. Angiotensinogen is produced by the liver and under normal conditions is always present in the plasma. Angiotensin I is then converted into angiotensin II by an enzyme termed *angiotensin-converting enzyme* (or ACE). ACE is bound to the luminal surface of capillary endothelial cells and is always expressed. Angiotensin II has various effects within the body, but the most important for sodium reabsorption is the stimulation of the adrenal glands to produce and secrete aldosterone into the blood. Aldosterone stimulates the cortical collecting duct epithelial cells to produce and express more sodium channels and sodium–potassium ATPase pumps. This effectively increases the reabsorption of sodium (or more accurately, decreases the excretion of sodium). An increased plasma volume has the opposite effect as described earlier, so that there is an increased excretion of sodium.

As mentioned previously, sodium drives the reabsorption of water within the nephron. As sodium ions begin to move out of the nephron, the osmolarity of the solution within the nephron decreases. A decrease in osmolarity also can be considered an increase in water concentration. As the solute moves out of the tubule lumen, the osmolarity of the interstitial fluid and/or epithelial intercellular fluid increases, and this also can be considered a decrease in the water concentration. Therefore, there now exists a concentration gradient and an osmotic gradient for water that will cause water molecules to diffuse out of the tubule lumen into the interstitial space. In general, the transporters that were discussed in this section only work in one direction and thus water will move out of the nephron unit to reduce the concentration of sodium.

Water movement across the tubule epithelial cells occurs by bulk diffusion across the tight junctions or through aquaporin channels on the apical epithelial membrane. The proximal tubule is very highly permeable to water, and large quantities of water are always reabsorbed within this segment of the nephron. The loop of Henle experiences both water reabsorption (descending limb) and water secretion (ascending limb) to maintain a countercurrent flow of other nutrients that are important, which will not be elaborated on here, but can be found in many physiology textbooks. The water movement through the distal tubule and the collecting duct is variable and is subject to physiological control. In a process similar to the regulation of sodium reabsorption, changes in the water reabsorption rates of the collecting ducts are controlled by the blood volume. Decreases in blood volume will reduce the arterial pressure, which is again sensed by baroreceptors within the cardiovascular system. This reduction causes an increase in the production and secretion of vasopressin (also known as antidiuretic hormone). Vasopressin is released into the blood and eventually makes its way to the collecting ducts. Vasopressin then stimulates the production of new aquaporin channels, which are placed into the collecting duct epithelial membrane. With a higher quantity of aquaporin channels within the collecting duct epithelial cell, permeability to water increases, and therefore, the reabsorption of water increases. With an increase in blood volume, the opposite response will occur, causing the permeability of the collecting ducts toward water to decrease, leading to a decrease in water reabsorption.

13.8 Autoregulation of kidney blood flow

The control of blood flow to and through the kidneys is central to the function of the kidneys. With significant changes in blood flow, we can imagine that the clearance of metabolic wastes would be altered, which would likely affect many other processes within the body. For approximately 100 years, many groups have investigated conditions that can alter the renal blood flow. It has been observed that changes in systemic arterial blood pressure (either increase or decrease) elicit negligible effects on the blood flow to and through the glomerular and peritubular capillaries. In fact, later work has shown that even a direct occlusion to the renal artery elicits only a short-term decrease in the renal perfusion that quickly returns to normal levels. Combined this suggests that mechanisms are present within the kidney to regulate and maintain the blood flow to and through the glomerular and peritubular capillaries at near constant levels. To take this one step further, groups have removed all kidney innervation and have observed that any exogenous alteration to flow through the renal artery is normalized out by the time that the blood reaches the glomerular capillaries (e.g., decreases in flow through the renal artery will be increased to normal glomerular perfusion levels in the absence of innervation and vice versa). This self-regulating property, in the face of changes to the arterial flow properties has been termed *autoregulation*.

We have already discussed that the nephrons are perfused differently based on their location within the kidney. Early work suggested that the limited changes to the kidney perfusion rate may be accounted for by autoregulation events that affect only certain regions of the kidney. This would suggest that with a decreased inflow pressure, certain regions of the kidney would experience a decreased flow, whereas other regions of the kidney would autoregulate to normal flow conditions. However, it has become apparent that all regions

of the kidney appear to have intrinsic autoregulation processes but they may and can act independently to adjust particular regions of the kidney at different rates, based on altered inflow conditions (e.g., some regions of the kidney may see increases in flow, whereas other regions may see decreased flow, but the overall glomerular filtration rate remains the same).

Many groups have tried to identify the regions of the kidney circulation that are responsible for the autoregulation events. It has been observed that the glomerular filtration rate and the filtration fraction of the kidneys remain relatively constant under altered inflow pressure conditions, and this suggests that the afferent arteriole or a vessel in close proximity to the afferent arteriole is primarily responsible for the autoregulation events that are observed. Changes to the afferent arteriole vascular resistance have been observed under altered inflow blood pressure conditions, and this can account for the return to control conditions for the glomerular blood flow rates. Robertson et al. altered the mean arterial pressure of rats from 60 mmHg to approximately 120 mmHg. Under these conditions, the glomerular perfusion rate and single nephron perfusion rates increased by approximately 30% to 40%; however, the single nephron filtration rates remained unchanged. Similarly, the hydrostatic pressure of the glomerular capillaries and the peritubular capillaries and the oncotic pressure of the afferent and efferent arteriole remained largely unaltered under the changes in systolic pressure. However, there was an approximate 200% increase in the resistance of the afferent arteriole accompanied by an approximate 20% reduction in the resistance of the efferent arteriole. Thus, autoregulation processes appear to be restricted to the afferent arteriole.

Some theories try to describe the mechanisms that are responsible for autoregulation changes. Many of these have been difficult to verify experimentally, but we will highlight them to illustrate possible mechanisms of action. The first theory is the cell separation theory, which states that a change in systemic pressure alters the degree and location of red blood cells within the vasculature. By altering the red blood cell concentration within the kidney microcirculation, the hematocrit is altered and thus viscosity and flow resistance are altered. In a similar argument, changes to the systemic pressure will alter the interstitial pressure and this may regulate the perfusion rate. These two theories have some experimental support but do not adequately describe all of the observations made during autoregulation conditions.

The myogenic theory, which was described in a different context in Chapter 7, states that changes to the vascular wall tension instigate changes to the tone of the vessel to minimize the changes to the vascular wall tension. Recall that the myogenic theory predicts that with an increased arterial pressure, there would be an accompanying increase in the wall tension. This would initiate a constriction of smooth muscle cells to inhibit the stretch-induced expansion of the vascular wall. Support for this mechanism stems from studies in which agents were added to the kidneys that inhibit the activity of vascular smooth muscle cells. Under these conditions, a significant portion of the autoregulation response was abolished; however, the kidney retained some ability to regulate the filtration rates.

The metabolic theory is the second major mechanism that aims to explain the autoregulation response of the kidneys. This theory suggests that with a decreased perfusion there would be an increase in the concentration of particular vasoactive compounds that would tend to induce vasodilation (the opposing argument would be made for an increase in perfusion pressure). A significant supporting argument for the metabolic theory is the close association of the distal tubule and the afferent/efferent arteriole at the juxtaglomerular apparatus. Although there are some clear observations of an altered tubule concentration effecting the flow rate by

juxtaglomerular signaling, the exact mechanisms of this potential feedback loop and the extent of its role during autoregulation responses remain to be identified. This feedback mechanism has been termed *tubuloglomerular feedback* and is a source of much debate. Again, it is likely that both the myogenic theory and the metabolic theory play different but parallel and complementary roles to regulate the nephron filtration rates. Note that we have mentioned the renin–angiotensin system as a regulating agent in previous discussions. This would appear to be a supporter of the metabolic theory; however, it is still unclear how this system initiates and what controls the release of renin from the juxtaglomerular apparatus.

A third mechanism for autoregulation is through the sympathetic nervous system. The renal sympathetic nervous system innervates the nephron tubules, the glomerular and peritubular capillaries, and the juxtaglomerular cells. In general, the activation of the renal sympathetic nervous system increases the reabsorption of sodium and water along the tubular system, decreases the renal blood flow and the glomerular filtration rate, and stimulates the release of renin from the juxtaglomerular apparatus. However, work that has been conducted on denervated kidneys has shown that the kidneys can still self-regulate the blood flow along the nephron unit and the composition of the glomerular filtrate. Thus, it is unlikely that the sympathetic nervous system plays a major role in the autoregulation of the kidney function.

13.9 Compartmental analysis for urine formation

This section will describe one of the mathematical techniques that can be used to describe the movement of solutes through the nephron. In general, this technique can be extended to describe the movement of solutes through any region(s) divided by some permeable membrane (we will start with simple two compartment systems, but this analysis technique can be applied to much more complicated systems). When analyzing the transfer of substrates within the body, it is typically convenient to describe the regions that are involved in the transfer as compartments. For instance, the tubule lumen, the tubule epithelial cells and the peritubular capillary lumen can all be individual compartments used to describe solute movement. With this analysis method, it is typical to assume that the boundary has a spatially uniform permeability (although the permeability can change with time, including this would only increase the complexity of the solution by including a time-varying component), and that the compartments have some known volume as a function of time. If the boundary has a spatially varying permeability, a function for this variation can be included within the solution or the single barrier can be subdivided into smaller barriers with uniform permeabilities. The solution approach would be dependent on the properties that are incorporated within the particular problem. In general, compartmental analysis problems are solved using mass conservation laws.

We will begin our analysis by solving for the transfer of a substance between two compartments separated by a thin permeable membrane. To solve for the change in solute concentration with time across a thin membrane, Fick's law of diffusion can be used and represented as

$$\frac{dc}{dt} = -\frac{DA}{V} \frac{dc}{dx} \quad (13.15)$$

In Eq. (13.15), c is the concentration of the solute, D is the diffusion coefficient, A is the surface area of the membrane separating the compartments, V is the compartment volume (constant in this case), and Δx is the thickness of the membrane separating the compartments. The simplest system is composed of two compartments (Fig. 13.8), and each quantity of interest would be denoted with a subscript to indicate which compartment is being referenced. In this case, Eq. (13.15) can be simplified to

$$\frac{dc_1}{dt} = -\frac{DA}{V_1} \frac{c_1 - c_2}{\Delta x} \quad (13.16)$$

assuming uniformity across the semipermeable membrane, homogeneous distribution within each compartment, and that we are referencing compartment 1. If at time 0, there is an initial concentration (c_0) of a solute in compartment 1 (with no solute in compartment 2 at time 0), mass conservation states that

$$V_1 c_1 + V_2 c_2 = V_1 c_0 \quad (13.17)$$

The multiplication of volume by a concentration obtains “quantity of solute,” and that is what can be measured and must be conserved within the two-compartment system (e.g., concentrations are a function of the volume and the quantity and generally are not conserved under most conditions). If Eq. (13.17) is solved for the concentration within compartment 2 and substituted into Eq. (13.16), we can obtain

$$c_2 = \frac{V_1 c_0 - V_1 c_1}{V_2} \quad (13.18)$$

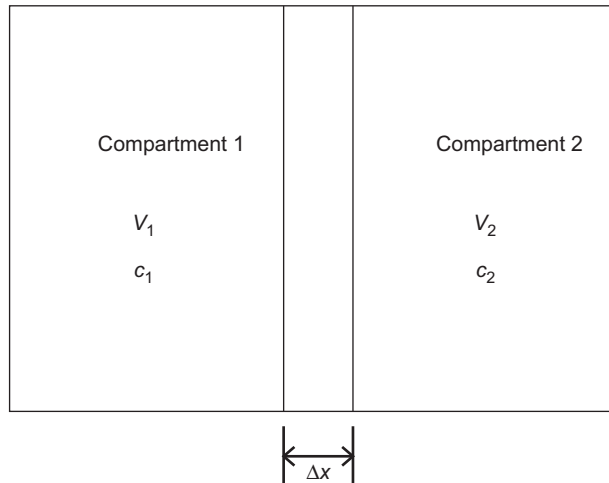


FIG. 13.8 Two-compartment model separated by a semipermeable membrane of thickness Δx . This type of model can be used to analyze the solute transport through the nephron. To increase the complexity of the model, multiple compartments can be included separated by different semipermeable membranes, possible with their own rate constants depicting movement across each barrier. Each compartment’s characteristics and the properties of the membrane would need to be defined for this type of analysis.

$$\frac{dc_1}{dt} = -\frac{DA}{V_1} \frac{c_1 - \frac{V_1 c_0 - V_1 c_1}{V_2}}{\Delta x} = -\frac{DA}{\Delta x} \frac{c_1(V_1 + V_2) - V_1 c_0}{V_1 V_2}$$

$$\frac{dc_1}{dt} + \frac{DA}{\Delta x} \frac{c_1(V_1 + V_2)}{V_1 V_2} = \frac{DA}{\Delta x} \frac{c_0}{V_2}$$

which is a first-order linear ordinary differential equation. Eq. (13.18) can be solved in a variety of ways, depending on the conditions of the problem. For instance, if V_1 is equal to V_2 , it will significantly simplify Eq. (13.18). The use of Laplace transforms to solve the differential equation may prove to be easy; however, other mathematical methods can and may need to be used to solve compartmental analysis problems. Regardless of the solution method, it will be typical to see that the solute concentration change with respect to time in one compartment will be described by an exponential decay, whereas the solute concentration in the other compartment will be described by an exponential rise (for a two-compartment system).

To use compartmental analysis to model the transfer of solutes between two compartments, the following assumptions are useful. First, assume that the volume of each compartment remains the same with time. This makes the time derivative only a function of concentration and not of volume (as shown in Eq. (13.18)). Also, we make the assumption that the solute is homogeneously mixed throughout the compartment immediately after it crosses the semi-permeable membrane. The only factors that affect the transfer of the solute across the membrane are accounted for within the diffusion coefficient, the cross-sectional area of the membrane, the membrane thickness, and the concentration gradient across the membrane.

Example 13.1

Consider the reabsorption and metabolism of glucose within the nephron as modeled by a two-compartment system. Assume that the input of glucose into the nephron is constant and defined by K_1 . The output of glucose from the nephron can be described by the metabolism of glucose by the nephron epithelial cells (K_2) and the reabsorption of glucose into the peritubular capillaries (K_3), where the K 's are defined as the transfer rate between the various compartments, which account for the diffusion coefficient and the membrane parameters. The initial quantity of glucose within the nephron is defined as q_0 . Solve for the time rate of change of the quantity of glucose within the nephron.

Solution

The mass balance of glucose quantity can be defined as the accumulation of glucose within the nephron and is equal to the input of glucose minus the output of glucose. Therefore, the mass balance equation is

$$\frac{dq}{dt} = q_{\text{in}} - q_{\text{out}}$$

Example 13.1 (*cont'd*)

The input quantity is defined as

$$K_1 q$$

The output quantity is defined as

$$(K_2 + K_3)q$$

Using this definition within the differential equation

$$\frac{dq}{dt} = K_1 q - (K_2 + K_3)q$$

$$\frac{dq}{q} = (K_1 - K_2 - K_3)dt$$

$$\ln(q) = (K_1 - K_2 - K_3)t + c$$

$$q(t) = C e^{(K_1 - K_2 - K_3)t} = q_0 e^{(K_1 - K_2 - K_3)t}$$

where C is the initial concentration of glucose within the nephron. With increasing complexity, these methods still can be applied, but it is necessary to quantify the time rate of change of each substance, within each compartment. This can lead to multiple differential equations that must be solved simultaneously.

13.10 Extracorporeal flows: dialysis

Dialysis is a method that can be used to separate solutes within a solution by means of diffusion through a semipermeable membrane. Blood dialysis is typically needed when the kidneys can no longer remove toxins from blood. When the kidneys fail, the patients must be maintained on dialysis; otherwise, they will die, because there will be a net accumulation of toxins within the body. As with any dialysis, there are three major components of the system (Fig. 13.9). The first is a compartment for the solution that will have substances removed. In our case, this will be blood. The second is a compartment containing a fluid with which the solutes will enter. The fluid in this compartment is termed the *dialysate*. The last is the

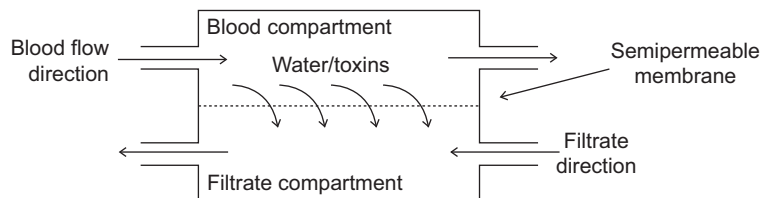


FIG. 13.9 Typical arrangement of a dialyzer to remove toxins from blood. A dialyzer would contain a semipermeable membrane that would be able to filter toxins from the blood and would leave all proteins, cells, and other necessary organic molecules within the blood. A countercurrent flow is used to maintain a concentration gradient along the entire membrane.

membrane, which is permeable to the substances of interest (e.g., toxins) and not permeable to other substances (e.g., plasma proteins). The design of these membranes is still of interest to many research groups, and there is significant work to miniaturize these devices and fabricate biological substitutes for these membranes. There are two common types of dialysis: the arteriovenous (AV) fistula method and the peritoneal dialysis method. The characteristics of these methods will be described briefly later.

Blood dialysis occurs in more than 300,000 patients in the United States. Before dialysis, the patient's blood is anticoagulated and remains so during the entire dialysis period. Blood is continually drawn from the body and enters the extracorporeal device. Water, toxins, and potentially some ions are removed from the blood and enter water (which is the dialysate) that contains ions in a similar concentration as the plasma. The ions are in a similar concentration as the patient's blood, to minimize the concentration gradient of these molecules between the patient's blood and the dialysate (thus, there should be minimal loss or gain of these solutes during the dialysis procedures). The semipermeable membrane used differs based on the patient's characteristics. Typically, membranes are composed of poly(methyl methacrylate), polyacrylonitrile, and polysulfone. These membranes allow the movement of molecules that are relatively small but block the movement of larger molecules. Importantly, these materials are biocompatible and do not activate inflammatory and/or thrombotic reactions.

To initiate the flow of water and solutes between the two compartments of the dialyzer, a hydrostatic pressure gradient and a concentration gradient (of the molecules of interest) are put into place across the semipermeable membrane. It is important to remember that the actual fluid flow through the dialyzer is typically slow, so that a countercurrent gradient is established and can be equilibrated. A countercurrent gradient means that the blood inflow is at the same physical location as the dialysate outflow. This location would theoretically have the largest concentration gradient between the blood and the dialysate. At the blood outflow location, which is aligned with the dialysate inflow, a relatively large concentration gradient exists as well. Using this approach, the concentration gradient exists across the entire membrane length and all of the toxins can be removed from the blood without multiple passes through the dialyzer. In contrast, a system that is set up to have the fluids flow in the same direction will typically equilibrate at some point along the length and there will be no more net movement of molecules past that location. In fact, the nephron uses a countercurrent multiplier system to efficiently transfer solutes from the nephron into the peritubular capillaries and vice versa (although this was not discussed in this textbook but can be found in physiology texts). If the blood and the dialysate flow in the same direction, the concentration gradient continually reduces over the length of the membrane and, again, typically equilibrates at some point.

To mathematically model these types of systems, a modified compartmental analysis method can be used to describe the convection of blood and dialysate through the extracorporeal device and the diffusion of solutes out of the blood. We would first need to consider the rate at which the solute enters the compartment and the rate at which the solute exits the compartment. These can be represented as

$$\begin{aligned}\frac{dq_{\text{in}}}{dt} &= \dot{q}_{\text{in}} \\ \frac{dq_{\text{out}}}{dt} &= \dot{q}_{\text{out}}\end{aligned}\tag{13.19}$$

These rates would also be equal to the volumetric flow rate of fluid into the compartment multiplied by the inflow or outflow concentration of the solute

$$\begin{aligned}\dot{q}_{\text{in}} &= \dot{Q}c_{\text{in}} \\ \dot{q}_{\text{out}} &= \dot{Q}c_{\text{out}}\end{aligned}\quad (13.20)$$

We can then describe the time rate of change of any solute within the compartment as

$$\frac{dq}{dt} = \dot{q}_{\text{in}} - \dot{q}_{\text{out}} = \dot{Q}(c_{\text{in}} - c_{\text{out}})$$

or

$$V_{\text{compartment}} \frac{dc}{dt} = \dot{Q}(c_{\text{in}} - c_{\text{out}}) \quad (13.21)$$

assuming that the volume of the compartment does not change with time, which is typically a good assumption for dialysis compartments. To completely model an extracorporeal device, a system of first-order linear ordinary differential equations would need to be coupled, such that the solute concentration in each compartment would affect the net diffusion across the semipermeable barrier and this would alter the concentration in the second compartment. Such a system would take the form of

$$\begin{aligned}\frac{dc_1}{dt} &= -\frac{\dot{Q}_{1 \rightarrow 2}}{V_1}c_1 + \frac{\dot{Q}_{2 \rightarrow 1}}{V_2}c_2 + \dot{Q}_1 \\ \frac{dc_2}{dt} &= \frac{\dot{Q}_{1 \rightarrow 2}}{V_1}c_1 - \frac{\dot{Q}_{2 \rightarrow 1}}{V_2}c_2 + \dot{Q}_2\end{aligned}\quad (13.22)$$

where $\dot{Q}_{1 \rightarrow 2}$ is the flow rate from compartment 1 into compartment 2 and $\dot{Q}_{2 \rightarrow 1}$ is the flow rate from compartment 2 into compartment 1.

Example 13.2

A patient is currently connected to an extracorporeal device to remove the excess salt from the blood (Fig. 13.10). Imagine that the inflow blood contains 5 g of salt and the blood inflow flow rate is 5 mL/min. The blood outflow rate is also 5 mL/min. The inflow rate of the dialysate is 2 mL/min, and the outflow flow rate is also 2 mL/min. There is a flow between the two compartments of 1 mL/min in each direction. The initial concentration of salt within the dialysate is 0 g, and the initial concentration of salt within the blood is 150 g. The volume of the blood compartment is 100 mL, and the volume of the dialysate compartment is 100 mL. Determine the salt quantity as a function of time for both compartments of this system.

Continued

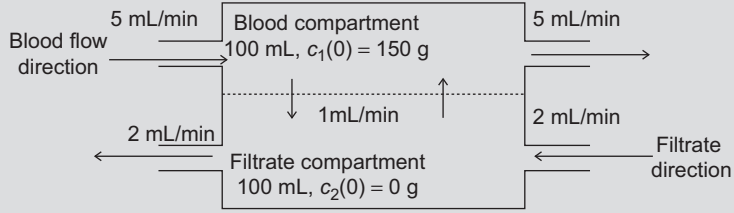
Example 13.2 (cont'd)

FIG. 13.10 Flow through an extracorporeal device for the in-text Example 13.2.

Solution

First, set up the differential equations and the initial conditions:

$$\begin{aligned}\frac{dc_1}{dt} &= -\frac{1 \frac{\text{mL}}{\text{min}}}{100 \text{ mL}}c_1 + \frac{1 \frac{\text{mL}}{\text{min}}}{100 \text{ mL}}c_2 + 5 \text{ g/min} \\ \frac{dc_2}{dt} &= \frac{1 \text{ mL/min}}{100 \text{ mL}}c_1 - \frac{1 \text{ mL/min}}{100 \text{ mL}}c_2 \\ c_1(0) &= 150 \text{ g} \\ c_2(0) &= 0 \text{ g}\end{aligned}$$

Using the Laplace transform to solve this system of differential equations, this system becomes

$$\begin{aligned}sC_1 - c_1(0) &= -0.01C_1 + 0.01C_2 + \frac{5}{s} \\ sC_2 - c_2(0) &= 0.01C_1 - 0.01C_2 \\ C_1(s + 0.01) - 0.01C_2 &= \frac{5}{s} + 150 = \frac{150s + 5}{s} \\ 0.01C_1 &= C_2(s + 0.01) \\ C_1 &= 100C_2(s + 0.01) \\ [100C_2(s + 0.01)](s + 0.01) - 0.01C_2 &= \frac{150s + 5}{s} \\ 100C_2(s^2 + 0.02s) &= \frac{150s + 5}{s} \\ C_2 &= \frac{1.5s + 0.05}{s^2(s + 0.02)} = \frac{-5}{s} + \frac{2.5}{s^2} + \frac{5}{s + 0.02} \\ C_1 &= \frac{150s^2 + 6.5s + 0.05}{s^2(s + 0.02)} = \frac{200}{s} - \frac{2.5}{s^2} - \frac{50}{s + 0.02} \\ c_1(t) &= 200 - 2.5t - 50e^{-0.02t} \\ c_2(t) &= -5 + 2.5t + 5e^{-0.02t}\end{aligned}$$

An AV fistula is a general term in which an artery is connected directly to a vein, bypassing the capillary network. This can occur as a pathological condition, and it would be characterized by a reduced blood flow to the capillary beds and thus a reduced nutrient delivery and waste removal from these capillaries. During dialysis procedures an artificial AV fistula (sometimes referred to as *hemodialysis*) can be created by directly connecting an artery and a vein. This fistula becomes part of the body and is typically a reasonably robust connection between the arterial side and the venous side of the circulation. This fistula provides relatively easy sites for the physician to connect to the blood supply. Peritoneal dialysis is a less common dialysis method compared with the AV fistula approach. During peritoneal dialysis the dialysate is perfused directly into the peritoneal space. The capillaries within the peritoneum serve as surrogates for the kidneys allowing for the wastes to be filtered into the dialysate. The dialysate is collected through a drain line. An advantage of peritoneal dialysis is that it can be conducted at home by the patient, because the peritoneal catheter is surgically implanted into the patient. However, there are some risks for infection with this approach and it should be used only in certain patients.

13.11 Disease conditions

13.11.1 Renal calculi

Renal calculi are commonly known as *kidney stones*. Most of the time, calculi appear in the kidneys as a result of urine becoming supersaturated with salts. These salts crystalize and become associated with an organic matrix and, therefore, are no longer soluble in the kidney fluids. As the solid crystals pass through the kidney tubule system, they may become lodged in a region or simply form in the larger tubules (commonly the ureter). When this happens, urine cannot be processed and the calculi must be removed by natural means (e.g., passing a kidney stone) or by laser or ultrasound to break apart the salt deposits. Approximately 75% of calculi are formed from calcium because there is a high daily calcium intake that cannot be handled/processed by the kidney when it also experiences a high salt environment. The easiest treatment for calculi is to decrease the intake of salts, which will reduce the load on the kidney. However, once a calculus has formed, it must pass through the urinary system or be removed by some other means.

Renal calculi are found in about 1% of the population; however, the reoccurrence rate in afflicted individuals is normally in the range of 70% to 80%. Kidney stones that originate from abnormal calcium concentrations typically take the form of calcium oxalate (CaC_2O_4) and calcium phosphate (e.g., $\text{Ca}(\text{H}_2\text{PO}_4)_2$). Calculi that are not composed of calcium are typically composed of uric acid, cysteine, or magnesium ammonium phosphate. Interestingly, inhibitors of crystal growth can hinder the formation of calculi, and these molecules include pyrophosphate, citrate, and glycosaminoglycans.

Five major abnormalities promote the formation of calculi. Absorptive hypercalciuria is classified by an increase in the absorption of calcium within the intestine. Renal hypercalciuria occurs when there is an impaired nephron tubule reabsorption of calcium. Resorptive hypercalciuria is characterized by an excessive bone resorption, usually associated with an increased secretion of parathyroid hormone. Hyperoxaluria is associated with an enhanced formation of oxalate secondary to a disruption of enzyme kinetics in the synthesis of oxalate.

Finally, hyperuricosuria is normally associated with an increase in the production of uric acid, but it may also be associated with altered dietary intake of purines. Regardless of the mechanism that initiates the calculi, the end product is similar.

13.11.2 Kidney disease

Kidney disease is a general term that can apply to many different diseases that affect different functions of the kidney. Here we will discuss some of the common diseases of the kidneys that may lead to dialysis. Typically, kidney diseases are identified through abnormal urine analysis in asymptomatic healthy patients. One of the most common findings of an abnormal urine analysis is proteinuria. Normally kidneys excrete approximately 150 mg/day of proteins and this is regulated fairly tightly by the glomerular filtration barrier. An increased protein concentration is indicative of a breakdown of this filtration barrier or a decrease in the reabsorption of proteins from the filtrate. Regardless of the cause, serious repercussions are associated with an increased protein excretion. A second common finding during kidney diseases is hematuria. Hematuria is characterized by an excretion of red blood cells within the urine. Under physiological conditions, the fenestrated endothelial cells do not allow for the passage of blood cells in the nephron filtrate. Thus, any blood cells in the urine (typically the urine turns reddish) indicate a significant breakdown of the glomerular filtration barrier. Similarly, leukocyturia is the presence of leukocytes within the urine. Less common findings associated with kidney disease are chyluria, lipiduria, and pneumaturia. Chyluria is associated with lymph entering the urine, which occurs when there is a breakdown of the lymph flow within the kidneys. Urine typically appears to be milky under these conditions. Lipiduria is associated with an increased concentration of fats (typically in the form of droplets) in the urine. Lipiduria is common with some poisonings (such as heavy metal or carbon monoxide poisoning). Finally, pneumaturia is characterized as gas bubbles in urine. This is commonly found during urinary tract infections, when the infectious agents (e.g., bacteria) produce gases that can become dissolved in the urine.

Diseases of the kidney are typically coupled with cardiovascular diseases. In many instances, with a reduced filtration, there would be an increased water retention (edema), circulatory volume overload, and hypertension. Acute renal failure describes any event in which the function of the kidneys is suddenly but briefly impaired, whereas chronic renal failure would typically be associated with a slower but longer lasting impairment of renal function. It is typically quantified under normal ingestion conditions as having a urine volume less than 400 mL/day. Under either of these conditions it may be necessary for dialysis to be prescribed.

Other diseases of the kidney include nephrotic syndrome, which is the consequence of sustained and heavy proteinuria. Typically, nephrotic syndrome is associated with edema, proteinuria, and hyperlipidemia. There are also common defects of the nephron tubule system. The majority of these are hereditary and can be characterized by a progressively reducing filtration rate coupled with altered plasma or urine concentrations of particular solutes. Some of these nephron tubule diseases are also associated with anatomical defects that alter the overall function of the nephron system. Depending on the particular disease, a different treatment course may be prescribed.

Summary

- 13.1.** The kidneys remove metabolic waste products and foreign particles from the body, as well as maintain the water volume and the concentration of various ions within the body. Urine formed within the kidneys passes through the ureters into the bladder, where it is held until it is excreted from the body. Blood is supplied to the kidneys by the renal arteries. Interestingly, the renal circulation is composed of two capillary beds that are separated by an arteriole. The efferent arteriole predominantly regulates the pressure in both capillary beds. The first set of capillaries forms the glomerulus, which is the site for blood filtration. The second set of capillaries, the peritubular capillaries, is involved in the reabsorption and secretion of compounds. The juxtaglomerular apparatus forms a direct feedback mechanism within each nephron to control the filtration rate based on the concentration of sodium ions within the nephron.
- 13.2.** The renal artery, which bifurcates from the aorta, passes through the hilum and branches into the interlobar arteries. The interlobar arteries bifurcate and bend and are termed *arcuate arteries*, which give rise to the radial arteries. The afferent arterioles that enter the nephron units branch off of the arcuate arteries. The venous circulation through the kidney follows a similar path, but in reverse to the arterial path. The principle differences between the peritubular capillaries and the vasa recta is that the peritubular capillaries do not penetrate as deep into the medulla. Blood flow to different capillary beds within the renal circulation is perfused differently.
- 13.3.** Glomerular filtration is the process by which compounds are removed from the blood and enter the nephron. Filtration is a bulk flow process that depends on the hydrostatic pressure within the glomerulus, the hydrostatic pressure within Bowman's capsule, and the osmotic pressure within the glomerulus. Under normal conditions, the total blood volume is filtered approximately 60 times per day. By knowing the plasma concentration of a compound, it is possible to calculate the nephron's filtered load for that ion.
- 13.4.** Tubule reabsorption is a process by which compounds within the filtrate can be brought back into the blood. Secretion is a process by which compounds that were not filtered can be brought into the nephron. Most compounds are reabsorbed or secreted by both passive and active transport mechanisms. The reabsorption of many molecules is coupled to sodium movement within the nephron. The amount of any substance that is secreted can be calculated from

$$\text{Amount excreted} = \text{Amount filtered} + \text{Amount secreted} - \text{Amount reabsorbed}$$

- 13.5.** Single nephron filtration rates are similar to the total glomerular filtration rates that were discussed earlier but are used to describe the actions of single nephrons. This can be quantified from

$$SNFR = Q_{\text{tubule fluid}} \left(\frac{[\text{inulin}]_{\text{tubule fluid}}}{[\text{inulin}]_{\text{plasma}}} \right)$$

In general, under physiological conditions, single nephron filtration rates average to approximately 100 nL/min, but can range from as low as 20 nL/min to as high as

200 nL/min. Using the single nephron filtration rate and the glomerular filtration rate, one can approximate the number of functional nephrons as 1.2 million per kidney. The resistance of the renal microcirculation is critical to the flows through the nephron units; these resistance values can be quantified from

$$R_{AA} = \frac{P_{MA} - P_{GC}}{Q_G}$$

and

$$R_{EA} = \frac{P_{GC} - P_{PC}}{Q_{EA}}$$

to give a total renal resistance of

$$R_T = R_{AA} + R_{EA}$$

- 13.6.** Previous work has shown that only approximately 5% of the net reabsorption within the proximal tubule system can be accounted for by the hydrostatic and osmotic pressure gradients that exist between that tubule system and the peritubular capillaries. Many studies have shown that the flow of sodium (and other ions) induces a net movement of water out of the proximal tubule system. This is accompanied by an increase in the hydrostatic pressure of the interstitial space. The reabsorptive coefficient, which is a measure of the nephron function can be represented as

$$K_r = \frac{SNFR - Q_{TS}}{\Pi_{PC} - \Pi_{IS} - P_{PC} - P_{IS}}$$

- 13.7.** Sodium reabsorption is regulated by the amount and type of channels present within the luminal surface of the nephron epithelial cells. Sodium movement into the epithelial cells is coupled to glucose or hydrogen movement. Sodium movement out of the epithelial cells is regulated by the sodium–potassium ATPase. The balance between sodium reabsorption and secretion is coupled to both the juxtaglomerular apparatus and the renin–angiotensin system. Water movement out of the nephron is by bulk diffusion or is facilitated through the presence of aquaporin channels. Reuptake of proteins (or amino acids) and other metabolically important molecules are typically coupled to sodium transport transporters that are highly specific to the renal epithelial tissue.
- 13.8.** Autoregulation of the kidneys is important to maintain the filtration conditions under altered inflow conditions to the kidney. A significant amount of work has shown that mechanisms are present within the kidney to regulate and maintain the blood flow to and through the glomerular and peritubular capillaries at near constant levels, and these mechanisms have been shown to be independent of the nervous system. A number of theories try to describe the mechanisms that are responsible for autoregulation changes, which include the cell separation theory, the myogenic theory, and the metabolic theory.

- 13.9.** Compartmental analysis is a technique that is used to describe the movement of various solutes throughout different systems. Fick's law of diffusion is the governing equation for this type of analysis. It states that

$$\frac{dc}{dt} = - \frac{DA}{V} \frac{dc}{dx}$$

Solving this for a simple two-compartment system, the change in concentration of a single species would be

$$\frac{dc_1}{dt} + \frac{DA}{\Delta x} \frac{c_1(V_1 + V_2)}{V_1 V_2} = \frac{DA}{\Delta x} \frac{c_0}{V_2}$$

- 13.10.** Dialysis is a method used to remove wastes from the blood, when the kidneys are no longer functioning properly or efficiently. An extracorporeal device is designed with both a blood compartment and a filtrate compartment. The direction of blood flow and filtrate flow is typically opposing to maintain a concentration gradient along the entire device. Various mechanisms can be used to initiate the dialysis; these include the arteriovenous fistula method or peritoneal dialysis. Each has advantages and shortcomings.
- 13.11.** Renal calculi appear when the urine becomes supersaturated with salts. These salts can crystallize, and therefore, they are no longer in solution. As these crystals pass through the nephron (or kidney) they can become lodged within the nephron tubule, thus preventing flow through downstream of the blockage (e.g., prevents urine formation/collection, etc.). Most renal calculi are formed from calcium salts. Many kidney diseases are characterized by altered urine production and/or altered concentration of compounds within urine. Some of these diseases are hereditary.

Homework problems

- 13.1.** The functional unit of the kidney is the nephron. Discuss some of the important functions that the nephron performs and how the nephron performs those functions.
- 13.2.** Urine formation involves all of the following process except which of the following and why?
- Reabsorption of water
 - Reabsorption of particular solutes
 - Hydrostatic pressure within the glomerular capillaries
 - Secretion of excess nutrients
 - Filtration of blood
- 13.3.** What is the effect of having two capillary beds within the renal circulation? How is the blood flow regulated within each of these capillary beds?
- 13.4.** By increasing the diameter of the afferent arteriole and decreasing the diameter of the efferent arteriole, what effect can one predict to occur for the glomerular filtration rate?

Continued

Homework problems (cont'd)

- 13.5. Discuss the juxtaglomerular complex functions and locations.
- 13.6. Calculate the expected filtered load for potassium ions, chlorine ions, and calcium ions. What would you anticipate the percent reabsorption for each of these ions to be? Why?
- 13.7. Some compounds are filtered by the kidneys but not reabsorbed (such as mannitol). Would a sudden increase in the mannitol concentration have an effect on the glomerular filtration rate and the amount of urine produced? If it has an effect, why?
- 13.8. The daily elimination of magnesium is approximately 0.15 g/day at a concentration of 14 mg/dL. Calculate the amount filtered and amount reabsorbed if we assume that the nephron does not secrete any magnesium.
- 13.9. Cellular matter enters the nephron at a rate of approximately 600 cells/mL of urine produced (combined red blood cells and white blood cells). What are some of the reasons that cellular matter can enter the nephron? If there was an increase in the red blood cell concentration in the urine, what would this suggest? What about an increase in the white blood cell urine concentration?
- 13.10. For the compartment system shown in Fig. 13.11, determine a single differential equation that depicts the movement of the solutes between the various compartments as a function of time, rate constants, and solute concentration. Assume that the concentration of solute in compartment 1 at time zero is $q_1(0)$, in compartment 2 at time zero is 0, and in compartment 3 at time zero is $q_3(0)$.

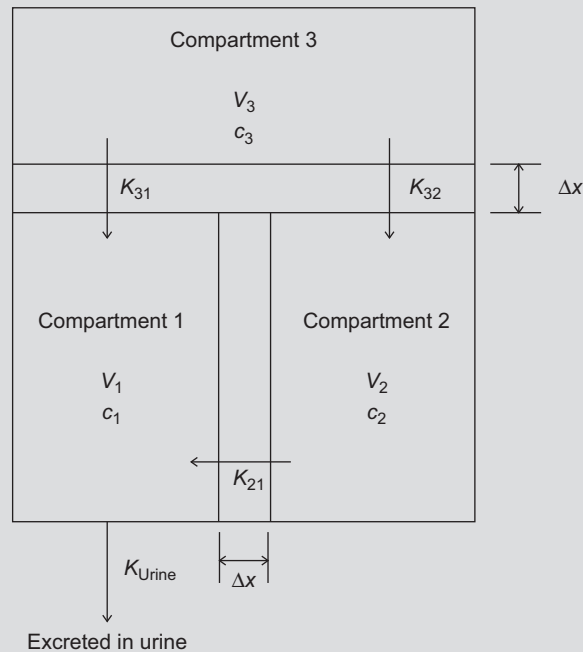


FIG. 13.11 Three-compartment model for Homework Problem 13.10.

Homework problems (cont'd)

- 13.11.** Find the maximum concentration of solute in the plasma if $K_1 + K_2 = 0.012 \text{ min}^{-1}$ and K_3 is equal to 0.034 min^{-1} . At time zero, 75 g of the solute was ingested into the digestive system compartment and there was no solute in the plasma. See Fig. 13.12 for the compartmental setup.

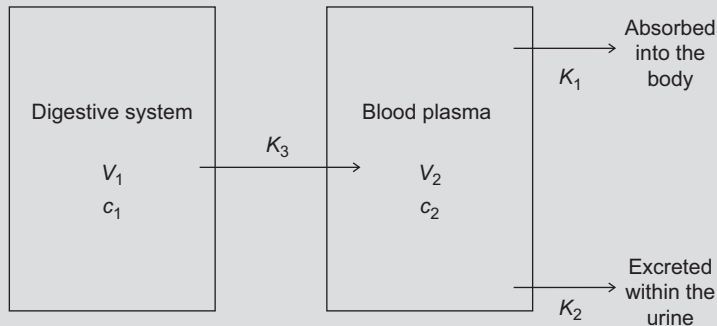


FIG. 13.12 Two-compartment model for Homework Problem 13.11.

- 13.12.** Renal arteriosclerosis is a risk factor for hypertension. Why and what are some of the treatments that you would recommend to decrease the blood pressure?
- 13.14.** Knowing one single nephron filtration rate, would you be able to accurately predict the glomerular filtration rate? What information would you need to make a relationship between these variables? What assumptions would you need to make regarding this relationship? Do you predict that these would be valid assumptions?
- 13.15.** We defined autoregulation in terms of vascular function in a previous chapter. The kidney has similar autoregulation features. Do you suppose that the autoregulation features of the vasculature and the kidney interact with each other or do they act autonomously? Would it be beneficial to have some overlap over these two systems, if you think there is no cross-talk?
- 13.16.** From your knowledge of inulin concentration in the plasma (which is approximately 3 mg%) and within the tubule fluid (you may need to approximate this), calculate the flow rate of tubule fluid if the single nephron filtration rate is 125 nL/min.
- 13.17.** Given that the single nephron filtration rate averages to 125 nL/min, that the single nephron filtration fraction is 0.35, and that the hematocrit in the afferent arteriole is 0.52, calculate the flow rate within the efferent arteriole. Additionally, if the pressure difference across the glomerular capillaries and the vasa recta is 35 mmHg, determine the resistance of the efferent arteriole.
- 13.18.** Discuss the reabsorptive coefficient for different segments of the nephron tubule system. Would there be differences in the reabsorptive coefficient along these different segments? If so, where would the differences manifest (e.g., in the net difference in the flow rates or in the net difference of the pressures acting across the segments of interest or both)?

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Splanchnic circulation

Liver and spleen

LEARNING OUTCOMES

- Describe the physiology and the anatomy of the liver
- Identify the functional unit of the liver
- Examine the filtration of salient species within the liver and spleen
- Describe the physiology and the anatomy of the spleen
- Discuss the salient aspects of the splanchnic circulation
- Compare the blood flow through the liver and spleen under various physiological and pathological conditions
- Describe the flow of blood through the microcirculatory units within the liver and the spleen
- Discuss how the liver can store and release blood under various physiological conditions
- Compare the active and passive components of the splanchnic circulation
- Examine the role of sympathetic nervous system activity on the spleen
- Discuss disease conditions that commonly affect the liver and the spleen

14.1 Liver and spleen physiology*

The splanchnic circulation is a specialty circulation associated with the gastrointestinal system and composed of the gastric (stomach), small intestinal, colonic (large intestine), pancreatic, hepatic (liver), and splenic (spleen) circulations. What makes this circulation especially distinctive is that these circulations are largely in parallel with each other, supplied by three major arteries. These arteries are the celiac artery, the superior mesenteric artery, and the

*This section is considered advanced and can be skipped without a loss of continuity.

inferior mesenteric artery, which branch extensively into anastomosing arterioles and capillaries. Additionally, the importance of the splanchnic circulation is illustrated by the distribution of the cardiac output to this circulation. Under normal physiological conditions, the splanchnic circulation receives approximately 20% to 25% of the cardiac output and this system extracts approximately 20% of the oxygen available in blood. Changes to this blood distribution and usage have been used as markers of stress within the cardiovascular system. We will focus our discussion on the liver circulation and the spleen circulation, which are of particular interest to biofluids mechanics. Each of these circulations has unique characteristics that relate to inflammation, thrombosis, absorption of nutrients, etc. Furthermore, these circulations are relatively different from those described previously; thus, we aim to broaden the readers' understanding of different types of circulations in the body.

The liver is the largest visceral organ in the human body (with a mass of approximately 1.5 kg), is at the center of many metabolic processes, and regulates many other metabolic processes that occur in the body. The liver is surrounded by a tough and fibrous capsule that protects the organ from injury. This capsule is divided by the falciform ligament that denotes the anatomical division between the left and right lobes of the liver. The falciform ligament thickens into the round ligament toward the posterior section of the liver. This ligament is a remnant of the umbilical vein, which is the outflow location of blood during fetal development. There is a small region on the posterior section of the liver, which is termed the *porta hepatis*. This is the location where the hepatic artery proper, the hepatic portal vein, and the common bile duct enter and exit the liver.

The blood flow to the liver is unique. Nearly one-third of the blood that enters the liver arises from the hepatic artery proper. The hepatic artery proper is a direct branch from the common hepatic artery, which is a branch from the celiac trunk. The celiac trunk directly branches off from the abdominal aorta (Fig. 14.1). Thus, this portion of the blood is typical arterial blood that was discussed in previous sections of this textbook. The remaining two-thirds of the blood that enters the liver comes from the hepatic portal vein. The blood within the hepatic portal vein is venous blood that comes from the capillaries of the esophagus, stomach, small intestines, and vast majority of the large intestines. Just for the sake of distinction, any blood vessel that connects two capillary beds is termed a *portal vessel*. The purpose of the hepatic portal system is to deliver nutrients absorbed from the gastrointestinal system directly to the liver for storage, excretion, or modification for later use. The hepatic portal vein obtains blood from the inferior mesenteric vein (which collects blood from the descending colon, the sigmoid colon, and the rectum), the splenic vein (which collects blood from the spleen, portions of the orad stomach, and the pancreas), and the superior mesenteric vein (which collects blood from the caudad region of the stomach, the small intestines, the ascending colon, the transverse colon, and a small portion of the pancreas) (see Fig. 14.1). Most of the flow within the hepatic portal vein is contributed by the superior mesenteric vein. The blood entering the liver eventually makes it into the liver sinusoids, which is the major location in which the concentration of nutrients in the blood is modified. After passing through the liver sinusoids, the venous blood is collected into the hepatic veins, which converge directly with the inferior vena cava. Under normal physiological conditions, the concentration of nutrients within the blood is stable, even directly after ingestion, because of the actions of the liver and this specialty circulation.

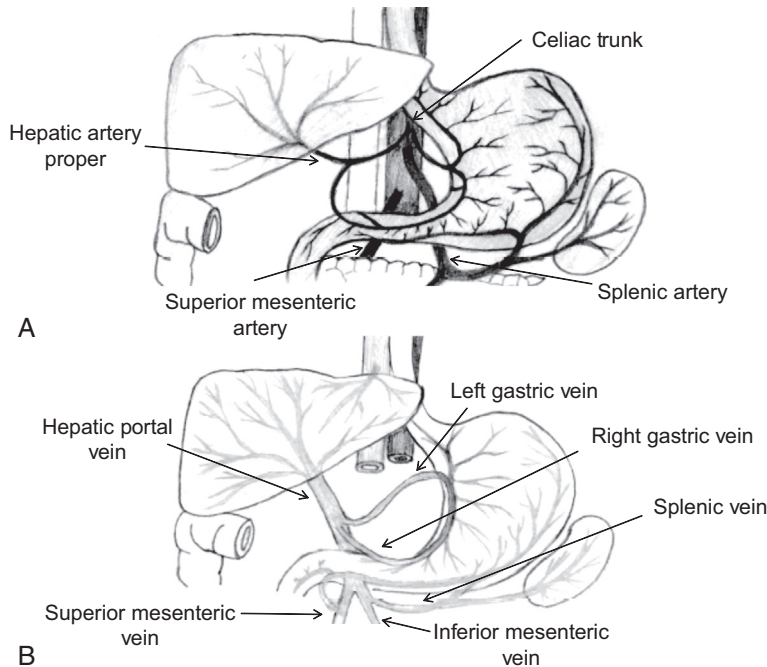


FIG. 14.1 Arteries supplying the superior abdominal organs (A) and the hepatic portal system (B). These vascular systems illustrate that the liver obtains blood from the main arterial systemic circulation (as a branch of the celiac trunk) and from the venous circulation from most of the gastrointestinal system. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath and Bartholomew, Pearson, New York, 2018.)

Each main lobe of the liver is divided into approximately 100,000 lobules, which are the most basic functional unit of the liver (Fig. 14.2). Each lobule is separated by an interlobular septum that helps prevent the transfer of materials between the different lobules. Lobules are relatively large, with an average diameter in the range of 1 mm, and each lobule unit has a hexagonal shape. At the center of each lobule is the central vein, which collects and mixes blood from both the hepatic artery proper and the hepatic portal vein. Each lobule is composed of numerous liver sinusoids, which are separated by a sandwich of endothelial cells (on the two blood sides, e.g., the bread of the sandwich) and hepatocytes (in between the endothelial cells, e.g., the contents of the sandwich). Blood flows through the sinusoids and collects in the central vein.

Sinusoids are a specialized type of fenestrated capillary beds that are found in various locations of the body. It is typical for cells that compose the sinusoids, including those found in the liver, to have a more flattened, rectangular shape instead of the more classic circular shape that is associated with typical capillaries. The endothelial cells that compose sinusoid capillaries are both fenestrated (e.g., have pores that pass through the cell from the apical side to the basolateral side) and have gaps between neighboring endothelial cells (e.g., the cell membranes of neighboring cells are not stitched tightly together) (Fig. 14.3). In many cases, the basement membrane surrounding the epithelial cells is very porous, thin, or even absent, which is the case in the liver sinusoids (compare this to the fenestrated renal filtration barrier

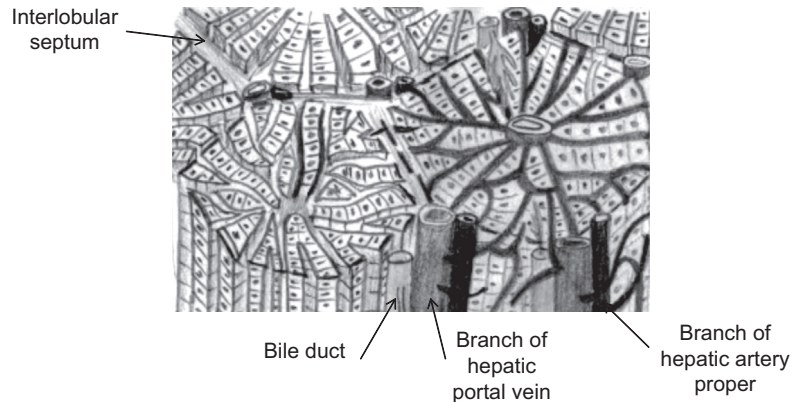


FIG. 14.2 A schematic view of the liver lobule structure illustrating that branches of the hepatic artery proper and the hepatic portal vein reach the lobule level at each vertex of a hexagon-like shape. Capillaries from the vessels penetrate toward the central vein region, which is illustrated in Fig. 14.4. Each lobule is approximately 1 mm in length. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath and Bartholomew, Pearson, New York, 2018.)

discussed in Chapter 13). The consequence of these large openings in sinusoids, including those of the liver, is that all constituents of plasma, including the largest plasma proteins, can diffuse out of the capillary network into the space adjacent to the hepatocytes (Fig. 14.4). A specialized macrophage, termed the *Kupffer cell*, resides in the liver sinusoids. Their role is to screen and engulf any foreign particle or damaged blood cell that enters the liver. Thus, the hepatic microcirculation is also specialized.

Blood enters the liver sinusoids from branches of both the hepatic artery proper and the hepatic portal vein. Recall that each lobule is a hexagonal shape made up of numerous sinusoids. A small branch from the hepatic artery proper, a small branch from the hepatic portal vein, and a small bile duct form a triad at each of the six corners of a liver lobule. Branches from the two blood vessels converge to form the sinusoids; thus, one side of the sinusoids

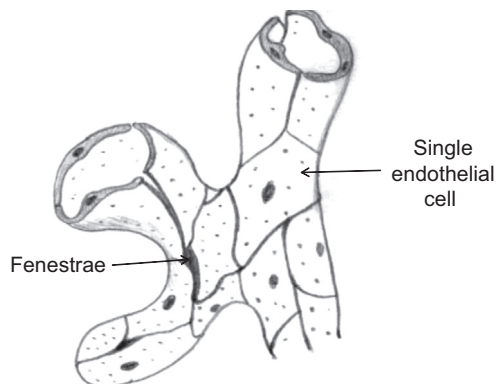


FIG. 14.3 Schematic of a fenestrated capillary system illustrating that there are large pores between neighboring endothelial cells. These large pores allow for the rapid exchange of water and solutes between blood and interstitial fluid and penetrate the entire endothelial wall. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath and Bartholomew, Pearson, New York, 2018.)

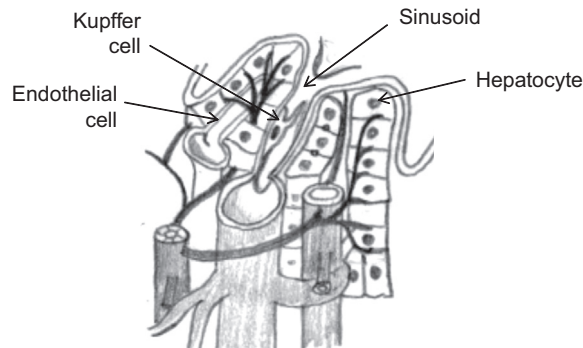


FIG. 14.4 Schematic of a single liver lobule illustrating both of the cells that make up the liver and sinusoid subunit. Blood from the hepatic artery proper and the hepatic portal vein converge at the sinusoid level, are filtered by hepatocytes and Kupfer cells, and then pass to the central vein location. (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath and Bartholomew, Pearson, New York, 2018.)

contains venous blood from the gastrointestinal tract, whereas the other side of the sinusoid contains arterial blood from the aorta. Because there is a very well-defined organization of the liver sinusoids, each triad delivers blood to three distinct liver lobules (e.g., the corner where three hexagons contact each other). The hepatocytes absorb solutes from the plasma throughout the length of the sinusoid and secrete plasma proteins into the plasma for later use. This modified blood enters the central vein, which eventually converges into the hepatic vein, which then converges with the inferior vena cava.

The liver is responsible for hundreds of functions, which fall into three general categories. The first of these functions is the regulation of metabolism. This function primarily occurs through the control of blood composition, which is also primarily regulated through the actions of the liver. As mentioned earlier, all blood from the gastrointestinal tract enters the liver first before entering the general systemic circulation. Because the nutrient concentration in blood is fairly stable, regardless of ingestion periods, this suggests that the liver extracts all of the excess nutrients from the hepatic portal system and corrects deficiencies in the nutrients (if any). This suggests that the liver is sensitive and responsive to nutrient concentrations and the liver can correct any divergence from normal nutrient values. Similarly, any toxin that enters the blood from the gastrointestinal tract, whose absorptive surface is technically outside the body, is cleared by the liver.

In terms of carbohydrates, the liver maintains the blood glucose level at approximately 90 mg/dL. If the glucose concentration exceeds this value, hepatocytes absorb glucose from the bloodstream and either store excess glucose as glycogen or synthesize lipids from the excess glucose. If the glucose concentration falls below this level, glycogen is broken down into glucose and the new glucose is secreted into the bloodstream. Similar mechanisms exist to maintain lipid and amino acid concentrations within the normal range. Excess of either of these metabolites can be removed from the circulation and stored for later use. When lipid levels drop, the liver secretes lipids directly into the bloodstream. The liver also stores minerals, such as iron, and fat-soluble vitamins. Many drugs can be metabolized within the liver, and waste products can be removed by actions taken by the liver.

The second major function of the liver is the regulation of blood components that are not related to metabolic needs of the body. For instance, the liver produces many plasma proteins, including albumin, clotting proteins, transport proteins, and complement proteins. Any damaged blood cell or a blood cell that is presenting a pathogen can be removed from circulation by the liver. The liver plays a prominent role in the recycling of released hormones, including insulin, epinephrine, and many of the sex hormones (e.g., estrogen), and in the removal of antibodies.

Finally, the liver produces and secretes bile into the gastrointestinal tract by the gallbladder. Bile is a watery mixture that contains some ions, bilirubin, and various bile salts (which are lipids). The bile salts help in the digestion of non-water-soluble lipids, by emulsifying the lipids. If the bile salts are not present, large ingested lipids coalesce to form large lipid droplets, which cannot be absorbed or broken down by digestive enzymes. The bile salts act to stabilize small droplets of lipids, thereby increasing the surface area for enzyme activities and allowing lipids to eventually be absorbed along the gastrointestinal tract.

The spleen plays a salient role in the lymphatic system and immune reactions that occur throughout the body. In fact, the largest lymphoid tissue in the adult body is the spleen. The adult spleen is approximately 12 cm long and has a mass of approximately 150 g. The spleen is located along the orad section of the greater curvature of the stomach and is close to the stomach, the left kidney, the diaphragm, and the pancreas. The posterior portion of the spleen toward the inferior portion contains a hilum, where the splenic artery, the splenic vein, and the splenic lymphatic vessels enter and exit the spleen (Fig. 14.5). The hilum is located at the junction between the gastric (stomach) region and the renal region.

The human spleen is surrounded by a thick fibrous tissue composed of mostly collagen and elastin (this is in contrast to other mammals, which have a layer of smooth muscle cells within this fibrous tissue, allowing for the spleen to actively “eject” blood components). The interior portion of the spleen is composed of the red pulp, which contains blood, and the white pulp, which is similar to lymph nodes.

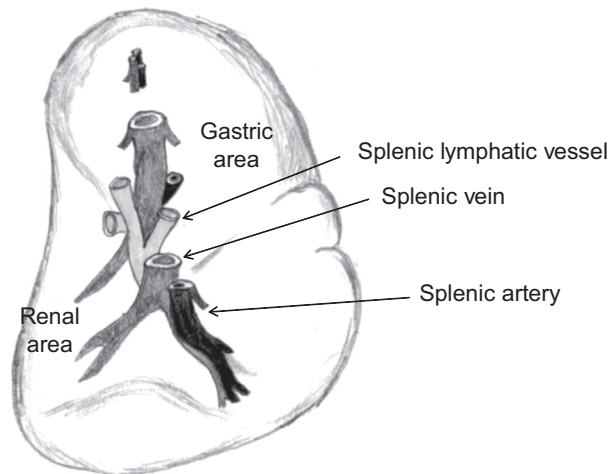


FIG. 14.5 Posterior view of the spleen illustrating the hilum where the splenic artery, splenic vein, and the splenic lymphatic vessel enter and leave the spleen). (Modified from *Fundamentals of Anatomy and Physiology*, 11th Edition by Martini, Nath and Bartholomew, Pearson, New York, 2018.)

Immediately after the splenic artery enters the hilum, it branches into small arteries, termed *trabecular arteries*, which spread throughout the red and white pulp. The trabecular arteries continually branch into small arterioles and capillaries that eventually enter the red pulp regions. In general, the white pulp surrounds medium-sized to small arterioles. The small capillaries empty into sinusoids that are lined by macrophages and that contain a mesh-like framework of proteins. The role of the macrophages and the mesh-like structure are to identify, filter, and engulf foreign particles. Additionally, because the white pulp, which acts as a lymph node, is close to this sinusoid, any inflammatory response is quickly sensed and cleared by lymphocytes in the white pulp. After flowing through the splenic sinusoids, blood enters small venules that converge to the trabecular veins and eventually the splenic vein.

In a general sense, the spleen has a function very similar to that of lymph nodes, which were described in Chapter 9, and some additional functions that are related to the regulation of blood properties. First, the spleen can remove abnormal and damaged blood cells, especially platelets, by phagocytosis mechanisms. Some materials from these cells may be recycled for use in other locations of the body. The spleen also has a relatively large store of red blood cells, primarily from the clearance and recycling of any damaged red blood cells. Finally, as with most lymph nodes, the spleen can initiate an immune response that involves B- and T-cells. Thus, the spleen plays a large role in the adaptive immunity reactions.

14.2 Hepatic and splenic blood flow*

As mentioned earlier, the liver obtains approximately 25% of the cardiac output, and approximately 70% to 75% of this portion of the cardiac output comes from the hepatic portal system. The distribution of hepatic portal blood and hepatic artery proper blood is homogeneous throughout the liver, meaning that there is a complete mixing of these blood components throughout the liver structure. Furthermore, it has been shown that when altering the inflow pressure of either branch there is little effect on this distribution and perfusion of liver tissue. However, it has been shown that when vessels before the lobule regions become obstructed there is a shift of blood from the vessel that is occluded (for sake of argument the hepatic portal branch) to the vessel that is not occluded (using the same argument the hepatic artery proper). This has been described fully in many experimental conditions in which a reduction in the blood flow within a branch of the hepatic portal blood flow elicited an increased flow through the neighboring branch of the hepatic artery proper. With a reduced flow in branches of the hepatic artery proper, a decrease in the vascular resistance of the neighboring branch of the hepatic portal vein was observed, but the flow through this vessel was not altered significantly. The result of these changes is that the overall flow through the liver lobule structures remains largely the same under many conditions. There are many theories explaining these mechanisms, but it appears that because the majority of the oxygenated blood comes from the hepatic artery proper, the liver vascular system is designed to either maintain this flow and/or to maintain the concentration of nutrients throughout the liver tissue. Many of these responses appear to be related to myogenic processes (described previously);

*This section is considered advanced and can be skipped without a loss of continuity.

however, there are some passive effects that have been observed in this system. The myogenic responses appear to be the more likely effects, because the pressures are drastically different between the hepatic artery proper system (in the range of 70 mmHg) and the hepatic portal system (in the range of 10 mmHg). Thus, small changes in pressure may be able to elicit significant and different changes within the hepatic artery proper system but have negligible effects in the portal system or the combination of the two systems.

Splenic blood flow appears to be more variable than other organs and averages approximately 100 mL/(min *100 g). It appears that splenic flow can be altered based on the activity of other organs, and there may be some rhythmic activity that can describe the filling of the spleen. The splenic flow is somewhat dependent on the activity of the splenic nerve and presence/absence of hormones within the blood. However, along with this marginal splenic activity, the human spleen does not have a large role as a blood reservoir (remember that other animals have smooth muscle cells surrounding their spleen to induce blood ejection, in fact rhythmic activity of the spleen of these animals has been linked to the cardiac cycle and the intraarterial pressure). In the case of the human spleen, it appears that the activity is restricted to the resistance of the splenic artery but the total volume of the spleen does not change significantly; thus, there is little ejection or absorption of blood based on the activity of other regions of the human body. It is possible that this activity is related to the storage of red blood cells within the spleen because the spleen tends to collect red blood cells that are toward the end of their useful time. If needed, these cells may be released before recycling processes based on the activity of the spleen.

14.3 Hepatic and splenic microcirculation*

We have previously discussed the anatomical organization of the hepatic microcirculation but the physiological relevance of this organization and the overall control of blood perfusion have not been described. Recall that the hepatic microcirculation is defined within the hepatic sinusoids. At this region, the circulation from the hepatic artery proper and the hepatic portal vein converge into a small capillary. The sinusoids have large fenestrae and large gaps between neighboring endothelial cells to allow plasma and the constituents of plasma to have free access to the spaces of Disse (an anatomical region between endothelial cells and hepatocytes) and the hepatocytes that line the sinusoids region. Recall that the hepatocytes have a large role in modifying the plasma protein concentration and the plasma solute concentration. The endothelial cells near the entrance to the sinusoid region and those that line the central vein have been shown to modify the intrasinusoidal pressure as a means of regulating the flow/pressure throughout the liver sinusoid. Under most conditions, the pressure throughout the sinusoids varies from approximately 12 mmHg at the inflow to 4 mmHg at the central vein. Note that the precapillary sphincters of the hepatic microcirculation are regulated by the nervous stimuli, hormones, and typical vasoactive substances that were discussed in previous sections.

There is an interesting segregation of activity within the hepatic microcirculation. Cells close to the inflow region of the liver sinusoids, where the hepatic artery proper and the

*This section is considered advanced and can be skipped without a loss of continuity.

hepatic portal vein blood mixes, are geared to absorption and secretion of sugars and amino acids. Cells closer to the central vein region produce or metabolize steroids and pigment. Thus, changes in the flow through the circulatory unit can drastically alter the composition of blood, because there is little to no sharing of functions between hepatocytes along the length of the sinusoid.

The anatomical organization of the splenic microcirculation has not been fully investigated at the time of writing. The splenic microcirculation is composed of sinuses similar to those described for the liver in previous sections; however, unlike all other sinuses in the human body, the splenic sinuses are not the equivalent of capillaries. Splenic sinuses initiate within the venous microcirculation and continue through the venules. This suggests that the splenic sinuses can be found in addition to well-defined typical capillary beds. In addition to this, the spleen contains cavities where red blood cells, white blood cells, and platelets can reside in the absence of containing endothelial cells. These regions are surrounded by fibroblasts and a well-defined extracellular matrix zone, forming an open mesh-like circulation.

There has been significant doubt in the splenic microcirculation field as to whether two different microcirculation architectures can be found in the spleen. The first is termed an *open microcirculation*, in which terminal arterioles drain into these well-defined open cavities that then collect into the venule sinuses of the spleen. This has been observed multiple times; however, an anastomosing closed loop system cannot be excluded based on the experiments conducted thus far. This closed system would act as a shunt around a typical capillary bed, where the terminal arterioles would be connected directly to the venule sinusoids. Although most studies have identified and suggest that the vast majority of the red pulp follows an open capillary structure, some of closed loop microcirculation has been observed in patients. It is unclear at this point if closed microcirculations are associated with pathological events that have happened previously or exist as predictive mechanisms for future events. Interestingly, it is also unclear how the physiology has been designed with the function to maintain platelets and white blood cells in a quiescent state when flowing through these spaces. Platelets and white blood cells tend to activate (either thrombogenic or inflammatory functions) when these cells contact extracellular matrix proteins. In particular when a platelet observes extracellular matrix, it would typically adhere and/or aggregate within this space. Thus, it is unclear how these structures can maintain platelets in a quiescent state. Also, and possibly most importantly, this open splenic microcirculation is the only known space in the human body where, under normal conditions, blood flows in a space that is not surrounded by endothelial cells.

14.4 Storage and release of blood in the liver*

As we have discussed, a significant portion of the cardiac output is delivered to the liver. Therefore, the liver can act as a blood reservoir and it is important to understand how the liver regulates these storage properties. One of the primary regulators of the blood volume within the liver is the hepatic sympathetic nerve. An increase in the activity of the hepatic sympathetic nerve, in the absence of any vagus nerve activity (studied under the conditions

*This section is considered advanced and can be skipped without a loss of continuity.

in which the vagus nerve was removed because of surgical procedures), causes a reflexive increase in the hepatic arterial resistance. This is the result of both an increase in the hepatic nerve activity and an increase in catecholamine release from the adrenal gland. The net effect of this activity is a reduction in the hepatic volume by approximately 5% to 10%. It also has been observed that a decrease in carotid artery pressure causes a net decrease in the hepatic volume by approximately 20%. This is due to a baroreceptor reflex that activates the hepatic sympathetic nervous system. Similarly, an increase in the carotid artery pressure induces an increase in the uptake of blood by the liver; thus, the liver in conjunction with pressure sensing locations in the vascular system can act to regulate the blood pressure by altering the blood volume. Under similar conditions, the cardiopulmonary receptors can also regulate the hepatic storage and release of blood. Decreased pressure at the cardiopulmonary receptors induced a decrease in the hepatic blood volume. The opposing effects were also observed; with an increased pressure at the cardiopulmonary receptor, an increase in the hepatic blood volume was observed.

Interestingly, most of the baroreceptor reflex responses occur very rapidly, generally within 1 minute of the receptor sensing a change. This suggests the importance of blood pressure to these locations (e.g., the brain and the lungs) and the importance of the liver as a source for blood and a regulator of blood volume and pressure. Under these rapid responses, it is common to see upward of 30% to 40% of the hepatic blood volume to be mobilized or an increase in hepatic blood volume of around 25%. These significant blood volume changes can produce substantial changes to the systemic blood pressure.

Other mechanisms that can regulate hepatic blood volume are the hepatic venous pressure, significant blood volume changes (e.g., hemorrhage), and vasoactive compounds. As expected, with an increased hepatic venous pressure there was a parallel, rapid increase in hepatic blood volume. The relative change in hepatic volume as a function of change in hepatic venous pressure differs based on the species, but in general with an increased hepatic venous pressure in the range of 10 mmHg, an increase in hepatic blood volume was observed to be approximately 40 mL/100 g of tissue. Some species exhibit a nonlinear rate between an increase in hepatic blood volume and hepatic venous pressure and in most instances as the pressure increases, the rate of storage of blood in the liver also increases. Thus this is an important mechanism to regulate rapid changes in blood volume. It is also interesting to note that for a general tissue, an increase in pressure disturbs the balance of the Starling forces for 10 to 15 min. After this time, either a return to steady state is observed, so that the exchange of nutrients and wastes is maintained, or a new equilibrated pressure is found that maintains the normal Starling balance of forces. However, in the liver, it has been observed that an increase in the hepatic venous pressure is coupled with an increase in the filtration/retention of fluid within the liver extravascular space. This is maintained, for many hours after the initial insult. Note that the liver is especially susceptible to changes in pressure, because the osmotic pressure gradient across the liver sinusoids is effectively zero (the liver pores are large, with no difference in the constituents, even including proteins, across the liver endothelial cells). The liver lymphatics and the peritoneal space can accommodate large changes in volume and thus do not hinder the net movement of fluid across the liver sinusoid wall.

In moderate to severe hemorrhage, a significant decrease in hepatic blood volume is observed, to approximately 80% of the normal liver blood volume. Although there was a decrease in hepatic blood volume, it was accompanied by an active constriction of the venous circulation. In anesthetized animals, it has been observed that a hemorrhage of up to 20% loss of systemic blood volume induces a similar release of hepatic volume (approximately 25% of hepatic blood was released with a 20% hemorrhage). Interestingly, this release of hepatic blood volume after severe hemorrhage has been shown to be independent of signaling from the kidneys, pituitary gland, adrenal gland, and nervous system; thus, local changes can regulate the hepatic blood volume in times of significant demand. However, under these conditions, the total demand for increased blood volume could not be met by the liver alone.

The liver is also responsive to various vasoactive compounds. For instance, when subjected to epinephrine, at either the hepatic artery or the portal vein location, a reduction in hepatic arterial flow was observed; however, there was no net effect on the venous outflow. Thus a net decrease in hepatic blood volume would be observed in response to epinephrine. Histamine infusion was observed to decrease the hepatic arterial resistance and increase the portal vein resistance. Under these conditions, a net increase in the hepatic blood volume was observed. Exposure to vasopressin had similar effects as histamine on the hepatic circulation and the hepatic blood volume.

14.5 Active and passive components of the splanchnic circulation*

We have already described some of the active components of the splanchnic circulation, but it is important to reiterate the role of these active components at this point. The importance of the splanchnic circulation is not solely restricted to times of ingestion or times of nutrient need. During exercise, the splanchnic blood volume has been shown to decrease rather rapidly to accommodate the increase in oxygen consumption from other tissues. These changes to the splanchnic blood volume have been linked to both active and passive components of the circulation. This will be reviewed briefly here.

The passive components of the splanchnic circulation are directly related to an increase or decrease in the flow rates into or out of the splanchnic circulation. With an increased inflow flow rate, there was almost an immediate linear increase in the splanchnic blood pressure and the splanchnic blood volume. Decreased inflow flow rate was associated with a decreased splanchnic blood pressure and a decreased splanchnic blood volume. Opposing effects are typically observed with alterations to the outflow flow rate (which is modulated at the hepatic portal vein). A decreased outflow flow rate would increase the splanchnic pressure and the splanchnic blood volume, whereas increased outflow flow rates would decrease the splanchnic pressure and blood volume.

Active components of the splanchnic circulation include the nervous innervation via the splanchnic sympathetic nerves. With an activation of this sympathetic nerve pathway, there is a relatively rapid decrease in splanchnic blood flow coupled with an increase in the splanchnic outflow. These changes were directly coupled to diameter changes of the splanchnic

*This section is considered advanced and can be skipped without a loss of continuity.

resistance and capacitance vessels. The degree of diameter change was correlated with the frequency of sympathetic nervous activity. We have already discussed the effects of the carotid baroreceptor reflex on the hepatic circulation, and this can be extended to the entire splanchnic circulation. A decrease in pressure along the carotid sinuses induced a mobilization of blood from the splanchnic circulation. Thus, an increase in splanchnic blood flow and a decrease in splanchnic blood volume would be observed under these conditions. Most of these changes were observed within splanchnic compliance vessels and not the resistance vessels. Many of the remaining active components of the splanchnic circulation mimic those already discussed for the hepatic circulation.

14.6 Innervation of the spleen*

The spleen has significant innervation that is specific for the arterial resistance vessels, the venous capacitance vessels, and the splenic capsule. On activation of the splenic sympathetic nervous system, there is a significant release of blood from the spleen. This is induced by a decrease in the diameter of resistance vessels, an increase in the diameter of capacitance vessels, and a contraction of smooth muscle cells located with the splenic capsule. The magnitude of the response of these changes is dependent on the frequency of firing and the amplitude of the changes observed. In the human spleen, the maximal responses were observed to occur when the stimulation frequency was in the range of 10 Hz; however, the change in splenic blood volume was relatively small because the capsule does not contain a significant smooth muscle cell population. Interestingly, animals that contain a significant smooth muscle cell region of the spleen released blood at a very high hematocrit (in the range of 80%) after sympathetic nerve activity. This shows the importance of the spleen red pulp as a source for red blood cells in a time of need.

As we discussed for the entire splanchnic circulation, the changes to the spleen blood volume and the spleen blood flow rate should exhibit both passive and active components. However, in the case of the spleen, it appears that either the passive components do not contribute to overall changes in the blood volume/blood flow rate or the active components are so significant that they overwhelm any other possible mechanisms. Work has been conducted on both the canine and feline splanchnic circulations to tease out this possible difference, and it was observed that splenic blood volume and blood flow are largely independent of the inflow pressure within physiological ranges. This suggests that the spleen can function somewhat autonomously, if it receives some blood supply. However, similar to the other organs within the splanchnic circulation, when baroreceptor activity increases, the spleen blood volume and outflow flow rate increase to increase the overall systemic blood volume and blood pressure. In the case of humans, it appears that sympathetic nerve activity and/or infusion of vasoactive compounds (the same compounds that were discussed earlier) altered the resistance of the resistance and capacitance vessels but did not have a significant effect on the spleen volume.

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14.7 Disease conditions*

14.7.1 Hepatitis

Hepatitis is any sustained inflammation of the liver that lasts for more than 1 year. Most cases of hepatitis are accompanied by hepatocyte death, and in the most severe cases of hepatitis a deterioration of the liver lobule/sinus anatomy is observed. Hepatitis can initiate by the hepatitis B or C virus, drugs, toxins, and other metabolic diseases. Different pathophysiology processes of hepatitis have been observed, but possibly the most common is periportal hepatitis, in which many different regions of the liver experience necrosis. These regions of inflammation tend to be very difficult to treat and are encapsulated by scar tissue that may be hard to penetrate by treatment modalities. The second most common type of hepatitis is the subacute hepatic necrosis, in which different necrotic regions tend to bridge together to form large masses of necrotic tissue. It is more typical for this form of hepatitis to be associated with a cirrhosis.

Most forms of hepatitis tend to be asymptomatic and many patients with hepatitis think they are suffering from the common cold, flu, or similar illnesses. The symptoms associated with hepatitis are loss of appetite, fatigue, muscle pain, nausea, and abdominal pain. If these symptoms persist and antibiotics do not take care of the infection, it may be common to check for hepatitis. In most instances, hepatitis B can be treated like any other viral infection; rest, eating healthy foods, and drinking plenty of water. Alcohol should be avoided because of the negative effects of alcohol on the liver. It has been observed that patients with hepatitis B who have consumed significant quantities of alcohol have done significantly more damage to their liver than what can be accounted for by the disease. Patients with hepatitis C are generally treated with a combination of therapies to mitigate the infection and disease symptoms.

14.7.2 Alcoholic and fatty liver disease

Alcoholic liver disease can manifest in many ways but is associated with the overconsumption of alcohol. It is possible for hepatitis, cirrhosis, or other diseases of the liver to manifest after significant overconsumption of alcohol. Constant chronic consumption of alcohol, which is primarily detoxified in the liver, leads to increased proinflammatory responses in the liver, including the release of cytokines and oxidative stresses. If these proinflammatory responses persist, it leads to hepatocyte inflammation and apoptosis. This disease is found in approximately one-third of heavy drinkers, but it does not seem to be related to the type, quantity, and rate of drinking among heavy drinkers, but instead appears to manifest as a result of a complex interaction of environmental and genetic factors. If alcoholic liver disease manifests, it is typically treated by a cessation of alcohol consumption. Liver damage may be reduced or even reversed after ending excessive alcohol consumption. However, medications and antioxidant treatments may be needed to correct some of the damage to the liver.

Fatty liver disease can be induced by alcohol consumption or other activities; here we will restrict our discussion to nonalcoholic fatty liver disease. Typically, this is classified as a fat

*This section is considered advanced and can be skipped without a loss of continuity.

content of the liver greater than 10% of the weight of the liver. For reference, the vast majority of heavy drinkers, upward of 90%, develop fatty liver disease. Nonalcoholic fatty liver disease is the most common cause of chronic liver diseases in the United States. Over 20% of the U.S. adult population have a form of nonalcoholic fatty liver disease. In some of these, the disease may never fully manifest; however, with poor diet and continued consumption of alcohol, the incidence of pathologic conditions associated with this disease increases. Causes for nonalcoholic fatty liver disease are typically associated with diet and heredity factors. Nonalcoholic fatty liver disease tends to be asymptomatic, but the patient may experience fatigue and a loss of appetite. Unfortunately, no medications or other standard treatments exist for nonalcoholic fatty liver disease. In most cases, a physician would prescribe lifestyle changes.

14.7.3 Splenomegaly

Splenomegaly is an observed enlargement of the spleen and is associated with an increased workload of the spleen. Thus, any disease in which there is an enhanced deterioration of red blood cells, white blood cells, or platelets may lead to splenomegaly. Splenomegaly can be classified as moderate (largest spleen dimension in the range of 11 to 20 cm) or severe (largest spleen dimension greater than 20 cm). Symptoms for splenomegaly tend to be associated with abdominal pain but sometimes may extend to back pain. In many instances, splenomegaly is associated with an infection such as syphilis or endocarditis, although many instances of metabolic diseases are associated with splenomegaly. The treatment for splenomegaly lies with the cause of the disease. In many instances, if the workload on the spleen is reduced, it is possible to see a reduction in the spleen size back to normal levels. However, in some instances, it is more common to remove the spleen from the patient, to minimize the complications associated with disease pathogenesis. The side effects of a splenectomy are the possibility for an increased infection rate and the possibility for increased platelet counts. Because the spleen acts to filter pathogens from blood it is possible that some of these pathogens may not be cleared by the blood. Likewise, the platelet count is somewhat controlled by the activity of the spleen, and, thus, with removal of the spleen, the count may increase to abnormal levels. An increased platelet count can lead to thrombosis at other locations with the circulation. Therefore, patients tend to be maintained on antiplatelets, antithrombotic, and antibody treatments.

Summary

- 14.1.** The splanchnic circulation is a highly unique and special circulation that is involved with the absorption of materials from the gastrointestinal system and the removal of risk factors and pathogens that enter the circulation from the gastrointestinal system. Most of these clearance functions are accomplished by the liver (which removes both pathogens and nutrients from the blood before the blood entering the systemic circulation) and the spleen (which removes pathogens and damaged blood cells). The

splanchnic circulation obtains approximately 20% to 25% of the cardiac output under physiological conditions, suggesting its importance to the overall composition of blood. The liver has two distinct circulations that converge within the sinusoids of the liver. The first is the hepatic artery proper, which is typically arterial blood, and the second is the hepatic portal vein, which is blood from the stomach, intestines, and spleen. The sinusoids of the liver are highly porous capillaries that allow for the exchange of plasma proteins. The liver has many salient functions related to homeostasis. The spleen plays a large role in inflammatory responses and is composed of two distinct sections; the red pulp, which contains blood, and the white pulp, which resembles a lymph node. Small capillaries of the splenic circulation enter the spleen sinusoids, which are an open circulation. This is currently the only known circulation that is not surrounded by a layer of endothelial cells.

- 14.2. The hepatic blood flow is homogenous under most conditions, showing that the liver regulates blood from the hepatic artery proper and the hepatic portal vein to a level that equilibrates their flow in the sinusoids. Splenic blood flow is somewhat variable and appears to be based on the activity of the other organs.
- 14.3. The microcirculatory units of both the liver and spleen are rather distinctive. The microcirculation of the liver is designed to modify all of the plasma constituents. The endothelial cells are fenestrated and provide blood with direct access to the hepatocyte layer, which is on the basolateral side of the endothelial cells. In addition, there are specialized regions within the hepatic microcirculation by which the cells absorb or secrete different compounds into the plasma. The splenic microcirculation is somewhat unique in that it provides an open meshlike system for blood to flow through. Many properties and functions of this mesh are still under investigation.
- 14.4. One of the important functions of the liver is to act as a reservoir for blood. Under pathological conditions, the liver can either store additional blood or release additional blood into the splenic circulation. The alteration in these flow conditions appears to be regulated at both the inflow arterial side of the circulation and the outflow conditions.
- 14.5. In general, all organs that feed the splanchnic circulation are regulated by both passive and active components. The passive components include the changes in blood flow rates and organ blood volume on alterations to the inflow pressure. The active components include the nervous innervation and the response to vasoactive compounds. The text highlights a number of these responses within the splanchnic circulation.
- 14.6. The importance of the splenic nervous system is somewhat up for debate, because in humans the spleen does not provide a large source of blood and the spleen cannot “eject” blood into the systemic circulation. In other mammals, these properties of the spleen are observed and are regulated by the autonomic nervous system. In these other mammals, the spleen contains a smooth muscle cell layer that is not present in humans. The spleen does show some passive components similar to the other organs involved with the splanchnic circulation.

- 14.7. Hepatitis, alcoholic and/or fatty liver disease, and splenomegaly are common diseases that affect the splanchnic circulation. Hepatitis is an inflammation of the liver that can degrade the sinusoid units. This reduces the functionality of the liver. Alcoholic liver disease is a degradation of the liver and a reduction of the liver function based on excessive alcohol consumption. Fatty liver disease is somewhat common and is associated with a large retention of fats within the liver, which may lead to liver diseases. Splenomegaly is an increase in the size of spleen, which is likely secondary to a primary disease that alters the properties of red blood cells, white blood cells, or platelets. With an increased destruction of these cells, the spleen enlarges to accommodate the removal processes. The spleen can be removed; however, significant risks are associated with this surgical procedure.

Homework problems

- 14.1. The splanchnic circulation has some unique features that are not found in many other vascular beds. What is it about the splanchnic circulation that makes it so unique and why are these anatomical features not found in many other vascular locations?
- 14.2. The blood inflow to the liver is also quite distinctive. What are the features of the arteries that feed the liver and why is this vascular bed so unique?
- 14.3. The functional units of the liver have a specialized organization that is critical to the function of the liver. Describe the organization, key features of this organization, and what role these features have on the circulation in general.
- 14.4. The spleen is also composed of units termed *sinusoids*. Do these sinusoids have functions similar to those of the liver sinusoids? Compare and contrast these functions.
- 14.5. The blood flow into many visceral organs is kept “constant” during normal physiological activities (e.g., do not consider the blood shift that occurs directly after eating). Why is blood flow to the spleen so variable during normal physiological conditions?
- 14.6. Fenestrated endothelial cells are found in particular locations within the liver. What is the purpose of these specialized endothelial cells within the liver?
- 14.7. What are the different microcirculation organizations that can be found in the liver and what would they be used for?
- 14.8. The liver can release significant quantities of blood. What would be the overall physiological effects of this blood release? Would the systemic blood pressure and/or peripheral resistance change as a result of the efflux of blood from the liver?
- 14.9. Why are there different controls on the splenic activity? Does one control affect the other control and do they act at different times for different purposes?
- 14.10. How would disease conditions of the liver and the spleen alter the systemic circulation? You can choose to discuss the disease conditions that we highlighted or others.
- 14.11. Develop a mathematical relationship, using any (or all) of the principles that we have discussed in the previous sections to describe the flow of blood through the liver sinusoids. Make sure to consider mixing, flow convergence, and transport when devising your relationship.

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In silico biofluid mechanics*

LEARNING OUTCOMES

- Use computational methods to describe the flow through various physiological geometries
- Describe the mathematics behind computational fluid dynamics
- Explain the need for fluid structure interaction modeling
- Use the Buckingham Pi Theorem to develop dimensionless numbers
- Analyze conditions for dynamic similarity
- Evaluate salient dimensionless numbers
- Describe some relevant areas of current *in silico* biofluid mechanics research
- Discuss some possible avenues for future *in silico* biofluid mechanics research

15.1 Computational fluid dynamics

In earlier chapters, we were able to solve the fluid mechanics governing equations for various fluid properties of interest by making assumptions that significantly simplify the Navier–Stokes equations, the conservation of momentum equations, the conservation of energy equations, and the conservation of mass equations. An exact solution could be reached only if these assumptions were made and the boundary conditions and the initial conditions were known or if “valid” reasonable assumptions were made regarding these parameters. Note that our statement does not touch on the accuracy of any of the solutions that we obtained, only that the solution can be obtained if a well-defined set of conditions was applied to the problem. However, in many situations, the Navier–Stokes equations cannot be easily simplified, such as when the flow is not steady, certain complex body forces need to be considered, or all three dimensions must be considered (e.g., if there are forces or flow in all directions) in the solution. Under these and other conditions, it becomes very

*This chapter is considered advanced and can be skipped without a loss of continuity.

difficult to solve the Navier–Stokes equations as a set of partial differential equations analytically along with any (or all) of the conservation laws that are of interest to the particular flow problem. Computational fluid dynamics is a tool often used to solve the coupled Navier–Stokes equations simultaneously with the conservation equations, omitting many but not all of the previous assumptions made in earlier chapters. Computational fluid dynamics techniques typically make use of numerical methods to define the flow conditions at discrete points within the volume of interest, and thus computational fluid dynamics does not obtain a continuous solution for the entire flow field.

As we know, the Reynolds number can be defined as

$$\text{Re} = \frac{\rho v d}{\mu} \quad (15.1)$$

where ρ is the density of the fluid, v is the mean fluid velocity, d is the diameter of the vessel (or some characteristic length to describe the vessel), and μ is the viscosity of the fluid. The equation for the Reynolds number (Re) can be reorganized to the following form

$$\text{Re} = \frac{\rho v^2}{\mu \cdot \frac{v}{d}} = \frac{\text{inertial forces}}{\text{viscous forces}} \quad (15.2)$$

Indeed, the Reynolds number reveals an important relationship between the inertial forces and the viscous forces applied to the fluid elements. For slow flows or flows with small Reynolds numbers (far less than 1), the viscous terms/factors dominate; therefore, we may be able to ignore the inertial terms and state that the viscous forces are more important than the fluid momentum (flows within the microcirculation may use this assumption under certain conditions). For faster flows or flows with Reynolds numbers far greater than 1, we may potentially ignore the viscous resistance, because the inertial forces (e.g., momentum of the fluid) dominate the flow conditions. By using the Bernoulli equations under these conditions, we may obtain an approximate solution to these types of flows (see Section 3.8). However, for flows in which the viscous terms have a weight similar to that of the inertial terms (e.g., the Reynolds number is close to 1), we cannot ignore either of the terms in the governing fluid dynamics equations, and it typically becomes very difficult to solve the Navier–Stokes equations by hand under these conditions. For example, when the fluid is relatively compressible (e.g., gases), typically the inertial terms and the viscous terms have a similar weight; therefore, not only do the Navier–Stokes equations need to be solved in the full form, but also the energy and thermodynamic relationships are needed to completely characterize the flow conditions. However, most of the fluids we discussed in this textbook (e.g., blood and interstitial fluid) are usually considered incompressible within the range of applied pressures (we would like to remind the reader that no true fluids are incompressible and that this is an assumption that should be applied only under well-defined conditions). We also know that the Reynolds number of most flows within the human body is close to 1, thus suggesting that computational methods may be needed to more accurately characterize the flow conditions.

When it becomes very difficult to solve partial differential equations analytically, the finite element method (FEM) or finite difference method (FDM) is often used. FEM is most often used to solve solid mechanics problems, because of its advantage in handling complex geometries. FDM and its related finite volume method (FVM) are often used to solve fluid mechanics problems. By using FDM, differential equations can be solved with numerical methods by using a finite value for Δx rather than allowing Δx to approach 0. Again, this would provide the flow conditions only at discrete points within the flow field Δx apart and would not provide a continuous solution throughout the entire flow field. Note that Δx can have a very small numerical value such that a continuous solution is essentially obtained and also that Δx does not need to have a fixed continuous value throughout the volume of interest. However, decreasing the spacing (Δx) may increase the computation time needed; thus, this balance must be considered and optimized during solution methods. One can also decrease the spacing at regions of interest within the volume of interest (this would provide more information about that location and possibly more accurate information compared with a large spacing value), and one can choose to increase the spacing at regions of less interest (which would provide less information at those locations and possibly less accurate information). This approach would at least attempt to balance the computational issues that may arise during solution methods. The mathematical equations behind the FDM can be developed from the Taylor series expansion for multiple independent variables. This method is derived by gridding (or meshing) the volume of interest with equal spacing in each direction (more complex solution methods relax the constraint of having even spacing, as mentioned earlier). In two dimensions, the rectangular grid in the x/y directions corresponds to i and j steps, respectively (Fig. 15.1). The spacing that defines the mesh are denoted

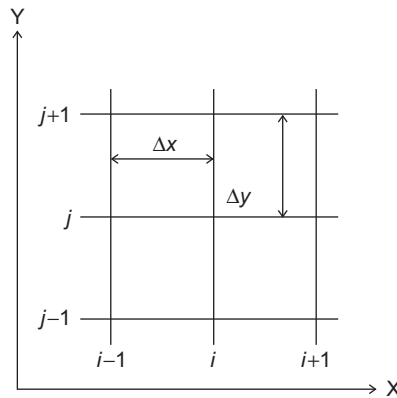


FIG. 15.1 Two-dimensional grid for the finite difference method (FDM) in which i denotes grid spaces in the x -direction and j denotes grid spaces in the y -direction. Note that the spacing does not have to be uniform across the entire geometry. By using either the forward difference method or the backward difference method, parameters of interest can be obtained from known boundary conditions and known initial conditions.

as Δx and Δy , in the i and j directions, respectively. Therefore, the location of subsequent points within the mesh can be identified by

$$\begin{aligned}x_n &= x_0 + n\Delta x \\y_n &= y_0 + n\Delta y\end{aligned}\tag{15.3}$$

where x_0 and y_0 are the initial points, at a predefined origin, within the mesh. Note that with this approach, Δx and Δy do not need to have equal numerical values, although for our illustration we will set them to be equal for convenience. For any given function (f) that can be described at each of these grid points, the Taylor expansion states that the function at neighboring points can be defined using the spatial partial derivative of that function, provided that the function is continuous or reasonably assumed to be continuous. It is defined that all flow properties are continuous at steady-state conditions, and this approach would try to identify those steady-state conditions. In one dimension, the Taylor expansion for a continuous function is defined by

$$\begin{aligned}f_{i+1} &= f_i + \left.\frac{\partial f}{\partial x}\right|_i \Delta x + \frac{1}{2} \left.\frac{\partial^2 f}{\partial x^2}\right|_i \Delta x^2 + \frac{1}{6} \left.\frac{\partial^3 f}{\partial x^3}\right|_i \Delta x^3 + \dots \\f_{i-1} &= f_i - \left.\frac{\partial f}{\partial x}\right|_i \Delta x + \frac{1}{2} \left.\frac{\partial^2 f}{\partial x^2}\right|_i \Delta x^2 - \frac{1}{6} \left.\frac{\partial^3 f}{\partial x^3}\right|_i \Delta x^3 + \dots\end{aligned}\tag{15.4}$$

To make use of Eq. (15.4), the first spatial partial derivative of f at i can be solved using a forward difference (Eq. (15.5)) or a backward difference approach (Eq. (15.6))

$$\left.\frac{\partial f}{\partial x}\right|_i = \frac{f_{i+1} - f_i}{\Delta x} + H.O.T.\tag{15.5}$$

$$\left.\frac{\partial f}{\partial x}\right|_i = \frac{f_i - f_{i-1}}{\Delta x} + H.O.T.\tag{15.6}$$

Note that the forward difference method makes use of f_{i+1} (using the trend ahead of the point of interest) whereas the backward difference method makes use of f_{i-1} (trend behind the point of interest). *H.O.T.* denotes all of the higher-order terms of order Δx^2 or more. These terms are typically neglected, which gives a truncation error in the FDM of the first degree. The *H.O.T.* can be neglected because they will typically be relatively small compared with the Δx term (if and only if Δx approaches zero, meaning that if Δx is small, then Δx^2 is much smaller, and so forth). If Eqs. (15.5) and (15.6) are added together and averaged, a formulation for the central difference method is obtained, which has a second-order accuracy (if the *H.O.T.* are ignored).

$$\left.\frac{\partial f}{\partial x}\right|_i = \frac{f_{i+1} - f_{i-1}}{2\Delta x} + H.O.T.\tag{15.7}$$

The central difference method considers the trend ahead of and behind the current point of interest, but it does not consider the trend at the point of interest when attempting solution methods.

By using any of these methods discussed, it is possible to calculate the velocity distribution through continuous geometries by relating the fluid motion at neighboring points. For instance, let us begin our analysis with a two-dimensional (2D) geometry in a sudden expansion (Fig. 15.2). In biofluids, we can idealize the flow of blood from the microcirculation (small diameter) into the venous circulation (larger diameter) or the flow through the aortic valve into the aorta with this geometry (note that this geometry is clearly not a very accurate representation of the physiological conditions, but for simplified illustration purposes we will make use of this geometry). Let us assume that the diameter of the vessel increases by 2.5 times at the step and the length of interest is 4 times that of the smaller diameter (the length of interest is denoted by the dashed lines in Fig. 15.2).

Taking the geometry illustrated in Fig. 15.2 and meshing it with a total of 5120 square elements, the FDM can be used to solve for the velocity field throughout the expansion (Fig. 15.3, solved with FEMLab, COMSOL software). To obtain this solution, it was assumed that the velocity at the inlet had a known parabolic profile. This simplified geometry also can be analyzed by hand (using Eq. 15.7), if the input boundary conditions and the wall boundary conditions are known. In general, the geometry and the grids do not need to be idealized as shown here; we are just making use of this simplified example to illustrate the concept of using numerical methods and a numerical solver to obtain a fluid velocity profile through a geometry. Later in this section, we will discuss some work that is being conducted using computational fluid dynamics, and we will see that the geometries and grids can be much more complex than what was illustrated here for discussion.

When turbulence develops in the flow field, we would have to consider the turbulent Reynolds stress, which includes time-dependent fluctuations that are difficult to solve by hand and that must be incorporated into the fluid dynamics equations. Recall that statistical methods were required for these formulations because turbulence cannot be accurately predicted but only observed. The solution to the flow profile does not depend on only the Navier–Stokes equations and the conservation of mass, but also the turbulent kinetic energy (k), which is defined as

$$k = \frac{1}{2} \overline{u_i u_i} \quad (15.8)$$

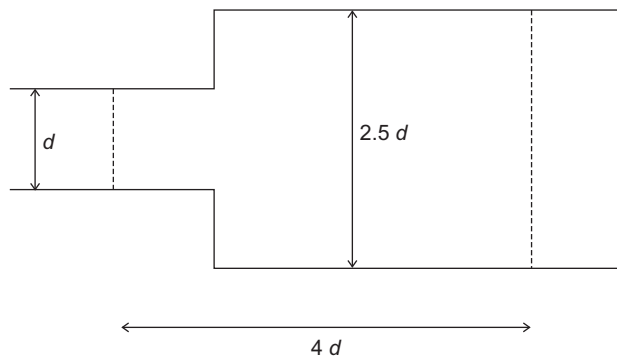


FIG. 15.2 Idealized flow in a sudden expansion from the microcirculation to the venous system. Clearly, based on the geometry, the computational results will differ, but with simple geometries a relatively accurate picture of the flow field can be established.

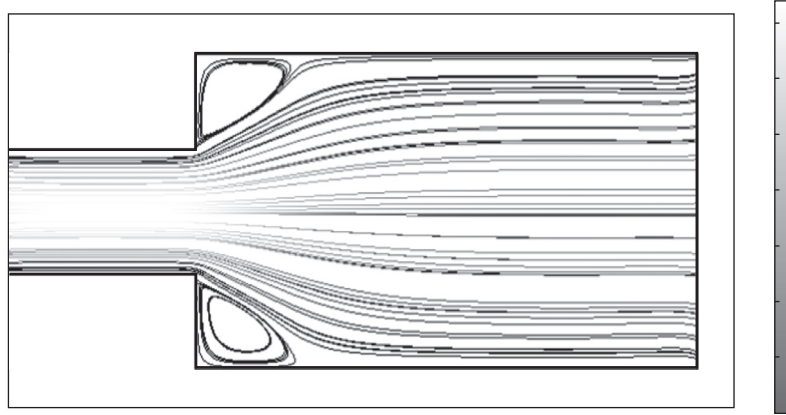


FIG. 15.3 Computational fluid dynamic solution for the flow conditions in Fig. 15.2. This illustrates that in a sudden expansion, there will be a stagnation zone in which the fluid becomes trapped. At this location, our solution shows a very slow, negligible velocity; recall that we used a relatively coarse mesh for this simple geometry.

where u_i is the velocity of the fluid. The other variable required in turbulent flows is the viscous dissipation rate of the turbulent kinetic energy, denoted as ε . The dissipation rate is defined as

$$\varepsilon = \nu \cdot \overline{u_{i,j} u_{i,j}} = \nu \frac{1}{\Delta t} \int_t^{t+\Delta t} \widehat{u_{i,j}} \widehat{u_{i,j}} dt \quad (15.9)$$

where $u_{i,j}$ is the velocity and ν is the kinematic viscosity. The turbulent viscosity μ_t is directly proportional to the turbulent quantities k and ε as

$$\mu_t \propto \frac{\rho_0 k^2}{\varepsilon} \quad (15.10)$$

In the macrocirculation, blood vessels are relatively large and the fluid velocity is relatively high, and therefore, the standard $k - \varepsilon$ turbulence model is commonly used to solve for the flow fields under these conditions (such as in the aorta). By using this model, one assumes an isotropic turbulence throughout the entire flow cycle with a high Reynolds number. However, when using the $k - \varepsilon$ model, it could become challenging to estimate the velocity and the stress distribution in the near-wall regions, where the turbulent viscosity has a large effect and varies significantly as a function of time and space. This would require a large amount of computational steps and a large processing time to accurately predict these spatial/temporal fluctuations. In addition, the Reynolds number in the sublayer of the turbulent field close to the vessel wall is usually low because the viscosity is large, making the standard $k - \varepsilon$ model inadequate. Therefore, a low Reynolds number Wilcox turbulence $k - \omega$ model is often

used in lieu of the $k - \varepsilon$ model, which can more accurately predict the velocity and stress distribution at the near-wall regions when the effects of the viscous forces are large. The $k - \omega$ model uses the turbulence frequency, ω , rather than turbulence viscous dissipation rate to characterize turbulence. In this model, the turbulence velocity u_t is related to k and ω in the form of

$$u_t \propto \frac{\rho k}{\omega} \quad (15.11)$$

As the turbulence frequency ω is related to k and ε by

$$\varepsilon = k\omega \quad (15.12)$$

The governing partial differential equations for the $k - \omega$ turbulence model are

$$\begin{aligned} \frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_j}(\rho U_j k) &= \rho P - \rho \omega k + \frac{\partial}{\partial x_j} \left[\left(\mu + \frac{\mu_t}{\sigma_k} \right) \frac{\partial k}{\partial x_j} \right] \\ \frac{\partial}{\partial t}(\rho \omega) + \frac{\partial}{\partial x_j}(\rho U_j \omega) &= \alpha \rho P - \beta \rho \omega^2 + \frac{\partial}{\partial x_j} \left[\left(\mu + \frac{\mu_t}{\sigma_k} \right) \frac{\partial \omega}{\partial x_j} \right] \end{aligned} \quad (15.13)$$

where α and β are closure coefficients, which are known constants.

In the near-wall regions, a majority of the turbulent kinetic energy is dissipated by the heightened shearing forces. Therefore, by including the dissipation rate within the solution, the $k - \omega$ turbulence model delivers a more accurate near-wall solution. In addition, by averaging the Navier–Stokes equations, changes in the turbulence properties are smoothed. A method to calculate the irregular changes within turbulent flows is the large eddy simulation, which follows the development of small turbulent vortices within the fluid. Another method of turbulence modeling is through the direct coupling of the Navier–Stokes equations and the continuity equations, which is termed the direct numerical simulation of flow properties.

Many biofluid mechanics laboratories make use of computational fluid dynamics to predict regions within the flow fields that are likely to facilitate cardiovascular disease development (aneurysm and atherosclerotic lesions are very common), model the performance of implantable cardiovascular devices, or model and predict the flow profiles within the body. These studies have significantly helped the biofluid community gain a better understanding of many of the biofluid mechanics principles discussed within this textbook. Also, the design of implantable cardiovascular devices can be significantly improved and perhaps optimized with the help of computational fluid dynamics. For instance, mechanical heart valves tend to disrupt the flow profiles distal to the valve compared with the native valves. A few research groups have built numerical models with accurate valve geometries to investigate how the implantation of an artificial heart valve affects the local flow field under transient and turbulent flow conditions. In addition, these groups have asked why the mechanical heart valves disrupt blood flow and how we can minimize the disruption to the fluid properties and biological properties during and after the implantation of a mechanical heart valve. With this knowledge, valve designs have been modified and performances of the artificial valves have been improved through various engineering optimization processes.

Studies have also been conducted by many research groups to identify areas in specific blood vessels (such as coronary arteries) that may induce large-magnitude transient shear stresses, oscillatory shear stresses, and large shear stress gradients. Altered shear stress in these regions has a higher potential to antagonize endothelial cells, platelets, and white blood cells to initiate activation and/or inflammatory processes. These changes tend to lead to an increased likelihood of cardiovascular disease formation at these areas. With early identification of these locations, it may be possible to target disease interventions toward these regions. Computation fluid dynamics modeling can be used to predict disease initiation and development.

For example, a model of a left coronary artery has been built using Ansys CFX (Version 12.0) (Fig. 15.4), and a stenosis can be (and has been) introduced downstream of the bifurcation where the left main coronary artery divides into the left anterior descending artery and the left circumflex artery. Using the Wilcox $k - \omega$ turbulence model, flow fields in the left coronary artery under normal and stenosis conditions can be characterized relatively easily, using a normal cardiac output as the inflow boundary conditions (these waveforms are, therefore, transient and physiologically relevant). Under normal flow conditions, because of the large bifurcation angle (about 75 degrees between the left anterior descending artery and the left circumflex artery), the flow through this bifurcation skewed toward the left

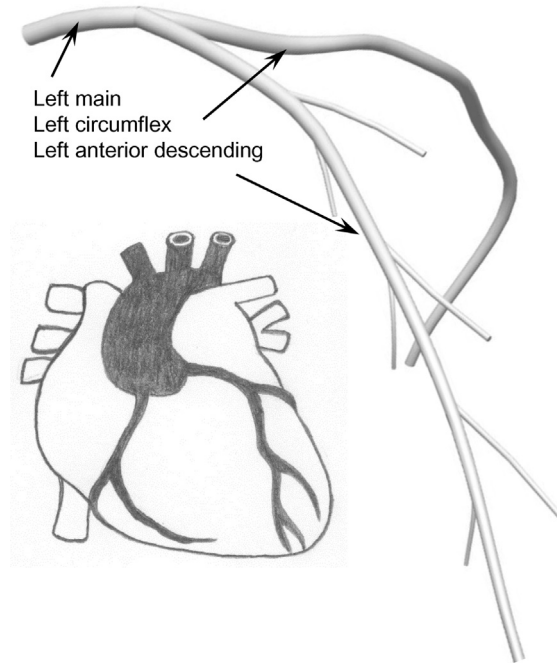


FIG. 15.4 A three-dimensional model of the left coronary artery with branches, generated by Pro-Engineering software. This geometry can be imported into most CFD software for flow field (e.g., velocity vectors, pressure) computation.

circumflex artery and separated from the blood vessel wall, causing a recirculation zone to develop near the bifurcation region (Fig. 15.5). With the presence of an 80% stenosis approximately 8 mm downstream of the bifurcation in the left descending artery, the flow field changes significantly. With the recirculation zone near the bifurcation, new recirculation zones developed immediately distal to the stenosis because of the jet flow induced by the vessel narrowing. Fig. 15.6A depicts the velocity vectors in the left coronary artery near the stenosis, with a zoom-in view of the velocity vectors in the recirculation zones shown in Fig. 15.6B.

With this model, one is able to calculate the velocity, velocity gradient, kinetic energy (k), energy dissipation rate (ϵ), and many other parameters for every single fluid element (there are approximately 2.2 million elements in the model illustrated in Figs. 15.4 through 15.6). For this particular flow condition, a no-slip wall boundary condition was used and the inlet velocity waveform mimicked the temporal changes in the cardiac output waveform during one cardiac cycle. The outflow was considered to be a pressure outlet. Based on the information obtained from the simulation, shear stress and pressure distribution in the left coronary artery under normal and stenosis conditions can be estimated directly and then used as an input during in vitro experiments to confirm results on altered stresses. It is also important to note that there are many other commercial CFD software packages available, such as ADINA, COMSOL, FLOW-3D, and many others.

However, complex fluid mechanics equations or models cannot provide all the information about biofluid behavior, because not only fluid mechanics but also biochemical responses are involved in physiological and pathological processes. The best case scenario would be when we want to simulate the behavior of blood within a blood vessel. We know that blood is composed of plasma and formed cellular elements, including red

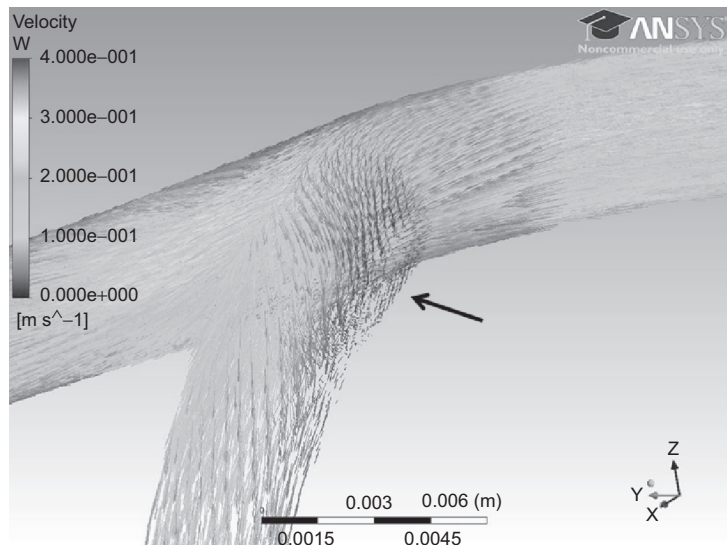


FIG. 15.5 Velocity vectors in the left coronary artery near the bifurcation. Because of flow separation at the bifurcation, a recirculation zone developed (arrow), which can potentially trap cells and induce abnormal shear stresses.

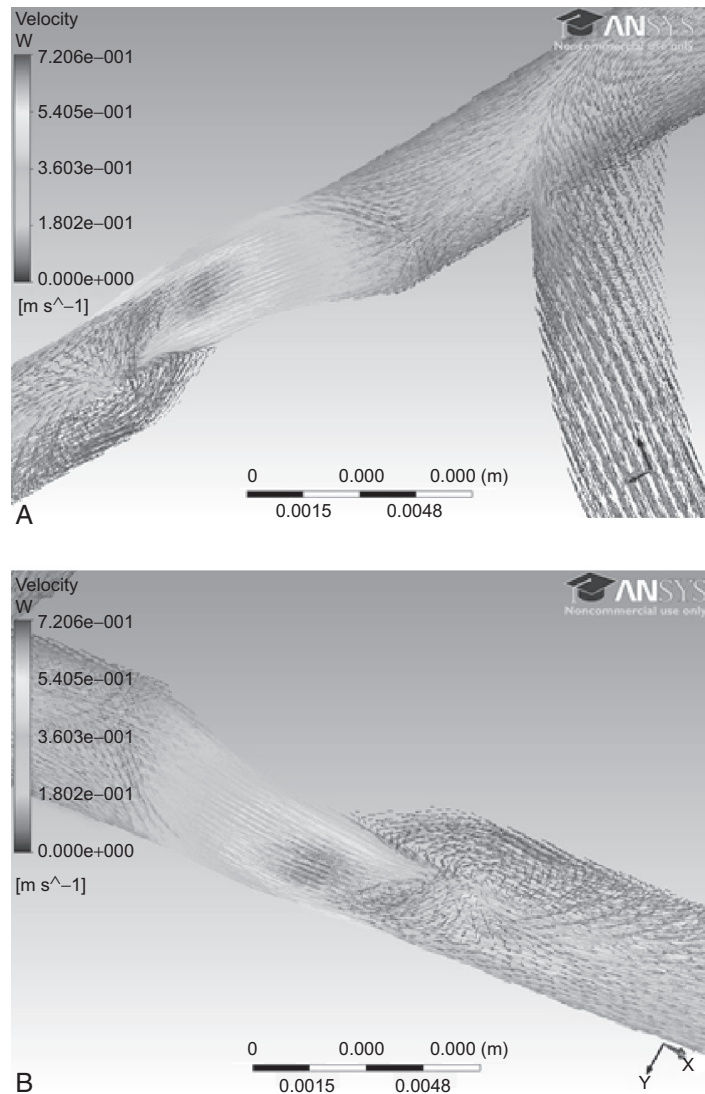


FIG. 15.6 Velocity vectors in the left descending artery with an 80% stenosis (A). Jet flow developed at the stenosis throat, inducing a large recirculation zone distal to the stenosis. The recirculation zone by the bifurcation upstream is still visible. A close-up view of the stenosis and the recirculation zone is shown in (B).

blood cells, white blood cells, and platelets. In large or medium-sized blood vessels, we usually do not need to consider the interactions between these formed elements and the fluid phase, as long as we are not studying the cellular responses to the fluid induced stress. Additionally, under physiological conditions, these cells tend to have little activity in large vessels; however, under pathological conditions these cells may have more significant roles in these large vessels and we may want to consider how the flow alters the function of

these cells. Undoubtedly, in small blood vessels, especially in the microcirculation, the interaction between the particle phase and the fluid phase becomes relatively important; therefore, the particle phase has to be considered when modeling both physiological and pathological flow conditions. Additionally, the functions of cells (such as red blood cell nutrient delivery and white blood cell extravasation) may be more important to consider at the smaller level. To model the cells as a second phase, discrete phase, or even a multiphase new and more complicated models can be used.

Many CFD software packages (including ANSYS) are capable of simulating the movement of discrete-phase particles, by calculating the energy and momentum exchange between discrete-phase particles and fluid elements. From previous chapters, we have learned that platelets are extremely sensitive to blood flow—induced shear stress and platelet biochemical responses are closely related to the local flow conditions and shear stress distribution. Using the coronary artery example again from Fig. 15.4, we can simply define platelets as a discrete phase and provide information on particle size, shape, density, viscosity, and release profile in ANSYS (note that this can be accomplished in other software packages as well). Thus blood, the fluid phase, can be treated as a continuum by solving the time-averaged Navier–Stokes equations (as before). The behavior of platelets, the particle phase, can be calculated through the flow field at each time step. These solutions can then be coupled together, and this is especially relevant when the particles can have an impact on the fluid motion and vice versa. Forces on platelets can be obtained from

$$\frac{du_p}{dt} = F_D(u - u_p) + F_x \quad (15.14)$$

where u_p is platelet velocity. F_x is an additional acceleration term, which relates to the force required to accelerate the fluid surrounding the particle. $F_D(u - u_p)$ is a drag force per unit mass term and depends on the shape, size, density, and velocity of the particle and density and velocity of surrounding fluid elements. It is typical that the fluid parameters (e.g., velocity/acceleration) are easily obtained from simulations and the forces would be back-calculated from equations similar to Eq. (15.14) or similar. Based on the velocity of a particle, its trajectory can be determined using the kinematic equation as

$$\frac{dx_p^i}{dt} = u_p^i \quad (15.15)$$

where index i refers to the coordinates' directions. To account for the effects of turbulence, a stochastic model developed by Gosman and Ioannides can be used to calculate particle phase velocity by adding random fluctuations obtained from the $k - \omega$ simulation to carrier phase velocity. Furthermore, the stress that one platelet experiences along its trajectory also can be estimated. For example, we can use the Boussinesq approximation to compute the total stress (laminar plus turbulent stresses) applied to a single platelet (or any other particle immersed within a fluid), as

$$\sum_{t=t_0}^{t_{\max}} \left(\frac{(\varepsilon_i - \varepsilon_{i+1})}{2} \times (\mu_i + \mu_i^t) + KE_i \times \rho \right) \times \Delta t_i \quad (15.16)$$

where ε_i is the strain rate, μ_i is the viscosity, μ_i^t is the turbulent viscosity, ρ is the density, KE_i is the turbulent kinetic energy, and Δt_i is the defined time step.

Fig. 15.7 shows platelet trajectories calculated using the methods discussed earlier. In Fig. 15.8, the shear stress history of single platelets with “interesting” trajectories was exported from the simulation along the trajectory for five cardiac cycles (hence, this was a time-varying input waveform), calculated using the Boussinesq approximation.

Using the approaches discussed earlier, more information about the discrete phase in blood (e.g., platelets in this case) can be gained, which, however, is still very limited. Huang and Hellums developed a population balance equation model more than two decades ago to describe platelet aggregation kinetics under shear flow, where platelet behavior was mostly described using collision/splitting formulations. A few years later, Tandon and Diamond developed a more physiologically relevant collision model to simulate platelet aggregation under shear flow, by incorporating fibrinogen and platelet surface glycoprotein GPIIb/IIIa bond formation and dissociation (this model would include kinetic principles). A 2D analytical platelet flipping model was established by Mody et al., more recently to describe platelet adhesion to von Willebrand factor under flow, based on images of platelet tethering to immobilized von Willebrand factor. In the past 10 to 15 years, various numerical models have been

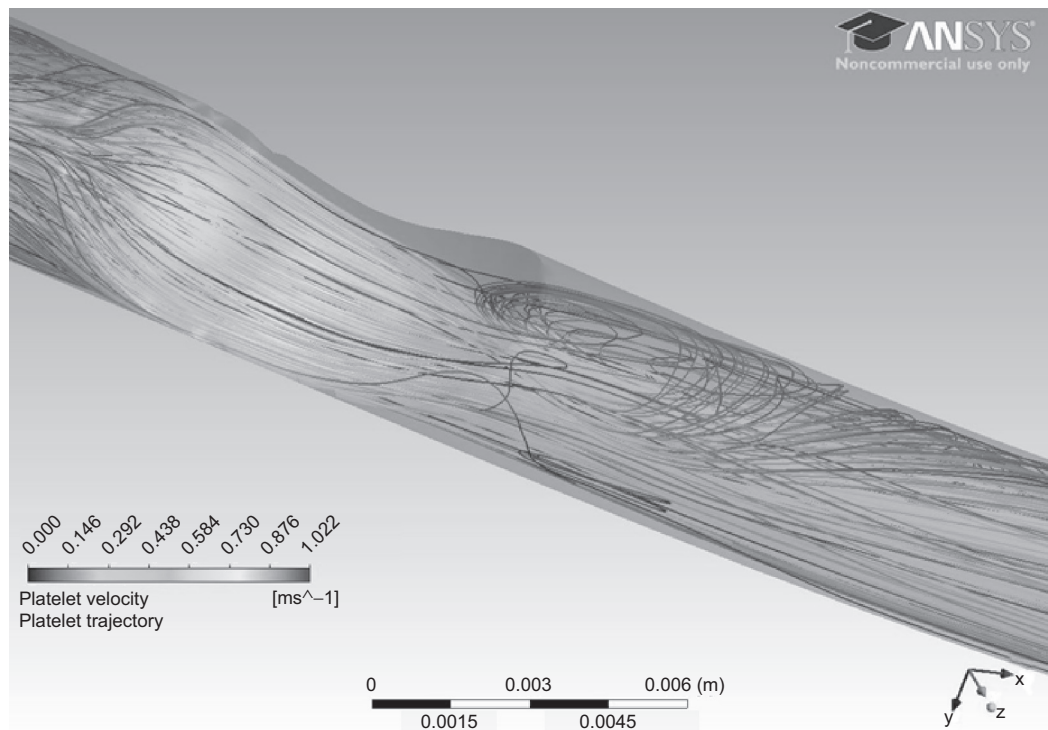


FIG. 15.7 A discrete-phase model can be used to estimate platelet trajectories after they pass an 80% stenosis in the left descending artery. This image shows the trajectories of every particle seeded at the inlet, and we can see that a significant proportion of these become trapped in the recirculation zone downstream of the stenosis.

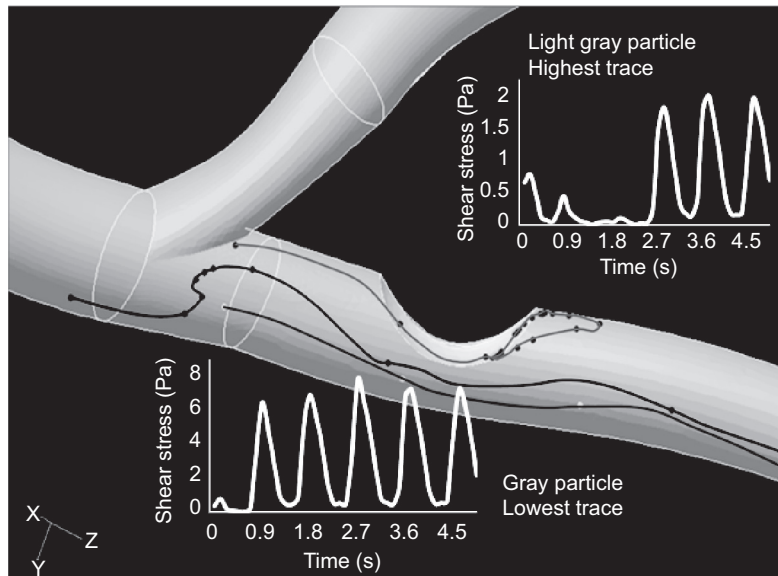


FIG. 15.8 The shear stress history of platelets within the left coronary model estimated using the Boussinesq approximation, following their trajectories for five cardiac cycles. The two exported shear stress histories are for the lowest trace (*gray particle*) and the highest trace (*light gray particle*).

developed to simulate platelet motion, collision, adhesion, and aggregation. Different mathematical models were employed in these studies to describe platelet translocation, slow translations close to the wall, tethering, and protein bond formation, providing detailed information on the physical forces applied to platelets and elucidating how platelet shape and force change affect platelet trajectory and associated biological responses.

Besides platelets, red blood cells and white blood cells, as well as proteins and many molecules in the bloodstream, can be treated as discrete-phase particles, and their motion and behavior can be simulated using discrete (or multiphase) models. To simulate leukocyte adhesion to the endothelium, Khismatullin and Truskey defined a leukocyte as a viscoelastic drop, and the receptor–ligand interaction (between the leukocyte and the endothelium) was described using a spring-peeling kinetic model.

Overall, to achieve more accurate information on the discrete phase, such as cell deformational change, microparticle shedding, surface protein expression, more complicated models and modeling techniques (including kinetic reactions), and sufficient physiological knowledge are required (this will be discussed in [Section 15.5](#)). No commercial software is available to conduct these types of simulations, and therefore, sophisticated and elegant programming will be required by the research group interested in these questions. User-defined programs need to be incorporated into commercially available code, or an entire new customized (or customizable) fluid dynamics simulation would need to be developed. Please note that the methods described previously may not be applicable for each cell type, based on the assumptions made (e.g., spring-peeling kinetic model for leukocytes is a good model, but it may not work as well for red blood cells).

There is one important concept that should be introduced regarding numerical modeling of physical events. We have illustrated two models in this section (see Fig. 15.2, with approximately 5000 elements [2D] and Fig. 15.4, with approximately 2.2 million elements [3D]) that used vastly different meshes. How do we know that the mesh that we made is sufficient to accurately predict the flow conditions and, furthermore, when can we stop adding elements to the simulation? To answer these questions, there is a concept termed *mesh independence* that should be considered for every numerical model that is attempted. Mesh independence states that the solution to the numerical model is independent of the mesh size (e.g., number of elements) and mesh shape (e.g., square versus triangular elements in 2D, etc.). If it is found that the solution of the model varies with the mesh chosen, it would not be clear which solution is accurately predicting the “real” flow conditions better. So how does one determine whether the solution to the model is mesh independent? A simple way would be to run the model with two different meshes. For instance, the model shown in Fig. 15.2 could have been run with a much coarser mesh (maybe 250 elements) and a much finer mesh (maybe 20,000 elements). For the sake of argument, let us assume that the solution between the 250-element model and the 5000-element model varied significantly, whereas the solution between the 5000-element model and the 20,000-element model did not vary significantly. This would suggest that the 5000-element model was sufficient to depict the flow conditions (typically, but not always, the more elements that you add the more accurate predictions can be made from the model, such that the 20,000-element model would be the most accurate). However, why would we run the 5000-element model in lieu of the 20,000-element model? The reason is that the computation time associated with a 20,000-element model would be significantly greater than a 5000-element model. This does not mean that we should choose models with a small quantity of elements to save us computational time. Instead, these concepts state that we can (and should) choose to use a model with a lower number of elements that is considered to be mesh independent in comparison to a model with larger number of elements. To ensure mesh independence, a general practice is to change the mesh size gradually until the solution difference is small (such as 1% to 5% or less). Therefore, when one reports findings obtained from numerical modeling, it is always important to report (1) if the model is mesh independent and (2) how many elements are used in the model, to ensure the readers that a sufficient number of elements have been used and the predicted results are reasonably accurate based on the conditions that were employed. Note that it also may be important to change the mesh geometry; we are just using the mesh size as an example of calculating mesh independence.

15.2 Fluid structure interaction modeling

Traditional computational fluid dynamics simulations can provide a great deal of information regarding the flow conditions. However, in some instances, assumptions regarding physiological aspects of the flow conditions may be made that reduce the overall relevance of the numerical solution. One modeling technique that is commonly used to make a more physiologically relevant model is termed *fluid structure interaction (FSI) modeling*.

The necessity for FSI modeling arises when a flexible structure either has a fluid flowing through it or the flexible structure is immersed within a fluid. One of the most common examples of FSI modeling is of blood flow through the cardiovascular system. As we have learned in previous sections, blood vessels are not rigid and they distend in response to the heart's pressure pulse (this is especially prevalent in the large arteries, which are common sites for cardiovascular disease development). Under cardiovascular disease conditions such as aneurysm, the distensibility of blood vessels increases, and the need for FSI modeling to more accurately describe these conditions is increased (in general the use of FSI modeling is recommended when the channels can distend; however, this factor may not significantly alter the fluid properties). During atherosclerotic conditions, the distensibility of the blood vessels tends to decrease; again, these altered parameters and the effects of these parameters on the flow conditions should be considered. As another example, blood cells are not rigid and the deformations of the cells may cause protein expression changes that can lead to pathological events. To accurately predict and understand the flow through these types of structures, the motion of the structure (or the cells) must be depicted. The mechanical properties of the vessel must be known or assumptions must be made about these properties so that the movement of the vessel and the relationship of this movement with the fluid flow can be accurately assessed. A number of different models can be used to solve these types of flow conditions, which include time-dependent motions, linear and nonlinear models, and time-linearized models. We will highlight some of the equations within these methods and discuss some of the current biofluid research that uses FSI modeling as one of the tools to characterize the flow through a system. More details about current research can be found in [Section 15.4](#).

Perhaps the easiest method that can be used to model a solid boundary movement is based on the pressure that the fluid exerts on that boundary at a particular instant in time and space. This can be quantified as

$$p = \rho u \left[\frac{\partial v}{\partial t} + u \nabla v \right] \quad (15.17)$$

where ρ is the bulk fluid density, u is the average fluid velocity, and v is the fluid velocity as a function of time and space. This model is fairly useful in most biofluid applications, but it is not necessarily accurate when the average fluid velocity is relatively large (e.g., close to the speed of sound, which we typically do not approach in biofluids). In addition, this model is simple enough that it can be used as an initial approximation to determine whether the model parameters are accurate and the flow through the vessel looks reasonable. As the simulation includes more parameters, such as the fluid viscosity and possibility for turbulence to develop, the equations become much more complex (this is termed the *full-potential theory/equations*). Using this method, a nonlinear wave equation would be coupled to the structure movement. The wave equation is nonlinear because of the elastic and viscous mechanical properties of the vessel wall. If one generalizes this formulation, considering that the motion of the body is relatively small and the pressure is uniform throughout the wall (with an inviscid, irrotational fluid), a small displacement form of the full-potential theory

can be developed. Making these assumptions, the convected-wave equation becomes linear and can be solved for any fluid property as

$$\nabla^2 \Phi - \frac{\partial^2 \Phi}{\partial t^2} - u \left[\frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2} + \frac{\partial^2 \Phi}{\partial z^2} \right] = 0 \quad (15.18)$$

where Φ is the fluid property of interest (e.g., velocity, pressure). There are various approaches to make the solution of these equations simpler. The first would be to solve a quasi-linear set of fluid equations that would govern the fluid flow through a system that is completely rigid. This solution would be able to determine the flow properties at each spatial location within the volume of interest. From this solution, the boundary is given a small temporal disturbance and then the changes in the fluid properties are calculated. This gives a direct coupling between the fluid properties and the solid boundary; however, with this simplification the fluid is not directly causing boundary motion and only the boundary is affecting the fluid properties.

The direct coupling of the fluid properties to the solid boundary properties is the most significant challenge of FSI modeling. For each time step within the computational solution, the fluid properties must be considered in relation to the motion of the boundary and changes in the boundary position induced by the fluid also must be considered. This coupling is what makes the complexity of FSI so great, and there are many examples of simplifications that have been used to obtain a solution. To give a brief idea of the formulations that need to be considered to model these types of flow conditions, a mechanical model would be needed to describe the induced motion, relaxation, elasticity, etc. of the fluid container. In parallel with this motion, the fluid properties would need to be updated to consider the change in the geometry (either increase or decrease in the available area). Since these parameters are solved for one time step, they are used as the initial boundary conditions for the next time step. A complexity of this technique is that within each time step, the mesh would need to be regenerated to account for the changes in area induced by the wall motion. This also means that it may be necessary to gain or lose mesh nodes to account for the changes in area. However, meshing complex geometries is not a trivial problem, especially if the research group makes use of varying density meshes to focus calculation points to an area(s) of interest. Furthermore, these adaptive meshes may pose a significant challenge when determining whether the solution is mesh independent. With the consideration of cell dynamics and vessel wall dynamics, these types of simulations can become quite complex. As with computational fluid dynamics, these simulations are useful in describing cardiovascular disease conditions and the flow around cardiovascular devices among many other biological flow conditions.

Let us use the example presented in [Fig. 15.4](#) again to demonstrate how an FSI model can be developed and how it affects the final solution. As we mentioned earlier, for a transient FSI model, at each time step during the simulation, the mesh needs to be regenerated because of the geometry change, which would add a tremendous load to the computation, especially when the number of elements is large. Therefore, for exercise, only a small portion of the artery (approximately 50 mm) was simulated using an FSI approach. The solid domain (the blood vessel wall) and the fluid domain (blood) were meshed separately, and mesh independence

was checked individually. The basic continuity equations and Navier–Stokes equations were used to solve the fluid domain as described before and the arbitrary Lagrangian–Eulerian methods were used to describe the blood vessel wall movement. Furthermore, the arterial wall was modeled as a nonlinear elastic solid using a Mooney–Rivlin hyperelastic model, when the displacement of the wall was prescribed based on reported *in vivo* studies. During simulation, the fluid domain solver (ANSYS CFX) and the solid domain solve (ANSYS Mechanical) were coupled iteratively, allowing total mesh displacement and total force to be transferred and shared between the two domains. The results demonstrated that in using the FSI model, flow velocity was slightly lower than that estimated using a rigid-wall model, because the extensible blood vessel wall would consume some of the kinetic energy of the system. Blood shear stress within the blood vessel and at the vessel wall was only marginally affected by the arterial wall motion. However, stresses within the vessel wall (because of axial, circumferential, and radial stretch of the blood vessel) were heavily dependent on the vessel motion. These results were consistent with that obtained by others using different FSI models. As we discussed earlier, vascular wall endothelial cells are sensitive to their mechanical environment and contribute greatly to the development of cardiovascular diseases. Therefore, employing an FSI model can improve the physiological relevance of our numerical model and help us better understand the mechanical stress/strain imposed on vascular wall endothelial cells, which will help us predict their biological responses to altered mechanical environment more accurately.

Besides simulating blood flow interaction with the blood vessel wall under disease conditions such as stenosis and abdominal aortic aneurysm, FSI models are also commonly used to describe heart valve movement, because hemodynamics associated with a heart valve could significantly affect the valve performance. FSI models also can be used to investigate the interaction of blood cells with the blood vessel wall. As discussed previously, platelets and white blood cells can adhere to endothelial cells under stress conditions. It is thought that this adhesion can mediate many cardiovascular disease conditions. To accurately portray this interaction, the movement of the blood vessel wall must be included because the wall is not rigid and there may be some rebound/recoil after impact. From these research projects, many fundamental biological events have been described and have been validated with experimental methods.

Example 15.1

Fig. 15.9 demonstrates the drainage route of aqueous humor based on Johnson and Kamm's model. Trabecular mesh was modeled as a porous elastic body, shown in the figure as springs. Schlemm's canal is modeled in two dimensions, with the outer wall (top) and the inner wall (bottom) being parallel to each other. The inner wall is permeable (so aqueous humor leaks through), and it deforms as the trabecular mesh work stretches. The local height of the canal is a function of position x and intraocular pressure (*IOP*). Under certain disease conditions (e.g., glaucoma), the size of Schlemm's canal may decrease as a result of the increase in *IOP*; therefore, aqueous humor drainage resistance increases. We can use FSI to model the interface of the moving inner wall and aqueous humor.

Continued

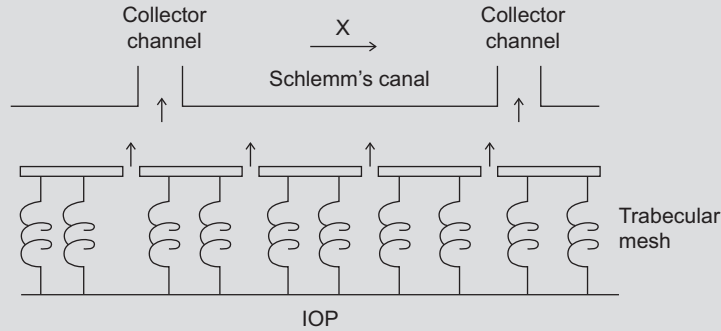
Example 15.1 (cont'd)

FIG. 15.9 Model of Schlemm's canal for in-text Example 15.1. *IOP*, Intraocular pressure. (Modified from M.C. Johnson, R.D. Kamm, The role of Schlemm's canal in aqueous outflow from the human eye, *Invest. Ophthalmol. Vis. Sci.* 24 (1983) 320.)

Solution

First of all, we need to develop the mesh motion for our model. According to Newton's second law, the acceleration of the inner wall is proportional to the net force acting on it. In differential form, the equation to describe the motion of the inner wall is

$$m \frac{dv}{dt} = F_{\text{flow}} - F_{\text{spring}}$$

where m is the mass of the inner wall (and assumed to be constant as a function of time), v is the velocity of the inner wall on y -direction, F_{flow} is the flow of the aqueous humor applied to the wall, and F_{spring} is the spring force applied on the wall through the trabecular mesh.

The velocity of the wall can be determined by the displacement of the wall as

$$v = \frac{y - y_0}{\Delta t}$$

and

$$\frac{v - v_0}{\Delta t} = \frac{dv}{dt}$$

The new displacement of the inner wall determines the spring force in the form of

$$F_{\text{spring}} = k_{\text{spring}}(y - y_0)$$

Therefore, the discrete form of the equation for the inner wall motion can be rearranged, and we can get the expression for the inner wall displacement as

$$y = \frac{F_{\text{flow}} + \frac{m}{\Delta t}(v_0) + \frac{m}{\Delta t^2}(y_0)}{\frac{m}{\Delta t^2} + k_{\text{spring}}}$$

Example 15.1 (*cont'd*)

$$F_{\text{flow}} = p(x)L$$

$$\frac{IOP(t) - p(x)}{E} = -\frac{y - y_0}{y_0}$$

where $p(x)$ is the local pressure in Schlemm's canal and E is the spring stiffness of the canal.

For each time step (Δt), the location of the inner wall (mesh changes) can be determined based on the equation derived previously, which depends on the $IOP(t)$, the local pressure $p(x)$, and the size of the time step.

Furthermore, the flow rate of aqueous humor can be determined by $p(x)$

$$\frac{dp}{dx} = 12 \frac{\mu Q(x)}{\omega h(x)^3}$$

where μ is the aqueous humor viscosity, w is the depth of the canal, and $h(x)$ is the local height of the canal, which depends on y and initial conditions.

15.3 Buckingham Pi Theorem and dynamic similarity

Many real flows cannot be solved by analytical methods alone, but even for those analytical models, the use of full-sized prototypes/simulation geometries may not be practical. To relate the actual flow conditions with the prototype or simulation, the model and actual flow conditions must be linked by some scaling factors. When the simulations and the real conditions match, they are said to be similar based on dimensional scaling. The Buckingham Pi Theorem is a mathematical approach that allows the formation of a relationship for a quantity of interest between the model and the real scenario. As an example, let us consider the drag force on a white blood cell. If we wanted to derive a relationship between the drag force and fluid properties, we would first make a list of all of the properties we thought were important (or could be important) in determining the drag force. For instance, we would probably include the fluid's velocity, the viscosity, and the density and some geometrical properties of the white blood cell. In symbolic form, we would state that the drag force F is a function of the fluid properties that we defined as being of interest

$$F = f(v, \mu, \rho, d) \quad (15.19)$$

In Eq. (15.19), d is the characteristic diameter of the white blood cell. Now in the relationship that we derived (as illustrated in [equation 15.19](#)), we may have unknowingly omitted parameters that are important (e.g., the material properties of the white blood cell membrane), and we may have included parameters that are not important (for sake of argument, maybe for this example we would have thought that the ratio of the cell diameter to the tube

diameter would have been important and included it, but it really only has a marginal effect on the drag force). If we wanted to experimentally determine the relationship between the drag force and the four parameters of interest we have chosen, let us consider the time it would take to complete this experiment. First, a suitable facility, including all experimental apparatus, would be needed to conduct these tests. Once this facility is built, the equipment is installed, and the equipment is validated, we can start our experiments. For these experiments, we would need to hold the fluid viscosity, density, and white blood cell diameter at fixed values and vary the velocity (imagine the difficulty of finding white blood cells with the exact same diameter for the entire duration of the experiment). We would then vary viscosity and hold the other three parameters fixed. This would then need to be repeated for the remaining two variables. Even if we only conducted these experiments for five different fixed velocity, viscosity, density, and diameter values, we would need to complete 625 experiments (not including repetition for statistical purposes). For 10 different values, we would conduct 10,000 experiments (again without repetition for statistical purposes). For fun, calculate how much time this would consume if each experiment took 1 hour to complete and you worked 40 h/week at 100% efficiency (for 10 different values, you would be working for just shy of 5 years for this one relationship, without considering the time it takes to build the facility). Also note that by conducting all of these experiments, you may learn that some of the parameters are not as important and that others are important (thus, this would cause an increase in your experimentation time). In addition, we all know and understand that repeated measurements would need to be taken for either statistical purposes or because there was some error in the experiment and that this can significantly increase the time required to complete one set of experiments. The Buckingham Pi Theorem is a relatively easy approach to minimize this work and obtain a potentially meaningful relationship between all of the fluid properties of interest. This relationship then can be tested for its actual validity in a much more efficient manner, allowing for an iterative process in which new parameters can be added and some parameters could be removed.

Using the same example as previously, we would assume that some physical property of interest is dependent on n independent variables. This can be represented as a function, h , which is dependent on any (or all) of the parameters of interest. For instance, we stated that under our conditions drag force (F) was a function of velocity (v), viscosity (μ), density (ρ), and diameter (d) (Eq. (15.19)). We would therefore build a function, h , such that some combination of all of the properties equate to zero

$$h(F, v, \mu, \rho, d) = 0 \quad (15.20)$$

The Buckingham Pi Theorem states that for any grouping of n parameters, they can be arranged into $n - m$ independent dimensionless ratios (termed Π parameters). The number m is normally equal to the minimum number of independent dimensions represented by the quantities of interest within the function h . By knowing all of the possible Π ratios of important parameters, it is then possible to simplify the results by testing which (if any) of the Π ratios match the data obtained (thus, you would not need to conduct all 10,000 experiments described earlier, but rather only a subset to characterize the data). The Buckingham Pi Theorem begins by listing all of the dimensional parameters involved in the particular problem (this is equal to n). A consistent fundamental dimension system must be chosen

(for *Système International d'Unités* [SI] units it is mass, length, and time [MLT]; for English units it is typically force, length, and time [FLT]). We then list the fundamental dimensions for each dimensional parameter and quantify the minimum number of independent dimensions, which is equal to m . We then select any set of m dimensional parameters that includes all of the primary dimensions and solve for a relationship between each of these parameters and the remaining parameters that is dimensionless. See the example for a more detailed discussion of this procedure.

Example 15.2

Determine all of the dimensionless groups possible to describe the drag force on a white blood cell, using Eq. (15.20).

Solution

List the dimensional parameters

$$F \quad v \quad \mu \quad \rho \quad d$$

Thus, for our case, $n = 5$, because there are 5 parameters in our list. Select MLT as the fundamental dimension set.

List the fundamental dimensions of each parameter of interest (this is simply writing the units of each parameter in terms of the fundamental dimensions (e.g., we do not write Newton or kgm/s^2 for force, but instead we would write $\frac{\text{mass} * \text{length}}{\text{time}^2}$ or $\frac{ML}{T^2}$).

$$\begin{array}{ccccc} F & v & \mu & \rho & d \\ \frac{ML}{T^2} & \frac{L}{T} & \frac{M}{LT} & \frac{M}{L^3} & L \end{array}$$

The minimum number of independent parameters is $m = 3$ (M , L , and T).

The number of Π groups is 2 ($n - m = 5 - 3 = 2$)

Pick v , d , and ρ as the subset of dimensional parameters and relate this to F (they represent M , L , and T). These values are related to F because this is the parameter for which we are trying to find a relationship. At this point, any grouping of three parameters that have M , L , and T represented would suffice.

The first Π group could be set up as

$$\begin{aligned} \Pi_1 &= F v^a d^b \rho^c \\ \left(\frac{ML}{T^2}\right) \left(\frac{L}{T}\right)^a (L)^b \left(\frac{M}{L^3}\right)^c &= M^0 L^0 T^0 \\ \left(\frac{ML}{T^2}\right) \left(\frac{L^a}{T^a}\right) (L^b) \left(\frac{M^c}{L^{3c}}\right) &= M^0 L^0 T^0 \\ ML(T^{-2})(L^a)(T^{-a})(L^b)(M^c)(L^{-3c}) &= M^0 L^0 T^0 \end{aligned}$$

Example 15.2 (*cont'd*)

The dimensions must equate to a zero power, because we are trying to find a dimensionless number that relates these parameters of interest. Separate each dimension and relate the exponents

$$\begin{aligned} M: 1 + c &= 0 \\ L: 1 + a + b - 3c &= 0 \\ T: -2 - a &= 0 \end{aligned}$$

From the mass equation,

$$c = -1$$

From the time equation,

$$a = -2$$

From the length equation,

$$b = 3(-1) - 1 + 2 = -2$$

Therefore the first Π group is

$$\Pi_1 = \frac{F}{v^2 d^2 \rho}$$

For our second Π group, we will pick v , d , and ρ as the subset of dimensional parameters and relate this to μ (they represent M , L , and T). We choose μ here because we already investigated F . Again, we could try to make a relationship for any of the variables that we think are important.

The second Π group will be set up as

$$\begin{aligned} \Pi_2 &= \mu v^a d^b \rho^c \\ \left(\frac{M}{LT}\right) \left(\frac{L}{T}\right)^a (L)^b \left(\frac{M}{L^3}\right)^c &= M^0 L^0 T^0 \\ \left(\frac{M}{LT}\right) \left(\frac{L^a}{T^a}\right) (L^b) \left(\frac{M^c}{L^{3c}}\right) &= M^0 L^0 T^0 \\ M(L^{-1})(T^{-1})(L^a)(T^{-a})(L^b)(M^c)(L^{-3c}) &= M^0 L^0 T^0 \end{aligned}$$

Separate each variable and relate the exponents

$$\begin{aligned} M: 1 + c &= 0 \\ L: -1 + a + b - 3c &= 0 \\ T: -1 - a &= 0 \end{aligned}$$

From the mass equation,

$$c = -1$$

Example 15.2 (*cont'd*)

From the time equation,

$$a = -1$$

From the length equation,

$$b = 3(-1) + 1 + 1 = -1$$

Therefore the second Π group is

$$\Pi_2 = \frac{\mu}{\rho v d}$$

From these two Π groups, we can state that

$$\begin{aligned}\Pi_1 &= f(\Pi_2) \\ \frac{F}{v^2 d^2 \rho} &= f\left(\frac{\mu}{\rho v d}\right)\end{aligned}$$

but the actual relationship between the Π groups would need to be determined experimentally (e.g., are there constants of proportionality or other factors that we did not consider?). However, the usefulness of this analysis technique is that we can obtain dimensionless parameters that can relate fluid properties. The usefulness of these relationships would need to be experimentally evaluated. In Example 15.2, drag force was related to the fluid's velocity, density, and a characteristic length, and the viscosity was related to the same three parameters. The relationship is different in each of the cases presented, or it may not even be correct, but at least now we have a starting point to analyze any experimental data that we collect.

Many different dimensionless parameters are important in biofluid flows, and we will describe some of these parameters here. This is not an all-inclusive list but rather is a list comprising many of the commonly used/discussed dimensionless parameters. The first parameter is the Reynolds number (Re), which is defined as

$$Re = \frac{\rho v d}{\mu} = \frac{v d}{\nu} \quad (15.21)$$

where d is some characteristic length that is typically the blood vessel diameter in biofluid mechanics examples (see Example 15.2 for Reynolds number formulation). The Reynolds number relates the inertial forces to the viscous forces and also is a criterion to describe the flow regime as either laminar or turbulent. As the Reynolds number becomes large, the flow is more likely to be turbulent. As the Reynolds number approaches 1, the inertial forces and the viscous forces balance and both are important to the flow conditions. As the Reynolds number approaches zero, the viscous forces dominate and the flow is normally slow and laminar.

Another important dimensionless number is the Womersley number (α), which relates the pulsatility of the flow to the viscous effects. The Womersley number is defined as

$$\alpha = d \left(\frac{\omega}{\nu} \right)^{\frac{1}{2}} \quad (15.22)$$

where ω is the angular frequency. When α is less than 1, the fluid can become fully developed during each flow cycle (a flow cycle is defined as the period of the pulse frequency within the flow field). As α increases (>10), the velocity profile is typically represented as a plug-flow scenario and the flow will never fully develop, because of the constant changes during the flow cycle. The Womersley number is important in biofluid mechanics because nearly all blood flow in the larger blood vessels has some pulsatility to it. It is important to be able to determine whether the flow can fully develop in between each pressure pulse or whether the flow never develops fully.

The Strouhal number (St) is another dimensionless parameter that is important in pulsatile flows. The Strouhal number is defined as

$$St = \frac{fd}{v} \quad (15.23)$$

where f is the frequency of vortex shedding, d is a characteristic length, and v is the fluid velocity. For a Strouhal number greater than 1, the fluid will move as a plug following the oscillating frequency of the driving force. As Strouhal numbers decrease past 10^{-4} , the velocity of the fluid dominates the oscillation and little to no vortices are shed. For intermediate Strouhal numbers, there is a rapid vortex formation and many vortices can be shed into the mainstream fluid. Interestingly, the Womersley parameter can be defined using the Reynolds number and the Strouhal number as

$$\alpha = \sqrt{2\pi ReSt} \quad (15.24)$$

The cavitation number (Ca) relates the local pressure to the vapor pressure and the fluid kinetic energy and provides a criterion for how likely it is for cavitation to occur. The cavitation number is defined as

$$Ca = \frac{p - p_v}{\frac{1}{2} \rho v^2} \quad (15.25)$$

where p_v is the vapor pressure of the fluid at a particular temperature. As the cavitation number decreases, it is more likely for cavitation to arise in the fluid. Cavitation is a phenomenon by which gases within the fluid can coalesce into large “bubbles” or gases surrounding the fluid enter and remain in the fluid in large quantities. Cavitation is typically a phenomenon that incurs damage on the surrounding tissue but has been used to break apart kidney stones.

The Prandtl number (Pr) is the ratio of the momentum diffusion to the thermal diffusion and provides criteria for whether the flow will deliver a significant amount of heat to the surrounding container or if it retains its heat. The Prandtl number is defined as

$$Pr = \frac{\mu c_p}{k} \quad (15.26)$$

where c_p is the specific heat of the fluid and k is the thermal conduction coefficient. As the Prandtl number reduces below 1, the fluid will not retain its heat very well; for example, the fluid dissipates large quantities of heat to the surrounding tissue. Flows characterized by a larger Prandtl number can retain their heat better than lower Pr flows.

The Weber number (We) and the capillary number (C) are important for flows with a free surface. The Weber number relates the inertial forces to the surface tension forces, and the capillary number relates the viscous forces to the surface tension forces. They are defined as

$$We = \frac{\rho v^2 L}{\sigma} \quad (15.27)$$

$$C = \frac{\mu v}{\sigma} \quad (15.28)$$

where v is the average fluid velocity and σ is the surface tension of the fluid. There are many more dimensionless numbers that can be used to describe fluid properties, but we will restrict ourselves to the ones listed here.

Depending on the exact conditions that describe the characteristics of a particular flow, some of these dimensionless parameters may not be applicable. In general, to model a particular flow condition accurately, as many of these dimensionless numbers should be matched as possible. This leads us to a discussion of similarity within the experimental or numerical model. For a model to be geometrically similar, the model has to be the same shape as the real flow scenario, and all lengths have to be related to the real scenario by the same scaling factor. For a model to be kinetically similar, the velocity at each location within the model has to be oriented in the same direction as the velocity under the real flow conditions. Additionally, the magnitude of each and every velocity vector must be related to the real flow scenario by a constant scaling factor. The hardest criterion to meet is that all of the forces within the model have to be identical (in magnitude by a constant scaling factor and direction compared with the true flow conditions). If these three conditions are met, the flows are dynamically similar. To maintain dynamic similarity all of the viscous forces, the buoyancy forces, the inertial forces, the pressure forces, and the surface tension forces, among others, must be matched at every location within the model. When dynamic similarity is achieved, the data obtained in the model can be related back to the real flow condition, typically by a single scaling factor.

From the in-text Example 15.2, which obtained the dimensionless group that related the drag force to the flow properties, we were able to develop a mathematical relationship that states

$$\frac{F}{v^2 d^2 \rho} = f\left(\frac{\rho v d}{\mu}\right)$$

Therefore, if we were considering a flow in which drag forces were important, it would be a necessary requirement that the Reynolds numbers equate between the actual scenario and the model. By satisfying this criterion, the forces acting on the immersed objects would be scalable between the model and the real flow scenario. This same analysis can be conducted for any of the dimensionless parameters (or as many as necessary) to satisfy similarity between the flow that is being modeled and the model itself. Although it is important to maintain dynamic similarity among all fabricated models, it may be unreasonable or not feasible to actually fabricate a dynamically similar model. Under these cases, it would be important to identify the key properties that should be similar and other parameters that should be as close to the true flow conditions as possible.

Example 15.3

Imagine that we are making a model of blood flow through an artery; however, we could use only water as our fluid flowing through the model artery. Calculate what the angular frequency of the pulsatile waveform and the initial inlet velocity should be if the characteristic length (diameter) of the blood vessel and the model of the blood vessel is 10 cm, the heartbeat is 72 beats per minute (angular frequency is 5.24 rad/s), and the inlet velocity is 50 cm/s.

Solution

Using the Reynolds number, we can calculate the initial inlet velocity of the model

$$\begin{aligned} Re_{\text{blood}} &= Re_{\text{model}} \\ \frac{\rho_b v_b d_b}{\mu_b} &= \frac{\rho_m v_m d_m}{\mu_m} \\ v_m &= \frac{\rho_b v_b d_b \mu_m}{\mu_b \rho_m d_m} = \frac{1050 \text{ kg/m}^3 (50 \text{ cm/s}) (10 \text{ cm}) (1 \text{ cP})}{1000 \text{ kg/m}^3 (10 \text{ cm}) (3.5 \text{ cP})} = 15 \text{ cm/s} \end{aligned}$$

Using the Womersley number, we can calculate the angular frequency of the model

$$\begin{aligned} \alpha_{\text{blood}} &= \alpha_{\text{model}} \\ d_b \left(\frac{\omega_b}{v_b} \right)^{\frac{1}{2}} &= d_m \left(\frac{\omega_m}{v_m} \right)^{\frac{1}{2}} \\ d_b \left(\frac{\rho_b \omega_b}{\mu_b} \right)^{\frac{1}{2}} &= d_m \left(\frac{\rho_m \omega_m}{\mu_m} \right)^{\frac{1}{2}} \\ \omega_m &= \frac{\mu_m}{\rho_m} \left[\frac{d_b}{d_m} \left(\frac{\rho_b \omega_b}{\mu_b} \right)^{\frac{1}{2}} \right]^2 = \frac{1 \text{ cP}}{1000 \text{ kg/m}^3} \left[\left(\frac{10 \text{ cm}}{10 \text{ cm}} \right) \left(\frac{(1050 \text{ kg/m}^3)(72 \text{ beats/min})}{3.5 \text{ cP}} \right)^{\frac{1}{2}} \right]^2 \\ &= 21.6 \text{ beats/min} \end{aligned}$$

What happens if complete dynamic similarity is not achievable, because there are too many parameters to match between the real scenario and the model? In some instances, by solving the dimensionless groups simultaneously, it can be found that no fluid exists that can match the properties needed. For instance, if one was modeling the flow around an airplane wing, you may want to make a $\{1/10\}$ or $\{1/50\}$ model, which would then dictate the other properties of the fluid and the experimental conditions. By matching as many parameters as possible (velocity, wave frequency, etc.), it is typical that the fluid viscosity or density is what needs to be modified to make the solution dynamically similar. What happens when there is no known fluid that exists that can match the required parameters? Should some of the other parameters be altered to find a suitable fluid? If there is an incomplete dynamic similarity, the only way to achieve a similar model is to use a full-scaled model, which may not be reasonable (what if your experiment is to try to understand the flow around a nuclear submarine or a single cell?). However, studies have shown that some of the data that are obtained from incomplete dynamically similar solutions are still useful. Therefore, it is best to match as many parameters as possible when modeling a real scenario, but if all of the parameters cannot be matched, this must be accounted for when analyzing the data.

15.4 Current state of the art for biofluid mechanics *in silico* research

In the remaining chapters of this textbook, we will discuss some areas of open research that are being pursued by current biofluid mechanics research groups. We do not intend for this discussion to encompass all of the areas of research that are being explored, but instead we use this as an area to describe current trends and provide the reader with an avenue of exploration on their own. As a data point only, at the time of writing, conducting a PubMed search (<http://www.ncbi.nlm.nih.gov/pubmed>) with the search string of “computational fluid dynamics” returns over 6100 publications (note that for the second edition of the textbook, which was published in 2015, this number was 3300). The same search string in ScienceDirect.com (<http://www.sciencedirect.com/>) or Google Scholar (<http://scholar.google.com/>) retrieves over 140,000 (2015 number was 100,000) and 2.27 million (2015 number was 1.68 million) publications, respectively. Clearly, computational fluid dynamics is a very active research field that could not be adequately described in this small section. This can be seen because in the last 4 years, there has been a significant boost in the number of publications that can be retrieved by our simple search string.

There are two very common fields in current *in silico* biofluid mechanics research that can branch into multiple avenues. The first is the evaluation of cardiovascular implantable devices (e.g., stents, heart valves) and the second is the understanding of the development of flow properties that instigate/propagate cardiovascular diseases. The first area of research has proven to be an invaluable tool in designing new devices that minimize damage to blood cells or disruptions to the flow field. The importance of this area of research is that many of the original implantable cardiovascular devices failed because of damage induced to blood cells or a disruption to the fluid flowing around the device. For instance, it was common for patients with mechanical heart valves to be placed on lifetime anticoagulant therapy to

minimize the negative reactions that the heart valves induced on the hemostatic system. Although the implantation of these valves would save the lives of the patients, there was an increased burden on patient lifestyle that could potentially lead to valve failure and/or death. Furthermore, with significant damage or disruptions, the patient may die.

Computational fluid dynamics approaches have focused on identifying critical geometries within the heart valve structure that elicit potentially adverse flow properties. Engineering optimization/design procedures have been implemented to redesign these critical geometries, and computational studies of the effects of these new geometries on the flow field have been conducted. The importance of this work is that the cost of conducting a computational fluid dynamics study to optimize particular properties of the flow conditions would be significantly less than building a prototype that can be used within *in vitro* or *in vivo* studies. "Good" designs can be refined, and "bad" designs can be excluded relatively easily with these techniques in a more cost-effective manner.

For the second area of research, atherosclerosis and aneurysm development are probably the two most common research areas for biofluid computational simulation groups. Groups can make use of patient-specific geometries to predict the onset of the disease or research groups can make use of these geometries to determine how the flow field is affected around the developing disease. Many fundamental fluid dynamics issues related to cardiovascular disease development have been elucidated through the use of these models. In more recent work, models with greater physiological relevance have been developed to more accurately predict disease onset or development. For instance, cells within the flow field and the mechanical properties of the blood vessel have been considered to more accurately predict the flow conditions.

There are many other avenues of research that make use of computational fluid dynamics approaches. For instance, recent work has investigated the airflow through the branching lung conducting pathways under normal and pathological conditions. One of the major purposes of this work was to determine the effective forces that act on the respiratory epithelial cells to determine possible disease conditions and mechanical changes during these disease conditions. Models have been made that approximate the flow through the nephron tubule system to observe how altered cardiovascular conditions or altered renal regulatory mechanisms can alter the flow through nephron units. Similarly, models of the flow through the gastrointestinal tract have been developed to determine the effects of altered pressure or chemical regulation on digestion and other processes.

It is important to note that regardless of the area of biofluid mechanics research that the particular group is pursuing, these models need to be validated by some other measures. Some of this validation can come from previous reports, but it is important to conduct experiments that have similar constraints as the model that is being developed. Without this validation, it would be difficult to determine how accurately the model represents the physiological flow conditions. It would also be difficult for readers external to the research group to interpret the findings.

Finally, all of the research areas that we have discussed can be investigated using FSI modeling and/or multiscale modeling approaches. We did not highlight the different studies in these areas, but be aware that each of these more thorough techniques can be applied to the general areas that we have discussed.

15.5 Future directions of biofluid mechanics *in silico* research

In the remaining chapters of this textbook, we will include a section about possible future directions of research that may be pursued to advance the field of biofluid mechanics research. As with the previous section of this chapter, this is not an all-inclusive list of possible future research endeavors, but instead our discussion is intended to highlight areas of research that we think can significantly advance knowledge of biofluid mechanics research.

In our opinion, it is crucial to make models that are more physiologically relevant and to incorporate more biological processes into the modeling approach. This would allow the model to more accurately predict the behavior of the system and also provide the community with more relevant information that can be used for the design of therapeutics and/or medical devices. More accurate FSI modeling and multiscale modeling approaches are two areas that may be developed in the near future to address the issues we are describing. There are many *in vitro* or *in vivo* studies that can be used to validate and/or guide these studies.

In [Section 15.2](#), we described the need for FSI modeling. This area, although it is currently in use in some biofluid mechanics laboratories, still needs significant development to become more widely used. For instance, to make these models more accurate, it would be important to incorporate more physiologically relevant/pathophysiologically relevant parameters within the model. This is principally related to the velocity/pressure waveforms and/or mechanical properties of the tissue/cells. As we have described, the interaction of fluid and solid elements is very important to the progression of cardiovascular diseases, and thus more relevant information regarding these interactions needs to be incorporated into models. These types of models may be able to elucidate how critical mechanical forces are to the generation and progression of cardiovascular diseases.

Multiscale modeling is an approach in which the model incorporates multiple length (or time) scales within each iteration. In the case of biofluid mechanics problems, the largest scale would typically consider the bulk flow of the fluid through the channel of interest. A scale below this may consider the motion of cells and/or the deformation of the containing volume or the cells themselves. A smaller scale could consider the motion of proteins or other molecular elements within the flow field (e.g., Do coagulation or inflammatory proteins come into contact with each other during the flow scenario?). Finally, the kinetics of these protein interactions can be modeled (e.g., coagulation cascade modeling or adhesion mechanics/dynamics between cells and the vessel wall). We described some of these modeling events in the previous section, but the difficulty in multiscale modeling arises principally from the coupling between the different scales. It is relatively easy to model the fluid flow through a channel, but to include the motion of particular discrete-phase elements would be considerably more difficult. Under these modeling conditions, if the discrete phase is given a true mass (and thus inertia/drag), the motion of the fluid alters the motion of the particles and the motion of the particle alters the motion of neighboring fluid elements. The motion of proteins or other dissolved elements would be even more difficult to include because most proteins typically do not have well-defined mechanical properties and the relationship between applied mechanical forces and geometrical considerations would be difficult to validate. Finally, if the dynamics of the proteins could be modeled, their interactions would need to

be modeled. The protein–protein interaction would elicit some product that would then need to be tracked (perhaps in molecular dynamic type simulations). Additionally, the kinetics of these interactions would need to be included within the time steps. Overall, the coupling of all of these processes would be extremely difficult to accomplish. However, these models would be able to provide us with the most relevant information because many of the processes that are of concern to the researcher would be investigated within a single simulation and considerations on how these areas interact could be taken into account. This would allow for the generation of a predictive model that could potentially look into many different physiological aspects of the flow conditions. At this time, it is typical for many simplifications to be included within the multiscale model, so that some data can be obtained.

The authors also would like to see the combination of models with different scales be combined with FSI models so that solid and fluid parameters can be included within the one simulation. This would provide significant information regarding the process under investigation. With that said, one has to consider which parameters are “important” to the flow and whether those parameters should be included within the flow conditions. For instance, if one is looking at blood flow through the coronary artery, the heart motion and the dynamics of the vessel opening and closing would be critical to include. This would necessitate FSI modeling. Discrete flow through capillary beds is less susceptible to motion within the vessel, and thus it may not be an important parameter to include within the flow conditions. Kinetics of cell adhesion can occur anywhere within the cardiovascular system, and it may be important to include; however, if adhesion is atypical under the particular conditions being investigated, it may not be important to include this parameter within the simulation. Thus, although more physiologically relevant models should be developed, the relevance of these additions to the model needs to be weighed against the possible differences (if any) in the data obtained from the simulation.

Summary

- 15.1.** Computational fluid dynamics is a method that can be used to solve the coupled governing equations of biofluid flows through complex geometries, without making many simplifying assumptions that have been discussed earlier in this textbook. The most common method to solve CFD simulations is to mesh a relevant geometry and then by using either the forward difference method or the backward difference method, the fluid properties can be obtained at subsequent grid points. The equation takes the form of

$$\left. \frac{\partial f}{\partial x} \right|_i = \frac{f_{i+1} - f_{i-1}}{2\Delta x} + H.O.T.$$

Under these simulations, it is also possible to incorporate turbulent flow properties into the numerical methods. The most commonly used models are either the $k - \varepsilon$ or the $k - \omega$ turbulence models, which are defined by

$$k = \frac{1}{2} \overline{u_i u_i}$$

$$\varepsilon = \nu \overline{u_{i,j} u_{i,j}}$$

$$\varepsilon = k\omega$$

A second useful tool that is incorporated into many CFD commercial software packages is the ability to solve for the discrete movement of particles within the fluid. By coupling Newton's laws to the fluid dynamics laws, equations can be composed that determine the forces that act on particles within the fluid. A common solution for the force and the velocity of a particle is

$$\frac{du_p}{dt} = F_D(u - u_p) + F_x$$

and

$$\frac{dx_p^i}{dt} = u_p^i$$

If the shear stress is a critical parameter in the flow scenario, the accumulation of shear stress with time can be calculated from

$$\sum_{t=t_0}^{t_{\max}} \left(\frac{(\varepsilon_i - \varepsilon_{i+1})}{2} \times (\mu_i + \mu_i^t) + KE_i \times \rho \right) \times \Delta t_i$$

- 15.2.** A more accurate model can incorporate the movement of the blood vessel wall and the deformability of particles within the fluid. This type of modeling would fall under the category of an FSI model, and in these types of models, mass, momentum, and energy can be transferred between the wall, the particles, and the fluid. This transfer of energy is accounted for in the solution period. The solution of these types of simulations makes use of the partial differential equation

$$\nabla^2 \Phi - \frac{\partial^2 \Phi}{\partial t^2} - u \left[\frac{\partial^2 \Phi}{\partial x^2} + \frac{\partial^2 \Phi}{\partial y^2} + \frac{\partial^2 \Phi}{\partial z^2} \right] = 0$$

which can be solved for any fluid parameter of interest. An important feature of FSI modeling is that the mechanical properties of the solid elements should be known under the conditions that are being observed. For instance, under disease conditions, it is likely that localized mechanical properties of the blood vessel wall are altered based on the deposition and/or removal of material. These changes are typically addressed within the model.

- 15.3.** To make the numerical model the most accurate possible, the models should be dynamically similar, which means that the length scales and the forces that act within the model are the same. A method to ensure that a model is similar is the Buckingham Pi Theorem, which devises a number of functions between a parameter

of interest and various fluid properties. In biofluid mechanics, a number of dimensionless parameters can be considered when making models or describing the flow conditions. These are the Reynolds number, the Womersley number, the Strouhal number, the cavitation number, the Prandtl number, the Weber number, and the capillary number, among others. These are defined, respectively, as

$$Re = \frac{\rho v d}{\mu} = \frac{v d}{\nu}$$

$$\alpha = d \left(\frac{\omega}{\nu} \right)^{\frac{1}{2}}$$

$$St = \frac{f L}{v}$$

$$Ca = \frac{p - p_v}{\frac{1}{2} \rho v^2}$$

$$Pr = \frac{\mu c_p}{k}$$

$$We = \frac{\rho v^2 L}{\sigma}$$

$$C = \frac{\mu u}{\sigma}$$

- 15.4. The current state of the art of *in silico* biofluid mechanics research areas is very broad and encompasses many different physiological and pathophysiological events. Many groups are making use of traditional techniques but are supplementing these techniques with customized codes that can depict particular aspects of the physiology that the group wants to investigate. These techniques have provided the community with a significant amount of information regarding disease progression and the development and optimization of new implantable therapeutic devices.
- 15.5. In the future, *in silico* biofluid mechanics research groups should focus on developing models that are more relevant and incorporate more fundamental processes to more accurately depict the pathological event (or whatever is being modeled), in our opinion. Some areas that are currently underdeveloped are the incorporation of multiple length scales into the model to depict the flow, cellular deformations, kinetics, etc. These types of models, if the initial conditions, assumptions, and linking functions can be assumed accurately, can provide a great deal of information to the research community.

Homework problems

- 15.1.** Using the central difference method in two-dimensional space, in which each point is the average of its four nearest neighbors, calculate the velocity through the specified channel with the known boundary conditions and the known inlet conditions as shown (Fig. 15.10). The velocity along the wall grid points (1, 2, 3, 19, 20, and 21) is 0 mm/s. The velocity at the inlet grid points (4, 9, and 14) is 40 mm/s. The velocity at the outflow grid points 8 and 18 is 20 mm/s, and the velocity at the grid point 13 is 35 mm/s. It may be easiest to use linear algebra to solve the system of equations that will be generated. Assume that the grid is uniformly spaced in the x - and y -directions.

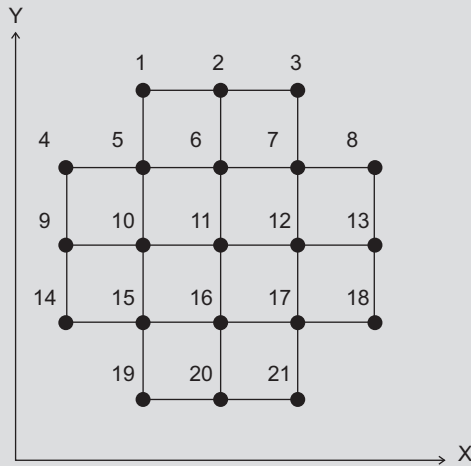


FIG. 15.10 Grid for Homework Problem 15.1.

- 15.2.** Using an available computational fluid dynamics software package, make a simple geometry for a rapid constriction (similar to Fig. 15.2, which was shown for a rapid expansion). Calculate the flow through this constriction. If no software is available, make a prediction for the flow through the constriction.
- 15.3.** The spin on particulate matter within blood may play an important role in the activation or recycling of the cell. Therefore, the spin dissipation rate may be an important parameter to know and characterize under particular flow conditions. We think that the torque on the particle, T , depends on the particle's speed (v), blood density (ρ), blood viscosity (μ), cell diameter (d), and spin rate (angular velocity, ω). Determine the dimensionless parameters that can be formed from this grouping of "important" variables.
- 15.4.** When a mechanical heart valve closes rapidly, a hammer pressure wave is initiated in the fluid. This high-pressure wave may damage the blood vessel wall distal to the mechanical heart valve (potentially shearing endothelial cells off the inner lining).

Homework problems (cont'd)

The maximum hammer pressure generated (p_{max}) is a function of the blood density (ρ), the blood velocity at time of closure (v), and the blood deformation modulus (E , which has the same units as a general elastic modulus). Determine the relationship between hammer pressure and the variables provided.

- 15.5. To match the Reynolds number between blood flow and a water flow model, using a twofold larger model (in geometrical dimensions), which flow will require the higher flow speed? How much higher will it be?
- 15.6. Develop an argument for the use of computational fluid dynamics methods in biofluid research. Consider and delineate the pros and cons of implementing a method such as this under various research fields. Are there better models that can be employed; what are the shortcomings of those models?
- 15.7. We described a handful of dimensionless parameters in this section that are important to biofluid mechanics computational research. Choose two or three of these parameters and describe situations in which they would be important in biofluid research. Additionally, are there other parameters that you can think of that should be included within this discussion (e.g., is there a grouping of variables that we did not list that should be included?).
- 15.8. Prepare a research report on the current state of the art for a field of your choosing within computational biofluid mechanics research. Describe the history of the field, how it has progressed to where it is now, and where you think future efforts should be focused.

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In vitro biofluid mechanics*

LEARNING OUTCOMES

- Discuss common experimental techniques that are used for in vitro biofluid mechanics studies
- Compare particle imaging velocimetry techniques and the data that can be obtained from these methods
- Describe the equipment necessary to conduct particle imaging velocimetry measurements
- Describe parallel plate and other viscometry techniques
- Mathematically represent the flow field within a parallel plate viscometer and a cone-and-plate viscometer
- Discuss the use and benefits of lab-on-a-chip techniques
- Discuss current and future work that makes use of in vitro biofluid mechanics techniques

16.1 Particle imaging velocimetry

Particle imaging velocimetry (PIV) is a computer-based technique that tracks a sequence of reflective particles through a flow chamber. In the most basic PIV technique, one camera is used to obtain flow information about one cross-section through the flow chamber. However, it is more common to use more than one camera to collect multiple views so that a more complete three-dimensional (3D) velocity flow profile can be obtained. In addition, flow patterns are more easily obtained from multiple cameras collecting information about the same particles within the flow field. There are multiple techniques that can fit into PIV, and we will discuss some of them here. The most popular technique is particle tracking. In this technique, one or more cameras are used to image a 3D velocity profile that is projected onto a 2D plane. If only one camera is used, information about the distance from the camera will be lost,

*This chapter is considered advanced and can be skipped without a loss of continuity.

because a single camera can project only a 3D image onto a single 2D plane (e.g., imagine taking a picture of a crowded train terminal, the exact position of every person cannot be obtained accurately from the one image). However, by adding more cameras, at different known locations, this information can be obtained through a cross-correlation of the data (also termed *triangulation*), and therefore, a full 3D image of the flow field can be generated (although you may not have information regarding the entire flow field, because this depends on the optics of the imaging system). To obtain these images of flow scenarios, it is preferred to fabricate an accurate (possibly scaled up or down) model that can depict the geometry of the real flow conditions. Dynamic similarity, which was described in Chapter 15, is used to make sure the scaling and the forces throughout the model are matched. The basis for collecting data with PIV is through the use of reflective beads, which are placed within the fluid that will be circulated throughout the model. A high-intensity light source (commonly a laser source) is focused onto a region of interest within the flow chamber. A digital camera with a high-acquisition frame rate is also focused at this region of interest to collect data on the particle motion over time. An external synchronization trigger is needed to control the illumination of the laser (which is typically pulsed), and a camera is needed that can be both focused on the area of interest (with an appropriate resolution) and controlled to image with the laser pulses. Particle motion is obtained through the light reflection from the seeded particles, which is captured by the digital camera. Using a computer algorithm, each subsequent image is correlated to the previous image, temporally, so that each particle's velocity can be calculated from a known change in position divided by the known frame rate of the camera. The position information can be obtained by scaling the camera images to the physical dimensions of the model. By collecting multiple datasets at each region of interest, it is possible to obtain mean velocities (magnitude and direction) throughout the flow field. A typical PIV setup is schematized in Fig. 16.1. It should be noted that it is possible for the particle tracking algorithm to not correlate the correct particles in subsequent images. For instance, if the particles are too concentrated within the flow field, the reflected light may be outside the camera's resolution limit, and thus the algorithm will be unable to discriminate between particles that are close to each other. In addition, if particular particles do not follow a "normal" trajectory, it may be difficult for the algorithm to determine the specific particle motion (normal is hard to define in this context, but if the particle motion is completely erratic, the algorithm may not be able to determine where the particle is in subsequent frames). Furthermore, if the particles are too sparsely populated, not enough information about the flow field would be obtained. Therefore, it is necessary to optimize the particle seeding density within the flow chamber. Besides the particle density, many of the issues regarding correlations between neighboring particles can be addressed by the optics and the optical control systems.

The usefulness of PIV systems in biofluid mechanics research is that new designs for cardiovascular implantable devices can be tested to determine whether they disrupt the flow field and by how much the flow field is altered. Computational methods typically provide a limited amount of insight, depending on the accuracy of the geometry of the model, the assumptions built into the model, and the algorithm used to solve the governing equations. In contrast, dynamically similar models can potentially provide some of this missing information. Using PIV systems, an actual device (e.g., mechanical heart valve, total artificial heart, or stent) can be investigated within a dynamically similar environment. This suggests that

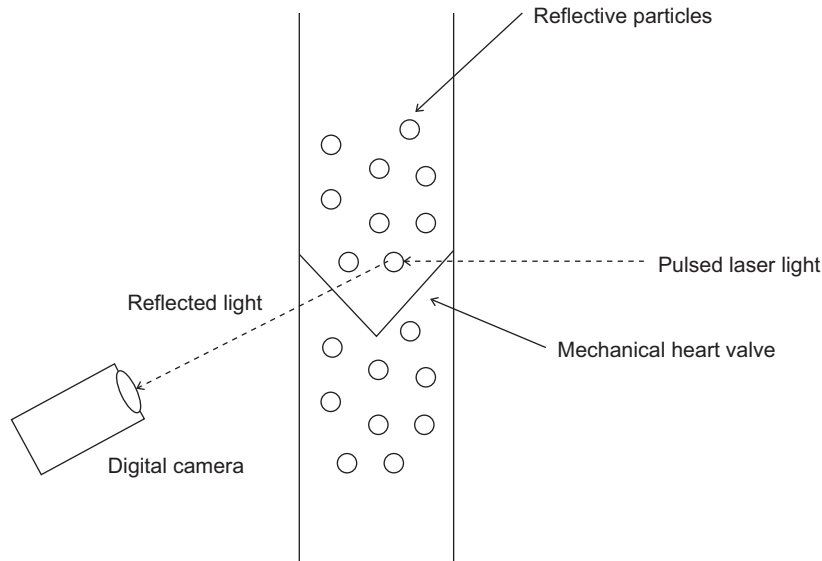


FIG. 16.1 Schematic of a typical particle imaging velocimetry (PIV) system that consists of a flow chamber (shown with a bileaflet mechanical heart valve inserted into the location of interest), a fluid seeded with reflective particles, a high-intensity laser light source, and a digital camera. Not shown is the computer system that would be coupled to both the laser and the camera to calculate particle velocities.

if a physical model can be fabricated with properties relevant to the actual flow conditions, a real device can be investigated within an environment that mimics the intended environment. For most cardiovascular in vitro simulations, it would be most appropriate to match the Reynolds number and the Womersley number to cardiovascular flow and the physical properties of the container to reach a dynamically similar solution (as discussed in Chapter 15).

There are a number of variations in PIV systems based on the incident light and/or the collection method. One of these methods, laser speckle velocimetry (LSV), makes use of the speckle pattern of particles suspended within the fluid instead of the reflective pattern as discussed previously for PIV. LSV is typically used when the exact velocity distribution is wanted at all locations within the fluid. The fluid is seeded with a high concentration of particles, whose reflected light would not be able to be distinguished by a PIV computer algorithm (and therefore the particles themselves could not be differentiated) coupled with a high-speed camera system and one particular bandwidth of incident light. For LSV, a coherent light source is used that generates a speckle pattern based on the interference of the particles. A coherent light source is needed so that the interference pattern is largely stable both over short time durations and spatial dimensions. This speckle pattern is collected by a digital camera, and more powerful computer processing techniques are needed to determine the flow profile based on this interference speckle pattern. This is typically used to model the movement of large solids, such as thromboemboli, through a dynamically similar system.

Another PIV technique, holographic PIV (or HPIV), is used to obtain a 3D velocity profile by collecting the particle location information on a hologram and then computationally

reconstructing this image. The advantage of HPIV systems is that a true 3D flow profile image can be obtained instead of projecting the 3D velocities onto a 2D plane. A more recent PIV technique can be used to investigate microflows, with the use of an epi-fluorescent microscope. Instead of using reflective particles, fluorescent particles are placed in the flow stream, and data are recorded through a camera coupled to an epi-fluorescent microscope. Fluorescent particles are useful because they excite at one particular wavelength of light and emit at a second wavelength of light. Through the use of appropriate filters, these wavelengths can be discerned precisely and all other wavelengths of light can be ignored. Also, common reflective particles are typically too large for studies on the microcirculation, but through the use of fluorescent molecules, clear and relevant images on a smaller scale can be obtained. A disadvantage of using a fluorescent source is that the fluorescence may overpower small features within the flow field.

16.2 Laser Doppler velocimetry

Laser Doppler velocimetry is primarily concerned with quantifying the microstructures of flows that are subjected to obstacles within the flow field (similar to PIV techniques). Direct measurements of the kinematics of the fluid motion can be obtained with this method. The benefit is that one can observe the smallest of flows surrounding these obstructions, which may not appear when imaging particles within a flow field. For laser Doppler velocimetry, the measurement of the fluid velocity is made at the intersection of two laser beams that are focused at a point of interest within the flow field. Laser light sources are required for this technique because the two beams must be monochromatic (one wavelength) and coherent, so that the intersecting beams can create an interference pattern. The interference pattern occurs within the fluid and is documented with a digital camera that is focused at the region of interest. Based on the wavelength of the incident beams and the angle between the two beams, fringe patterns would be formed with a spacing of

$$d = \frac{\lambda}{2\sin\left(\frac{\theta}{2}\right)} \quad (16.1)$$

where d is the fringe pattern spacing, λ is the wavelength of the laser light, and θ is the angle between the two laser beams (Fig. 16.2). As a particle moves through the laser beam area of intersection, scattered light will have a different intensity and different frequency compared with the normal fringe patterns. This new frequency (ω) is defined by the velocity of the particle and the fringe spacing as

$$\omega = \frac{v}{d} = \frac{2v\sin\left(\frac{\theta}{2}\right)}{\lambda} \quad (16.2)$$

where v is the velocity of the particle in the direction perpendicular to the fringe patterns. This frequency can be obtained by the Fourier transformation of the intensity signal acquired by a

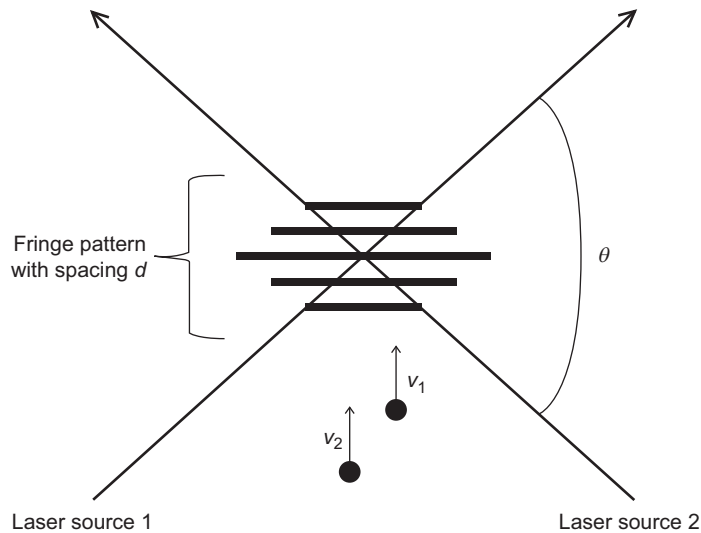


FIG. 16.2 Schematic of a laser Doppler system, with fringe patterns that are distorted by particles within the fluid. A digital camera (not shown) would be focused at a region of interest that contains the fringe patterns so that as particles distort the fringes, information can be obtained about the particle and fluid velocity. As shown in Eqs. 16.1 and 16.2, v is the velocity of individual particles entering the fringe pattern and θ is the angle between the two laser sources.

camera focused at the region of interest. By using a camera with a high frame rate, multiple particle velocities can be obtained and correlated by measuring the distortion at different subsequent fringes as the particle moves through the region of interest. Similar to PIV techniques, particles can be tracked through the flow field as they continually distort the flow pattern. In this way, various properties of the flow field can be obtained from the single experiments.

The only component of a laser Doppler system that may hinder the use of this technique is the size of the particles within the fluid. Small air bubbles and dust (present within the fluid) can be used to generate distortions within the fringe pattern, but they might not be present in a large enough quantity to obtain meaningful data. By overseeding particles within the fluid, it becomes difficult for the computer program to determine where the distortion is coming from because the particle distortions can be very large and may overlap. An ideal system would have 10 to 20 particles passing through the various portions of the fringe pattern at any instant in time (e.g., you do not want all of the particles at the center of the pattern, but distributed throughout the pattern). Additionally, the use of forward scattering techniques can collect the most data from the system, but this may not always be attainable based on the geometry or physical structure of the device of interest. Back- or side-scattered fringe patterns typically lose most of the information from the pattern because the intensity of these scatterings is not as large as forward scattering. However, with careful design one may be able to limit all of the shortcomings of the laser Doppler system and obtain meaningful data for the particular flow conditions.

An improvement over laser Doppler systems is a dynamic laser Doppler light-scattering velocimetry technique. Here, the total intensity of the scattered light is measured, as is the fringe pattern distortion. The intensity is typically averaged over time so that some of the

time-dependent fluctuations induced by differences in particle size, location, or scattering properties can be removed. Without going through all of the mathematical equations required to smooth the intensity signals of a distorted fringe pattern, this technique can provide a direct measurement of fluid velocities based on time-averaged values of scattered intensities. This is a better collection method than laser Doppler velocimetry, but it is more difficult to implement because of the cross-correlation needed between particles.

16.3 Flow chambers: parallel plate and cone-and-plate viscometry

Many cells that we have discussed so far in this textbook are subjected to shear stress in their natural environment (endothelial cells, epithelial cells, and all blood cells, among many other cell types). Therefore, there is a need for an accurate experimental technique that can be used to expose cells to precise physiological shear stresses. There are two types of flow chambers that are typically used in laboratories, and they are the parallel plate-based flow chambers and the viscometer-based flow chambers.

Parallel plate-based systems use a pressure gradient to drive the fluid motion through the system. The most commonly used is termed the *parallel plate flow chamber* (Fig. 16.3), which uses a driving force to push fluid through a rectangular channel. Cells can be cultured on the bottom surface of the flow chamber or can be seeded within the fluid itself. Typically, these devices are designed so that the velocity is fully developed (a parabolic profile) at the location where the cells will be subjected to shear. The wall shear stress can be approximated by the Poiseuille equation and is therefore only dependent on the inflow flow rate, the fluid viscosity, and the channel dimensions (thickness and potentially length). The advantage of this type of system is that cells can experience a particular shear stress (if adhered to the bottom plate) or can be subjected to varying shear stresses if they are in the fluid solution (similar to the in vivo conditions for blood cells). At the same time, the inflow rate can be temporally varying and thus, the cardiac waveforms, respiratory waveforms, or others can be simulated under these conditions.

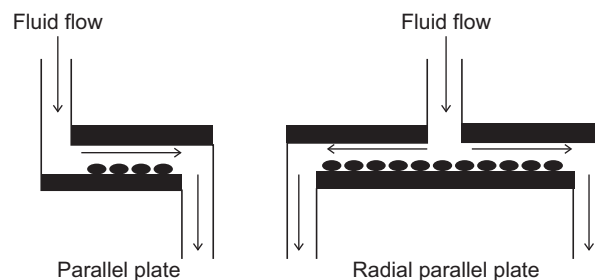


FIG. 16.3 Schematic of a parallel plate and a radial parallel plate system. In both of these systems, cells (shown as black ovals) can be adhered to the bottom of the plate or can be seeded within the fluid. The shear stress can be modulated based on the fluid properties and the channel dimensions, and therefore, many different physiological conditions can be investigated.

A slight modification of the parallel plate system is termed the *radial parallel plate flow chamber* (see Fig. 16.3). In this case, fluid flows into the system from an opening within the center of the plate, and it exits in all radial directions. The shear stress depends on the radial position and therefore is not constant for all cells that may be adhered to the bottom surface of the plate. The shear stress gradients need to be accounted for during data analysis techniques, and therefore, the data may not be as easy to report (e.g., one shear stress value) for cells adhered to the bottom surface in the parallel plate studies. It is typical in a radial flow chamber to use steady flow (instead of pulsatile), which simplifies the analysis slightly but definitely makes the waveform easier to report.

Viscometer-based systems are most commonly used to expose cells in solution (e.g., blood cells) to a uniform shear stress, meaning that the shear stress throughout the fluid has the same value. Cells can be grown on the bottom surface, but there is no advantage to this type of system compared with the parallel plate system for adherent cells. In these systems, the velocity profile is linear (not parabolic) because one of the constraining walls is moving whereas the other is held fixed. In cone-and-plate viscometry, a cone (the top plate) is rotated to generate the flow profile (Fig. 16.4). The cone has to have a small incident angle so that the velocity profile does not become disrupted (e.g., is no longer linear or turbulent) when the distance between the cone and the plate increases. The design of these systems is somewhat difficult because the angle between the flat plate and the cone (α in Fig. 16.4) is on the order of 0.5 to 1 degree and the spacing between the walls of the cone and the constraining cylinder needs to be equal to the maximum spacing between the cone and the plate. In these systems, the fluid velocity depends on the angular velocity of the cone, the cone angle, and the distance between the plate and the cone. The shear stress in these systems depends only on the viscosity, the angular velocity, and the cone angle, which are all typically held constant in experiments. However, the cone's angular velocity can be modulated to mimic transient waveforms. This is an advantage over parallel plate experiments, in which it is normally more difficult to control the fluid flow rate. Again, there could be a slight variation to this design, where the top disc would be parallel to the bottom plate. This is termed the *parallel disc viscometer*. The velocity is then dependent on the radial location, and the shear stress is no longer constant throughout the flow field. This arrangement is the least common of the methods discussed, because there is limited advantage to this system.

One advantage of the plate designs over the viscometer designs is that it is typically easier to design a plate system that is optically transparent. This would give the advantage of

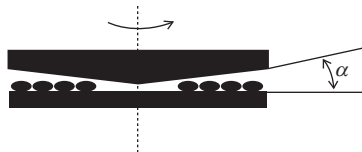


FIG. 16.4 Schematic of a cone-and-plate viscometer. In these systems, cells within the fluid would be subjected to a uniform shear stress, which depends only on the fluid viscosity and the angular rotation of the cone. This is the case if the angle between the cone and the plate remains small, so that the velocity profile is linear.

imaging the effects of the shear flow conditions on cells of interest in real time. In fact, many groups have fabricated a system in which the bottom portion of the chamber is composed of a glass coverslip so that (1) cells can be cultured on the “disposable” glass under normal cell culture conditions and then placed within the plate and (2) an objective of a microscope can be brought into close proximity to the coverslip. A viscometer-based system typically cannot include this component because the cone is directly attached to a motor or belt system, which would interfere with the optical path. Cells can be imaged after the shear exposure conditions in a viscometer system.

16.4 Lab-on-a-chip and lithography

As we have discussed in earlier sections of this text, many biological flow processes, including physiological and pathological flow conditions, occur at the microcirculation level. Although many of the previously described techniques can be applied to replicate or simulate the microcirculation, it has become common practice to make use of lab-on-a-chip type devices to more accurately model these flow conditions in laboratory settings. Additionally, lab-on-a-chip and the more recent organ-on-a-chip techniques can very accurately control flow conditions and can simulate/replicate many biological processes in a controlled and repeatable manner. It has been shown that a significant amount of information can be gained from these types of devices about biological processes that occur within the microcirculation. Furthermore, with careful design of the channels, the investigator can control the direction of flow, mixing, biological processes, time exposed to particular conditions of interest, and many other parameters. However, the production of these devices is somewhat labor intensive and require very precise processing parameters to ensure repeatable processing and therefore repeatable experimental conditions. The long-term success of these techniques and the products produced with these techniques will require advances in processing to ensure accurate device formation.

One of the most commonly used techniques to fabricate microchannel patterns to be used for *in vitro* microcirculation studies is photolithography. This technique uses optical methods to transfer a highly specific pattern (which can have dimensions on the order of microns to tens of microns, although the equipment used would need to be very precise and accurate, but it is typically more common to use patterns with larger dimensions) to a substrate. Lithography begins by choice of the substrate and then preparing the surface of that substrate for subsequent processing. Very-thin-sliced silicon wafers, with very-well-defined thickness, radius, and electrical properties (e.g., resistivity), have been commonly used as the substrate. The surface of the substrate is prepared by cleaning it to remove impurities and other common fouling agents. Cleaning with water, ammonium hydroxide, and hydrogen peroxide (the RCA cleaning technique) is a popular preparation technique (especially for silicon wafers) to ensure that the surface is prepared for subsequent techniques. Completing the RCA cleaning technique requires proper training, knowledge of the process, and safety equipment; do not undertake this technique if you are unsure about any of the steps. After this first wash, the RCA cleaning technique calls for a second wash (in water, hydrochloric acid, and hydrogen peroxide; again, do not

undertake this cleaning without proper training and knowledge of the risks associated with the chemicals used). Cleaned wafers are generally dried under a noble gas stream (such as argon) and are typically either stored under sterile conditions or used immediately.

Once the substrate is cleaned (note that the substrate does not need to be cleaned with the RCA technique), it can be coated with a photo-active polymer, termed the *photoresist*. A process termed *spin coating* is generally used to apply the photoresist to the substrate at a uniform thickness. The thickness of the photoresist is critical as a nonuniform photoresist thickness will alter the patterning steps. Furthermore, if the photoresist will be used as a stamp, an uneven thickness will change the pattern transfer steps. Finally, if the resist is too thick or too thin, this may alter the exposure procedures that will be needed. There are two types of photoresists that can be used depending on the sensitivity of the polymer to exposed light. Polymers that have chemical bonds that break down under light exposure are termed *positive photoresists*, whereas those that form additional bonds under light exposure are termed *negative photoresists*. After spin coating, the photoresist is soft-baked, which both removes the organic solvent(s) from the photoresist and also increases the efficiency by which the photoresist can absorb energy from light.

At this point, the photoresist is ready to be exposed to a light source (typically ultraviolet radiation) to begin the process of patterning. The prepared substrate with soft-baked photoresist is aligned under a light source, and a mask (which has the pattern that you would like to transfer to the photoresist) is placed between the light source and the substrate. The design of the mask is based on the particular needs of the channel and can be very simple (e.g., a straight channel with uniform dimensions) or highly complex, with many interconnecting channels of various dimensions. On exposure to light radiation, chemical bonds within the photoresist will either break down (positive resists) or form (negative resists). After exposure to light radiation, the substrate and resist are baked a second time (this is termed the *postexposure bake*), which further improves certain sections of the photoresist's ability to withstand degradation by chemical means. For a positive resist, the sections not exposed to light radiation would be improved by the postexposure bake, whereas for a negative resist, the section exposed to light radiation would be improved by the postexposure bake step. At this point, the photoresist is exposed to a chemical developer, which removes the sections exposed to light radiation (positive photoresist) or those not exposed to light radiation (negative photoresist). The substrate may be exposed to a last baking step (typically termed the *hard-bake*) that improves the strength of the remaining photoresist.

At this point, the substrate with patterned photoresist can be cleaned and kept under sterile conditions for later use. In many applications, these patterned substrates are further used as a mold for soft-lithography techniques. Soft-lithography typically makes use of a pourable curable polymer (such as polydimethylsiloxane, PDMS) to make a positive mold from the negative patterned substrate. PDMS (mixed at a particular ratio of the elastomer base to the elastomer curing agent) can be poured over the negative patterned substrate and then baked to accelerate the curing of the polymer. Once fully cured, the PDMS can be peeled off of the substrate. The patterns are replicated with high fidelity through this process; furthermore, with one accurate mold, many positive polymer substrates can be made. These positive molds can be sealed with a mirror-imaged mold or glass or various other methods to make a channel through which fluid can flow. The complexity of these microfluidic channels can be as sophisticated as deemed by the need of the experiment.

There are many examples of these types of systems used for biological applications. Furthermore, numerous companies have positioned themselves in the field of making customizable microfluidic devices for biological applications. Some of these systems also integrate mechanical, chemical, electrical, or biological cues to govern the function of the device. These normally include some sensing element, which we will not discuss here, that can transduce a change in function in the fluid domain. Instead we will focus the remainder of this section on three examples of microfluidic devices that have been used in biological applications.

One of the first microfluidic devices that was used for biological purposes was used to deliver therapeutics and monitor some biological response to the therapeutic to dictate how much of the therapeutic was delivered and whether this delivery was sufficient or in excess. These devices are typically much more complicated than the simple structures that we have described thus far because they involve piezoelectric pumps, actuators, and sensors to control the flow through the channel. Without going into the details of these systems, because they are beyond the scope of this discussion, it is important to note that these systems tend to control the flow rate very accurately within a certain range of pressures. These types of delivery systems have also been shown to have response times that are on the order of milliseconds (approximately 50 to 200 msec). As the complexity of the system increases, valves can be included to more accurately control the flow. A good example of this type of system is an insulin pump system. This system mimics the actions of the pancreas and has the ability to sense glucose in the bloodstream. Depending on the plasma glucose concentration, the system will release insulin in a controlled manner. These devices have been in use for decades, and it is important to point out that they must monitor blood glucose concentrations 24 hours a day every day.

In more of a laboratory setting, microfluidic devices have been used to more accurately control and monitor chemical reactions, kinetic reactions, diffusion of biopolymers, effect of external physical cues on biological processes, effects of flow on biological processes, etc. For kinetic reactions, the rate at which the enzyme and substrate are exposed to each other can be very accurately controlled and monitored on this small scale. Real-time monitoring of reactant formation also can be monitored relatively easily. The effects of temperature, pressure, exposure to shear flow, etc. can all be included within the experimental variable and monitored in terms of number of products formed. Microfluidic systems can also act as small-scale bioreactors to observe how chemicals react, mix, or affect other processes. These bioreactors also can be used to monitor consecutive reactions in which the products of reaction 1 become mixed with a second set of reactants to form a second set of products. Cells or biological compounds can be seeded into the channel to monitor processes of biological importance. As one can imagine, the use of these devices can be extended to very different applications both in the biological context and outside of biological applications. The importance of their usage is that the flow conditions can be precisely controlled to accurately control how the molecules in the flow field react with each other. With the added control on temperature and pressure and the proven use of these devices as drug delivery systems (as briefly described for insulin), these types of devices have become very popular tools for studying and modulating biological processes.

16.5 Current state of the art for biofluid mechanics *in vitro* research

As with the previous chapter, in which we focused on a very small subset of computational research techniques that are commonly used by biofluid mechanics research teams, we will only highlight some of the current research topics being investigated using common *in vitro* techniques. Because there are many techniques and many studies being conducted in this field, it would be difficult to provide a comprehensive overview of the research field, but instead we invite the reader to conduct literature searches in the areas of research that interest them.

As we discussed earlier, the benefits of PIV are that scaled models can be fabricated and, by using dynamically similar flow conditions, the flow field about these models can be investigated and documented. In parallel to these studies, blood can be used in the dynamically similar models and the effects of the documented flow fields on blood functions (inflammation, thrombosis, hemolysis, etc.) can be investigated. One of the current major areas of research for velocimetry techniques is understanding the flow patterns around obstructions or disease conditions using patient-specific geometries. The advantage of patient-specific models is that the researcher can focus on the effects of flow in one patient and try to predict specific outcomes for that patient. Few to no assumptions about the geometrical profile need to be made when using these models (non-patient-specific models would need to use averaged or assumed values for the geometry, and many geometries of interest to biofluid mechanics researchers are quite complex). A downside of patient-specific models is that translating these predictive models to a clinical setting may be difficult (with the current state of the technology) because each patient would need to go through the imaging procedures and then the 3D geometrical model would need to be constructed and used for velocimetry experiments for each patient. The modeling, the fabrication of the model, and conducting the experiments may take a significant amount of time, and this may prove to be too laborious for clinical adoption. In some instances, patients are in a critical condition and would need immediate attention, whereas under other conditions, a patient presenting with mild conditions may be able to wait for the experiment time. However, a similar or analogous technique that does not have the same time constraint as these techniques may be applied to clinical applications. With that said, patient-specific models can provide some information that can be translated between different patients.

Regardless of the limitations of these models, many researchers are using these techniques to evaluate existing biofluid implantable devices (especially cardiovascular devices) in assumed or patient-specific geometries. For instance, the effects of carotid artery stenosis severity on plaque formation and shear stress levels has been evaluated by a number of research teams. Other groups have evaluated the microrheological changes of the extracellular matrix when a tumor is present. In addition, flow through the normal and dysfunctional heart, unstented and stented aneurysms, and the ability of cells to pass between different cellular aggregates have all been investigated with velocimetry techniques. The purpose of highlighting these varying fields is to illustrate that many of the biofluid mechanics topics that we have discussed can be evaluated with velocimetry techniques. The different biofluid mechanics topics that have been evaluated with PIV techniques illustrate the ability for PIV to evaluate different length and time scales, when one carefully considers the model parameters.

Laser Doppler velocimetry has become more popular than many of the other PIV techniques because this technique can be applied to living patients and animals. Although we will not discuss these techniques at this time, one can imagine the usefulness of monitoring flow conditions under their innate conditions. Similar to PIV techniques, uses for Doppler velocimetry techniques have included patient-specific geometries and the implantation of biofluid mechanics devices. As with PIV techniques, the goal would be to understand the flow conditions near these high-risk areas and potentially predict the occurrence of future events. Similar shortcomings of fabricating a model would be applicable to Doppler techniques; however, because this technique can be used with a living patient, some of the intrinsic challenges associated with fabricating a model may be overcome. The computations associated with the prediction ability of the measurements may still reduce the overall applicability of this technique. Many areas of research that are currently under investigation with PIV techniques are also being investigated with Doppler velocimetry techniques. Thus, we will not reiterate these areas but include some references that readers can review at their leisure.

Both parallel plate flow chamber systems and cone-and-plate viscometry systems have allowed biofluid mechanics researchers to evaluate the behavior of cells to precisely controlled flow fields. Major advantages of this system are that the flow field can be precisely controlled and the behavior of cells can be monitored in real time (or near real time). However, disadvantages stem from the ability to machine precise parts (e.g., with slight variations in the cone geometry the flow field can be significantly altered from what we would expect) and the limitations on the motor response times (e.g., motors with very fast response times may be too costly for these systems). In addition, in some instances, the programmed waveforms may have assumptions built into them. For instance, the waveforms may come from a numerical model or some other experimentally obtained scenario that will have its own intrinsic limitations.

Even though there are some intrinsic limitations to the use of flow chamber-based systems, the information they provide on the basic biological processes of cells under flow conditions is invaluable. Many groups use these systems to determine the effects of flow condition on many cellular responses or flow conditions coupled with other risk factors on these same cellular responses (e.g., our group has added tobacco smoke to the perfusate as a means to model a cardiovascular risk factor exposure). Under these conditions, it is possible to evaluate how these systems alter the physiological response of cells. It will be quite difficult to list all of these research areas succinctly because there are many widely varying avenues of research. A quick Internet search (with particular keywords of interest) can help the reader find topics of interest. Some areas of research include evaluating the genetic profile of a particular cell under shear flow, the proteomic profile of a particular cell under shear flow, how multiple cells interact under shear flow, kinetic reaction rates under flow, adhesion and migration of particular cells under shear flow, or biocompatibility of new devices under flow conditions. In parallel, disease progression can be monitored, disease conditions can be simulated, or new therapeutics can be evaluated under shear flow. A major benefit of these techniques is that users can evaluate a system from many different standpoints while using the same exposure conditions. Cells can be sampled over time (up to days of shearing) to observe how they respond and adapt to altered loading conditions.

16.6 Future directions of biofluid mechanics *in vitro* research

As with the previous chapter, we will discuss here some possible future directions in biofluid mechanics research using *in vitro* techniques. The authors are not trying to suggest that these are the only avenues of research or the only important avenues of research; rather, we are attempting to generalize some salient areas of research that may be or should be addressed in the near future. In the author's opinion, one of the major current limitations of *in vitro* biofluid mechanics research is in the availability of models that mimic multiple realistic physiological conditions. For instance, we have focused our discussion in [Section 16.4](#) mostly on current models that use patient-specific geometries and/or patient-specific flow waveforms. This has provided the biofluid mechanics community with a significant amount of insight into the pathophysiology of diseases and the overall effect of shear flow on cellular responses; however, other physical, biochemical, and/or mechanical factors can be included within the experiments to more accurately simulate the disease conditions.

For instance, most of the techniques that we have discussed in this chapter make use of "rigid" wall containers or containing vessels with wall mechanical properties that are drastically different from those of biological tissue. For groups that are investigating the progression of atherosclerotic plaques or aneurysms, it would be beneficial for them to simulate the blood vessel wall mechanical properties within their measurements. It is especially important to simulate wall mechanical properties for these two diseases, because the blood vessel wall becomes more rigid during atherosclerotic processes and less rigid during the progression of an aneurysm. These mechanical changes are likely to elicit changes in the flow conditions around these pathologic conditions and may even alter the cellular responses of vascular smooth muscle cells and endothelial cells that reside within/along the vessel wall. If these mechanical properties can be incorporated into PIV techniques, it would be possible to obtain more realistic flow patterns and waveforms around these pathologic conditions. These more realistic waveforms could then be used in other experiments, such as viscometry techniques, so that a better understanding of the basic biology can be obtained.

As for parallel plate and viscometry techniques, a major hurdle to these experiments is not only the mechanical properties of the channel wall but also the relevance of the fluid that is perfused throughout the device. In many instances, biofluid mechanics research groups make use of a standard cell culture media or a physiological salt solution as the perfusate. Although this is beneficial from the standpoint of controlling experiments and/or consistency within experimental conditions, this type of perfusate does not match the physiology well. It may be more relevant to include blood cells within the perfusate (if simulating cardiovascular conditions), air particles (if simulating respiratory conditions), cytokines, risk factors, and hormones, among many other biological relevant chemicals. This may complicate the experimental conditions and make the data analysis more challenging, but the information garnered from studies such as these may be more accurate when modeling biofluid mechanics conditions.

Parallel plate and other viscometry techniques would also benefit from mechanical/flow conditions that are more physiologically relevant, as discussed for velocimetry techniques. Studies on the effects of altered fluid mechanics on flow would be more relevant under these simulated conditions instead of under steady flow or rigid channel conditions. However, the

challenge with altering these properties would be in the design of a system that can maintain the precisely controlled flow fields while allowing for some flexibility in the container. Systems are being developed that allow this flexibility, and the use of these systems in future biomedical work will result in significant progress in the field of biofluid mechanics research.

Summary

- 16.1** PIV is a computer-based technique that tracks a sequence of reflective particles through a flow chamber. A computer program is used to control a high-intensity light source (normally a laser) and correlate the data obtained regarding the movement of particles through the fluid. Based on the known particle displacement and camera frame rate, it is possible to obtain the velocity of the particles seeded within the fluid. Through the use of multiple cameras, true three-dimensional velocity fields can be obtained. Laser speckle velocimetry (LSV) and holographic particle imaging velocimetry (PIV) are more specialized PIV systems.
- 16.2.** Laser Doppler velocimetry is used to quantify the microstructures of flows. Two monochromatic light sources are focused at a region of interest, and this forms a fringe pattern that is based on the fluid velocity. By seeding particles within the fluid, the fringe pattern changes, based on

$$\omega = \frac{v}{d} = \frac{2v \sin\left(\frac{\theta}{2}\right)}{\lambda}$$

and this is the information that can be collected by the digital camera. Most laser Doppler systems have the intrinsic problem of transient fluctuations in the fluid properties, caused by imperfections in the experimental system, which can confound the results. By using a dynamic time-averaging system, these transient changes can be smoothed.

- 16.3.** Flow chambers are used to subject cells to particular shear stresses. Through the particular design of the chamber, cells can be subjected either to uniform stresses along the walls of the chamber or to varying stresses. It is most common to use either a parallel plate system or a cone-and-plate viscometer system to model physiological conditions *in vitro*.
- 16.4.** Many laboratories have turned to lithographic methods to accurately fabricate small channels that can be used to study various biofluid phenomena. For instance, highly accurate flow profiles, chemical compositions, or transition times can be applied to cells flowing through these channels. The design of these systems can be very complicated or very simple depending on the need of the experiment; however, it is cautioned that the replicability of these channels must be investigated during the fabrication stages such that the repeatability of the experiments be accurate.
- 16.5.** The current state of the art for biofluid mechanics research is primarily focused on obtaining realistic geometries for velocimetry techniques. These patient-specific

geometries would be helpful in obtaining a predictive model; however, the applicability of these solutions to the clinical needs must be addressed before their use. Viscometry techniques are primarily used to determine the basic biological process that underlies pathological events and/or how shear flow alters cell behavior. One of the shortcomings of each of these techniques is that although groups are aiming to increase the relevance of these models, technological limitations still exist that prevent physiologically relevant model fabrication, with considerations on multiple biochemical and biophysical properties.

- 16.6.** In the author's opinion, future efforts in in vitro biofluid mechanics research should focus on fabricating models that are more relevant to the physiological conditions. For instance, incorporating materials that simulate the mechanical properties of the biological tissue would help increase the accuracy of the models. Similarly, the addition of biologically relevant and active compounds to the perfusate that are similar to the particular flow conditions would help researchers to understand the basic biology of the particular process.

Homework Problems

- 16.1.** Compose a small algorithm that can be used to quantify approximately 10 particle velocities, within subsequent digital images, for a PIV system.
- 16.2.** In a laser Doppler system, two monochromatic laser light sources are placed 80 degrees apart. The wavelength of light emitted from these two lasers is 540 nm. Calculate the normal fringe spacing for these laser light sources and the anticipated change in frequency if a particle intersects the laser at a velocity of 20 mm/s. If the light sources are changed to a laser that emits at 650 nm, how does this affect the calculations?
- 16.3.** Using the Navier–Stokes equations, model the flow through a parallel plate flow chamber and a cone-and-plate viscometer. Assume that the parallel plate is only under pressure-driven flow $\left(\frac{\partial p}{\partial x}\right)$, the channel height is h , and that the fluid viscosity is μ .
The cone-and-plate has a radius of r , an angle of α (assumed to be small), and an angular velocity of ω . Gravity can be neglected for both systems.
- 16.4.** Discuss a possible redesign of a flow chamber that can be used to model physiological flows within the microcirculation.

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In vivo biofluid mechanics*

LEARNING OUTCOMES

- Discuss the need and use of live animal preparations in biofluid mechanics
- Describe the necessary components of an intravital microscopy system
- Explain the use of Doppler ultrasound technology
- Calculate the apparent Doppler frequency shift
- Discuss magnetic resonance imaging techniques
- Understand the basic physics behind magnetic resonance imaging
- Discuss current work and future trends related to *in vivo* biofluid mechanics research

17.1 Live animal preparations

Although a great deal of information can be learned from *in vitro* experiments, *in vivo* studies may provide the closest, most accurate, and most relevant models for researchers to understand what occurs under undisturbed physiological conditions. We make this distinction between disturbed conditions and undisturbed conditions because we will focus this section on intravital microscopy, which is a technique in which a vascular bed is dissected out of the animal, but it remains connected to the feeding vessels, nerve cells, musculature, and other biological structures. Therefore, the vascular system under investigation (usually from muscle tissue) is still under physiological regulation (e.g., nervous, hormonal), but there may be some other unanticipated factors that alter the flow through the vascular bed that stems from the dissection procedures or handling procedures. For these experiments, animals are placed under anesthesia to allow for the researcher to dissect the

*This chapter is considered advanced and can be skipped without a loss of continuity

tissue, and then comprehensive observations of changes within the flow conditions can be made throughout the dissected tissue (these changes can be induced by various mechanical, chemical, pharmacological, or other stimuli). Traditional intravital microscopy uses the mesenteric capillary beds or various skeletal muscle capillary beds to observe changes in flow under various conditions of interest. These capillary beds are used because it is relatively easy to access the tissue and the tissue is relatively thin and transparent, allowing for optical microscopes in conjunction with recording equipment to be used to document the flow through the vascular bed. However, many other capillary beds can be used for intravital microscopy techniques as long as the preparations can be made from a thin section of tissue to allow for enough light to pass through the tissue.

When these preparations are being observed on the microscope stage, various conditions can be investigated to determine the effects of these conditions on flow properties, vascular tone, or blood cell motion. For instance, various agonists can be added to the tissue perfusate, which is used to keep the tissue moist during the experiments, to determine how the addition of a compound to the entire vascular network affects that vascular bed (e.g., flow through it, communication along it). For clarification, this perfusate bathes the entire dissected tissue so that it does not dry out, and thus any effect that the agonist induces would potentially alter the entire vascular structures. In some regards, this type of measurement provides a measure of a global effect of the compound, but not all compounds are released in sufficient concentrations to alter the entire network physiology or not all locations within the vascular bed can respond to particular agonists. A modification of this approach uses micropipettes. Under these conditions a micropipette can be used to localize the injection of or exposure to agonists to determine the endothelial cell communication throughout the vascular network and how that communication affects flow conditions, among many other properties (e.g., the function of vascular smooth muscle cells in slightly larger vessels). Micropipette techniques may provide more accurate measurements of physiological changes but induce some technical difficulties when trying to ensure that the same location is antagonized in multiple trials (e.g., with different concentrations, or with different agonists). Changes in the vascular network, such as vessel diameter, flow rate, and cell volume, can be investigated with intravital microscopy. Therefore, there are many possible outcomes for this type of research and many different research avenues.

The information that has been collected from intravital microscopy has improved significantly with better optics, better optical techniques, better cameras, and better antibodies/fluorescent probes (targeting, longevity, and optical properties). Better optics/cameras have allowed the researchers to target smaller capillary bed segments and small blood vessels more accurately. The use of better antibodies/fluorescent markers has allowed researchers to target specific compounds, specific cell receptors, and other indicators to understand the changes that occur within the vascular bed down to the molecular level. As an example, many cellular processes are regulated by the movement of calcium through a single endothelial cell and subsequently by the calcium and other ion movement through gap junctions connecting neighboring endothelial cells. By using fluorescent markers that can target intracellular calcium compartments and/or intracellular calcium signaling molecules, intravital microscopy can investigate physiological and pathological events instead of just physical parameters of the vascular bed. In addition, signal transduction pathways, gene regulatory proteins, and many other processes that occur during the regulation and control

of gene expression can be observed. How the gene expression relates to physical changes also can be observed. For instance, changes in blood cell flux, hematocrit, and blood pressure can all be related to intracellular ion concentrations, and the expression of cell membrane-bound receptors. Also, the adhesion/rolling of white blood cells onto the endothelial cell membrane and how this relates to disease processes and the expression of cytokines can be investigated with intravital microscopy. Therefore, many physiological and pathological conditions such as ischemia/reperfusion, inflammatory responses, endothelial cell barrier integrity, graft success, and nutrient delivery can be investigated with this technique.

A standard intravital microscopy apparatus (Fig. 17.1) consists of an epi-fluorescence upright (or inverted) microscope, which is connected to a camera, and then feeds directly into a recording device and a live video monitor. A perfusion system is needed to keep the tissue moist during the experiment. An anesthesia control system is needed to make sure that the animal is kept under anesthetic during the entire experiment, which can last up to 6 to 8 hours. When conducting intravital microscopy studies, it is critical to choose anesthetics that do not alter vascular properties, otherwise there may be confounding variables altering the collected data. A micropipette system can be used to locally inject antagonists within the vascular bed, or they can be injected by the perfusate. Data collected from this apparatus are typically fed into an image analysis system, which can be used to accurately quantify the data of interest from the experiment. It is critical that these systems are integrated properly and the technicians are well trained so that they can collect and analyze the data correctly. Remember that a poorly trained technician can alter the results during the dissection or data collection, simply because of inconsistency within the employed technique.

Intravital microscopy is a very powerful research tool to investigate changes to vascular networks under multiple conditions. The importance of this method is that the vascular network that is under investigation remains connected to the animal and is under

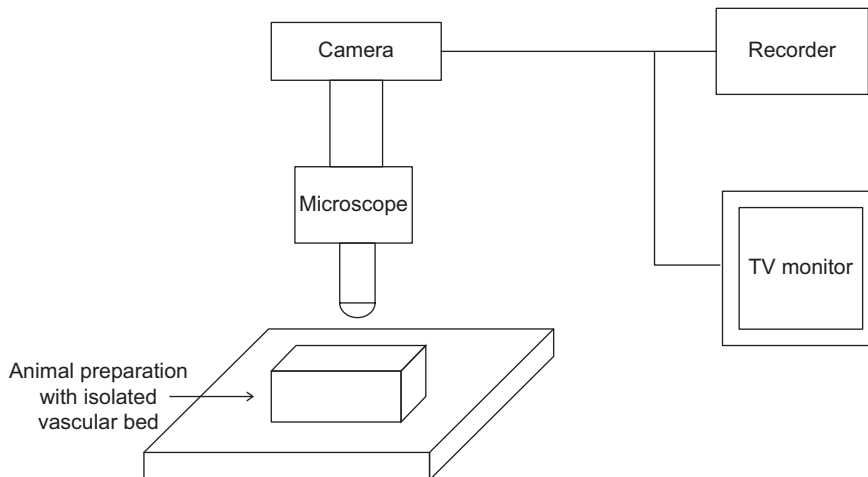


FIG. 17.1 Schematic of a typical intravital microscopy system. The key parameters are the microscope, which is coupled to a live-feed imaging system, and a real-time data acquisition component. Intravital microscopy can be used to monitor disease progression, therapeutic efficacy, clearance, and distribution of blood cells within the microvasculature.

physiological regulation from the animal. Many groups use this technique to understand the development of diseases and fundamental vascular physiology because, as described earlier, various conditions can be applied to the entire tissue or locally to individual cells. Other benefits of this approach are that relatively long *in vivo* effects can be monitored because the animal preparation can be maintained for at least 6 hours. Therefore clearance of new therapeutics can be investigated in tandem with the local effects of the therapeutic agent. Therefore, this technique has applications in not only basic biology of the microcirculation but also the design of drugs, implantable devices, and anything that may come into contact with or interact with the vascular system.

17.2 Doppler ultrasound

Before we discuss the Doppler mode associated with ultrasound image acquisition, we will discuss the general procedures involved in three-dimensional (3D) ultrasound technology. The first device necessary to acquire ultrasound images is the ultrasound scanner, which is used to emit and collect sound waves aimed at specific tissue locations. Standard probes are equipped with a transducer that emits a frequency in the range of 1 to 10 MHz. Ultrasound technology also requires the use of an electromagnetic position and an orientation measurement device, which normally consists of a component that is located within the examination table and a second component located within the ultrasound probe. This device records the spatial location of the probe in relation to the fixed examination table position. The angle of the probe in relation to the fixed axis is also recorded by this device, because an ultrasound probe has 6 degrees of freedom, and an accurate distance and angle of incidence are needed to analyze the data properly. By sweeping the ultrasound probe over a tissue bed, multiple images can be obtained to observe the tissue from different locations. The importance of these locators cannot be understated; they are analogous to multiple satellites being put into use to triangulate the location of a device (e.g., a global positioning system). If these devices are not calibrated properly, the recordings and information obtained will not be accurate.

Multiple imaging modes can be used in conjunction with the ultrasound probe. The one of most interest to this textbook is the Doppler mode, which can obtain a significant amount of information about the flow of blood through vascular networks that are located relatively close to the skin. Doppler ultrasound technology takes advantage of the apparent change in the ultrasound frequency caused by the velocity of blood and the incident angle of the sound wave in relationship to the blood vessel (Fig. 17.2). The apparent frequency shift can be calculated from

$$f_D = \frac{2vf_0}{c} \cos(\theta) \quad (17.1)$$

where f_D is the recorded Doppler frequency, v is the blood velocity, c is the speed of sound, θ is the angle between the ultrasound probe and the blood vessel, and f_0 is the emitted frequency from the probe. Since the blood velocity is variable based on the radial position within the blood vessel (spatial variation) and the pulsatile nature of blood (temporal

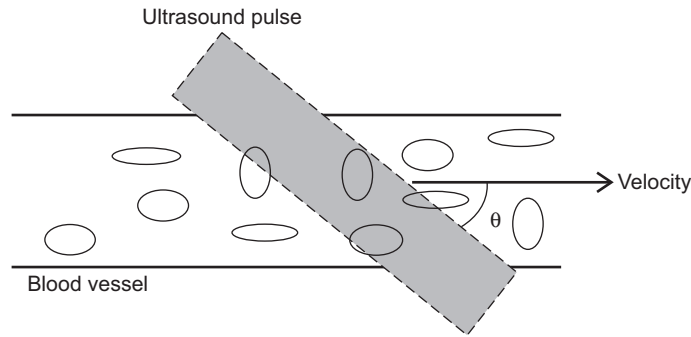


FIG. 17.2 Doppler ultrasound wave intersecting with a blood vessel. Based on the apparent shift of the ultrasound frequency, one can obtain information about the blood velocity. This shift occurs because of the reflection of sound waves after contact with blood particles.

variation), the recorded frequency is variable. Therefore, a spatially and temporally varying velocity distribution can be obtained if the receiving equipment is sensitive enough to differentiate between these small changes in frequency within a small blood vessel. An additional software component to the general Doppler ultrasound technique is the use of the color flow imaging module. This add-on module can color-code the blood velocity, providing a real-time depiction of the relative blood flow speed across the radial direction of a blood vessel and the direction of the blood flow. Color Doppler scans are normally obtained in conjunction with the spectral Doppler mode (also known as the duplex *Doppler mode*). Using the spectral Doppler mode, images can obtain a time-dependent mean velocity waveform over a small section of the blood vessel. Therefore, one can determine whether there are temporal shifts within the blood flow of that vessel. The usefulness of this technique is that the blood velocity can be compared between vessels of similar sizes. This would help determine whether regions are not obtaining enough blood, potentially resulting from a partially blocked vessel upstream of the imaging location or other existing pathologies. Additionally, these techniques can be applied to both humans and animals, and thus, the effects of therapeutic agents on the flow through vascular networks among other changes can be observed. Finally, Doppler ultrasound is useful to quantify the frequency of emboli or other large particulate matter by recording high-magnitude transient changes to the velocity profile. These high-magnitude changes occur only when there is a large shift in the velocity that is generated by a “rigid” material flowing through the velocity field.

Doppler ultrasound has proven to be a good research tool to characterize the potential for new cardiovascular devices to induce thromboemboli within the cardiovascular system. These new devices can be implanted into an animal, and after postoperative recovery the generation of high-intensity transient events can be compared with the generation of these events before implantation to determine whether this device induces significant new emboli formation. The ultrasound probe is noninvasive, so it is also possible to investigate the changes in emboli formation months to years after implantation. A good example of this application is the transcranial Doppler ultrasound system, which is often used to record high-intensity transient Doppler signals (HITS) in human patients or large animals (such as sheep). HITS are usually induced by microemboli, which can generate a high-pitched sound, different from

the sounds the blood flow normally makes and different from the normal particle matter within the blood. The duration of HITS is usually less than 50 ms, and the amplitude of HITS is usually much higher than the background blood flow signal. Based on the velocity and duration of HITS, the nature of the microemboli, for example, particle emboli (more dangerous to patients) or gaseous emboli, can be distinguished. Again, this is based on the relative size of the particle relative to the size of the blood vessel.

Another major use for ultrasound technology is to obtain vascular architectures. The advantage of ultrasound technology is that it has a low cost, is not harmful and is noninvasive, and has the ability to carry out real-time imaging and the ability to obtain flow information at the same time as geometry information. This capability makes it possible to form a feedback loop for calculating the flow through real geometries and validating the flow calculations with the ultrasound recordings. The disadvantage of this technique is that most ultrasound probes have a limited scanning depth (at larger depths, the resolution decreases) that restricts the usage of this technique to superficial blood vessels, such as the carotid arteries, which are critical blood vessels related to brain perfusion, or capillaries in the skin, which are typically not considered to be critical blood vessels for pathological disease progression. However, if an ultrasound probe can be inserted into the body, deep blood vessels or perfusion through tissue can be assessed in real time. A good example is the transesophageal echocardiography. With this technique, an ultrasound probe is inserted into an animal (or human patient) through the mouth and passed into the esophagus. By using this technique, a technician/physician can place a probe close to the aortic root and, importantly, the aortic valve. Short-axis and long-axis views of the aortic valve and the left ventricle can be obtained, and therefore the diameter of the aortic root can be determined. Meanwhile, the pressure gradient across the aortic valve, blood flow velocity, and other fluid properties can be calculated. By adjusting the location and angle of the probe head, information about the left ventricle and right atrium can be obtained as well. Actually, transesophageal echocardiography is often used in patients before a heart valve replacement surgery, to determine the size of the original heart valve (before the surgical intervention) and local blood flow conditions. The risks of using a transesophageal probe are relatively low; however, the usage of this type of imaging modality for different locations and pathologic conditions is somewhat limited.

Commonly, ultrasound measurements are carried out under the brightness mode (B-mode), which renders a 2D image of the blood vessel, where the intensity could be correlated to the blood velocity. Based on the brightness mode imaging, 3D ultrasound images also can be obtained, as the ultrasound probe is normally small and handheld. 3D images can be obtained by moving the probe in relation to the imaging location. This set of 2D brightness mode images then can be reconstructed into a 3D image. A few groups have investigated the use of this technique to obtain information about blood vessel architecture and the flow through these blood vessels, and they all found that it was necessary to either have a precise computer-controlled mechanism to maneuver the probe or an accurate monitoring system for the probe location in relation to the imaging area. This has proved to be relatively difficult to carry out, but the information gained from obtaining ultrasound images from different orientations has proved to be beneficial. Additionally, the amount of noise associated with the image is reduced by overlaying and reconstructing images from multiple directions. Therefore one clearer image can be obtained from the same location. However, most 3D work has not been conducted on imaging the vascular system. Instead, there has been a large

population that has investigated the use of 3D ultrasound techniques in imaging the heart motion, including heart valve motion.

17.3 Phase contrast magnetic resonance imaging

We will briefly discuss standard magnetic resonance imaging (MRI) to highlight the general technique employed for this image acquisition mode, before we move to phase contrast MRI. MRI has been successful in imaging the entire human body because the body has a very high water content (approximately 60% of the total body weight is from water). Hydrogen atoms have a single proton in their nucleus that spins continually. As this proton spins, a small magnetic field is created about the atom. The basis of MRI is to place the water ions in a large static magnetic field, which aligns all of the water molecules within the body. When the magnetic field is removed, how rapidly the water molecules return to their “normal” spin state is quantified and can provide a great deal of information about the tissue composition. Two magnetic fields are generated as the water molecules move back toward their “normal” positions, and those two magnetic fields provide information on the thermal tissue properties (longitudinal field) and the tissue inhomogeneities (transverse field).

A magnetic field can be generated in several ways to affect the atomic structure of water. Two easy ways to form a magnetic field are either by driving a current through a wire or by applying a voltage field across a magnet. No matter how the magnetic field is generated, there are a few important measurable effects on the atomic structure that concern MRI. The first is the spin state of the electrons. Electrons generate their own small magnetic field that can be measured, and this relates to the energy required to change the electron spin state. This transformation energy is

$$\Delta E = h\nu \quad (17.2)$$

where ΔE is the change in energy, h is Planck’s constant, and ν is the orbital frequency of the electron, which is equal to

$$\nu = \frac{\gamma B_0}{\pi} \quad (17.3)$$

where γ is the magnetic ratio and B_0 is the applied magnetic field. The magnetic ratio for the hydrogen isotope most often used in MRI measurements is 42.58 MHz/tesla (T), which is reasonable to measure within an MRI electric field less than 4 T.

The second atomic parameter that is commonly measured during MRI is the precession of the atoms. In a stationary 2D magnetic field (e.g., x – y plane), it is common for an electron to spin along the z -axis. This is very difficult to measure, and therefore, a magnetic force is applied to the substrate that pushes the electron to spin off the z -axis and into the x – y plane (it is possible to have three rotational directions, but for illustration we use the 2D example). This downward spiraling orbit is termed the *precession of the electron*. To induce electron precession, a temporal magnetic field is applied perpendicular to the z -axis. This causes the net electron magnetic field to precess at angle ϕ from the z -axis. By measuring the change in the

direction of the magnetic field and the time for the magnetic field to return to an aligned state, information about the tissue composition can be obtained.

There are a few major components to an MRI system, including a superconducting magnet, surface coils that can induce a transient magnetic field (to investigate precession), and data collection and analysis components. The superconducting magnet is used to generate a static magnetic field within the interior of the MRI system. This static magnetic field is used to align all of the atoms within a certain axis. This static field is normally around 3 T, although both stronger and weaker magnetic fields do exist and can be used. With a higher magnetic field strength the resolution of the image increases. The surface coils use transient magnetic fields, typically within the range of 5% of the static magnetic field to localize the spin, precession, and time constants for the atoms as they are pulled away from their alignment and return to the aligned configuration. The data collection software can detect the magnetic fields generated by the electrons themselves. The data analysis software takes the collected frequency data and determines the average tissue homogeneity and composition. Image processing techniques can then be used to generate a 2D image of the tissue composition. It is typical that the magnetic field alignment is changed during the image processing time (e.g., from the z -axis to the y -axis) to allow for the data acquisition at different slices/orientations throughout the body. Images can be acquired on the order of every 50 ms with the current technology.

MRI technology has been applied to many different functional applications to detect changes within the tissue composition. Changes in brain activity can be quantified by changes in cerebral metabolism, blood flow, or oxygenation, in response to various stimuli. Changes in these parameters are all linked, because increased metabolism generally decreases tissue oxygenation, whereas increased blood flow increases tissue oxygenation levels. This is typically quantified as differences in the alignment and time constants of hemoglobin. Phase contrast MRI has been used to obtain pictures of arteries and entire vascular networks. This has been used to diagnose the likelihood of cardiovascular disease onset (such as stenosis and/or aneurysm). Two common techniques have been used to image the vasculature with phase contrast MRI. The first is through the administration of a paramagnetic contrast agent, most commonly gadolinium, into the bloodstream. That contrast agent (similar to standard angiography) is responsive to changes in the magnetic field and emits a strong signal that can be recorded by the MRI data acquisition equipment. A second technique, termed *flash low angle shot (FLASH) MRI*, saturates the tissue that neighbors a vascular region of interest. As new blood enters the vascular bed, the blood itself will not be saturated; therefore the MRI signal from the blood is much higher than the MRI signal from the surrounding tissue. This provides a direct measurement of velocity changes and the vascular architecture.

17.4 Review of other techniques

Angiography or arteriography is a technique to visualize blood vessels in vivo. Usually, a catheter will be inserted through the femoral artery of a patient, with a contrast dye being injected into the vasculature. X-ray images then will be taken and the structures of the blood vessels can be studied. Digital subtraction angiography is most commonly used because it

can subtract the surrounding tissues and bones, leaving only the vessels filled with the dye visible. This enables cardiologists to identify stenosed or blocked vessels. Coronary angiography is performed to examine blood in the coronary arteries; cerebral angiography is used to visualize arteries and veins in the brain; peripheral angiography is commonly performed to identify stenosis in peripheral circulation, such as in the legs and feet.

Besides the techniques discussed earlier, there are many much simpler methods that can be used to conduct *in vivo* studies and collect information on blood or other biofluids. For example, a simple pressure cuff can be used to measure blood pressure and air-puff tonometry can be used to measure intraocular pressure. Even though compared with Doppler ultrasound or MRI information acquired from these methods is very limited, these more straightforward methods may suit the need of one's study and provide the information desired. In addition, associated experimental procedures are typically simpler for these techniques and the equipment/devices involved are relatively inexpensive. But if more detailed information is required, one would certainly turn to the more complex techniques mentioned previously or many of the techniques not discussed in this chapter.

17.5 Current state of the art for biofluid mechanics *in vivo* research

As with the previous chapters in this section, we will turn our focus onto some of the current areas of biofluid mechanics *in vivo* research that use some of the techniques discussed within this chapter. We highlighted very few techniques in this section, but we will illustrate here how those techniques can be applied to salient research topics in biofluid mechanics.

Intravital microscopy is a very powerful technique for understanding the flow properties, cellular communication mechanisms, and cell distributions, among many other parameters, as a function of cardiovascular antagonists, new therapeutics, new materials, etc. Thus, it is quite difficult to summarize its current uses concisely, but we will try to highlight some major focus areas that make use of this technique. Groups that are interested in the microcirculation and changes to microcirculatory parameters commonly use intravital microscopy techniques, because this technique focuses on visualizing these small vessels and changes to these small vessels in real time. A significant portion of microcirculation research is focused on understanding the basic biologic factors of the microcirculation in response to physiologically relevant stressors. For instance, the effects of various cardiovascular risk factors on disease progression have become a very important area of research. As with the techniques described in Chapters 15 and 16, it is important to understand the effects of these mediators on disease progression, so that new therapeutics and intervention techniques can be designed. Investigators that make use of intravital techniques can study the effects of these mediators on the microcirculation when it is under physiological control.

Other groups make use of ischemia-reperfusion models to determine the effects of localized hypoxic conditions followed by altered biomechanical factors (rapid increase in pressure and shear stress) on various microcirculatory parameters. One of the goals of more recent work in this area is understanding how inflammatory reactions proceed under these conditions and how these inflammatory reactions can interact with other cardiovascular mechanisms (e.g., thrombotic reactions) to alter the physiologic condition of the microvascular

bed. In parallel with this work, new drugs to minimize the inflammatory and thrombotic reactions induced by ischemia can be evaluated.

Some groups have used intravital microscopy to evaluate new blood vessel growth in response to various biochemical and biomechanical stimuli relevant to the microcirculation. Again, the importance of this work stems from the ability to observe new blood vessel growth under physiological control. This allows the research group to augment and control the innate response(s) and try to determine what conditions are important during new vessel growth. Importantly, the ability for new materials to sustain new vessel growth can be evaluated under these conditions. There are many other areas of research that make use of intravital microscopy; a quick search on pubmed.gov with a keyword of “intravital microscopy” finds approximately 10,000 papers.

The other major techniques that we discussed in this section were Doppler ultrasound and MRI techniques. Again, there are many research avenues that can make use of these techniques, and we will focus our discussion on a very brief subset of these techniques. Most of the work that makes use of ultrasound or MRI techniques is interested in understanding the flow patterns around pathologic conditions and/or the flow patterns that instigate pathological events. In many instances, the subject will be treated with a risk factor, recreational drug, or therapeutic drug, and the effects of these treatments on flow properties will be evaluated. A great deal of information regarding the flow conditions can be identified from these investigations. Additionally, much of the information can be used within *in vitro* or *in silico* experiments as known parameters related to the flow conditions and/or the geometries. It is also common for these techniques to be used in case studies on particular clinical pathologic conditions that present at hospitals.

17.6 Future directions of biofluid mechanics *in vivo* research

As in previous chapters, we would like to discuss some possible directions for future research interests that make use of some of the *in vivo* research techniques that we have described. Again, we are not suggesting that these are the only avenues of research or the only important avenues of research; rather, we are attempting to highlight some avenues of research we think are important to develop. In our opinion, one of the major current limitations of *in vivo* biofluid mechanics research is the availability of equipment and model systems that can more fully characterize systems of interest. For instance, although intravital microscopy is a very powerful technique for the investigation of microcirculatory parameters, many cardiovascular disease processes are localized to the macrocirculation. Therefore, it would be important to understand and correlate occurrences within the macrocirculation and the microcirculation to fully understand disease progression.

To accomplish this type of integrated system, it would be important to couple imaging techniques that can be used in parallel. For instance, groups are working on combining positron emission tomography (PET) scanners with both traditional and more modern imaging techniques. PET scanners have a strong history of evaluating the functional activity of the heart, and if PET imaging can be coupled with other techniques that can quantify blood

flow dynamics or transient signaling molecules within the small blood vessels, a larger picture of hemodynamic changes under pathological conditions could be obtained. Currently, groups who make use of intravital microscopy try to evaluate the macrocirculation through *ex vivo* investigations of disease progression. For instance, it is common for groups to dissect key organs or blood vessels from the macrocirculation after the intravital microscopy procedures have been completed and evaluate lesion growth and leukocyte infiltration, among other disease progression markers. However, a real-time correlation of these two events would be more beneficial.

Perhaps the most likely candidate for coupling two or more systems together is a system that includes a Doppler ultrasound imaging technique. In general, the instrumentation associated with ultrasound techniques is minimal and would not interfere with other imaging modalities, such as intravital microscopy. We envision that an intravital microscopy preparation can be designed that allows for a tissue to be antagonized with a specific factor of interest, and one can observe both the localized and the systemic changes (if there are any). Clearly, collecting, segmenting, and processing all of the data that would be generated from such a system would be a challenge, because the viability of the data is largely collected/assessed in real time (e.g., the imaging locations, the focus of the imaging locations) and the majority of the data quantification is completed afterward. With careful consideration on the locations of the probes and the associated equipment, we think that information gained from this type of system would be invaluable in understanding the real-time effects of risk factors (or other antagonist) on both the microcirculation and the macrocirculation.

One of the other advantages of systems designed with multiple imaging modalities at multiple length scales is that information gained from this work can be used to develop more comprehensive models. Both *in silico* and *in vitro* models would benefit significantly from a more comprehensive understanding of possible interactions between the microcirculation and the macrocirculation. All of these improvements would be able to positively feed back on one another, and we may be able to gain an improved understanding of the basic biology of these reactions while correlating them to modeling techniques and other predictive techniques that can be used to diagnose and characterize the systems of interest.

Again, there are many techniques, avenues of research (both current and future), and new technologies that can be developed to facilitate *in vivo* biofluid mechanics research. Our goal was to highlight one of these topics that we think should be a focus in coming years.

In the third edition of this textbook, we choose to include sections regarding current research areas and possible avenues of future research in biofluid mechanics. It is our hope that through this very brief overview of techniques the reader understands the complexity of the biofluid system of interest and that one particular experimental technique and/or focus will not be sufficient to fully characterize the system of interest. The benefit of multiple techniques that are investigating different properties of the same physiological event is that each of these techniques can focus on different aspects and gain new information that can help refine and focus the other techniques. This feedback is one of the major positive aspects of conducting studies at these different levels.

Summary

- 17.1.** A significant amount of information can be gained from *in silico* and *in vitro* work; however, *in vivo* models may provide the closest, most accurate, and most relevant conditions to study biofluid mechanics. In some of these studies, there is some manipulation of the *in vivo* tissue, and in others there is no manipulation. This may or may not affect the obtained results. Using intravital microscopy, blood flow through microvascular networks can be observed, to determine changes in blood cell populations, efficacy of new therapeutic agents, and cell–cell communication within the vascular network, among many other parameters. Research fields such as wound healing, angiogenesis, or cardiovascular disease development or progression can all be documented with intravital techniques.
- 17.2.** Doppler ultrasound techniques can be used to obtain three-dimensional images of biological tissue. For our interests, it also can be used to quantify blood flow through superficial blood vessels. This makes use of an apparent Doppler frequency shift that can be calculated from

$$f_D = \frac{2vf_0}{c} \cos(\theta)$$

By rotating the Doppler probe in space, in relation to the location of interest, it is possible to obtain a three-dimensional image of the blood vessel with a known velocity profile throughout the vessel.

- 17.3.** MRI makes use of the spin and alignment of ions within the body. Under normal conditions, the magnetic field generated by ions within the body is randomly distributed, but when the body is placed within a large magnetic field, all of the ions (especially hydrogen) align with the magnetic direction. When the magnetic field is removed, the time it takes for the ions to move back into a random arrangement can be quantified. Individual tissues with different compositions will have multiple times for the hydrogen ions to return to the respective normal random directions, and therefore, pathological conditions (such as cancer within a tissue) can be identified from this technique.
- 17.4.** Angiography or arteriography is a technique to visualize blood vessels *in vivo*. Digital subtraction angiography is most commonly used because it can subtract the surrounding tissues and bones, leaving only the vessels filled with the dye visible. There are many much simpler methods that can be used to conduct *in vivo* studies and collect information on blood or other biofluids.
- 17.5.** There are many current areas of *in vivo* biofluid mechanics research that cover a very broad range of topics. We chose to highlight some of those topics in our discussion, and this was primarily related to the use of intravital microscopy for understanding the basic biology of various physiological and pathological events, drug diagnostics, and/or materials compatibility testing. We also highlighted how ultrasound and MRI techniques can be used to identify pathological locations and/or

predict the occurrence of pathological events. These techniques also may be used to gather information for model development or initial model conditions.

- 17.6.** The future of in vivo biofluid mechanics research is ever evolving. We think the future research efforts should be focused on combining length and time scales, so that real-time information can be gathered about disease progression in multiple locations. For instance, in the cardiovascular system, it would be interesting to uncover both local and systemic effects induced by agonist exposure. To accomplish this, new techniques need to be developed for simultaneous evaluation of these different length scales. As we have discussed throughout Part 5 of this textbook, we think that the information gained from any experimental technique needs to be put into perspective with other techniques. For instance, information gained from in vivo techniques can be used to develop better in vitro models. These better in vitro models may provide us with a better understanding of the basic biology of the underlying processes, which may help the community refine areas of interest for investigation and/or prediction tools/algorithms for disease diagnostic purposes. Combining all of the sections of Part 5, we would like the reader to understand that no single technique will be able to provide all of the information needed to understand these complex processes, but the combination of these techniques may help us better understand the underlying physiology of the events that are being observed.

Homework Problems

- 17.1.** Discuss some of the difficulties that may be encountered when conducting live animal preparations. Are there any ways to minimize these difficulties? Are these new methods associated with their own difficulties?
- 17.2.** An ultrasound probe is being used to image a blood vessel. The probe is emitting a sound wave at a frequency of 2 MHz. Calculate the Doppler frequency if the angle between the blood vessel and the incident wave is 65 degrees and blood is flowing at 50 mm/s.
- 17.3.** The magnetic ratio being used in an MRI system is 42.5 MHz/T. Determine the orbital frequency for an electron within a 2-T magnetic field. How can we enhance the imaging with this machine?

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