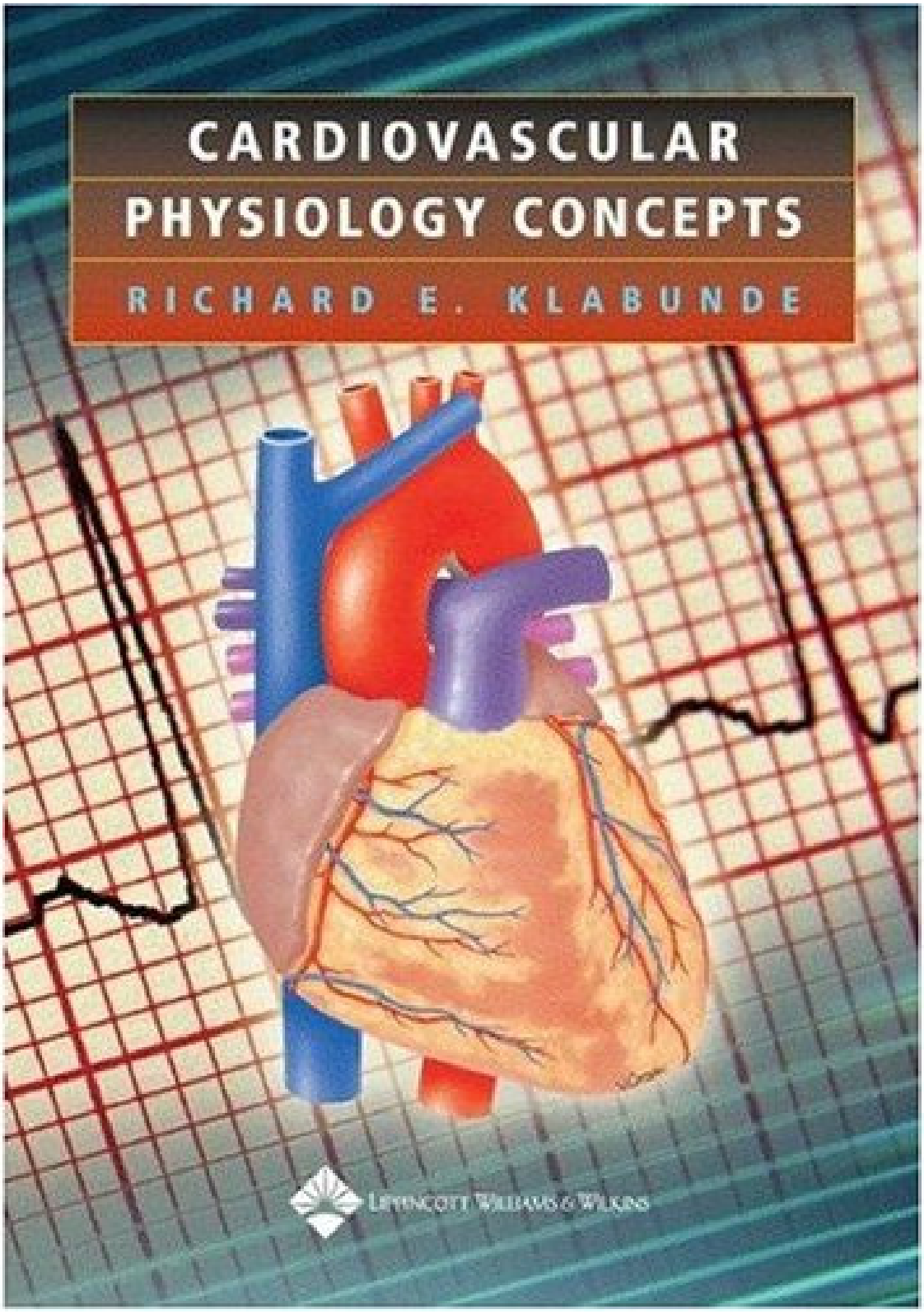
CARDIOVASCULAR
PHYSIOLOGY CONCEPTS
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LIPPINCOTT WILLIAMS & WILKINS

chapter

1

Introduction to the Cardiovascular System

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Explain why large organisms require a circulatory system, while single-cell and small multicellular organisms do not.**
2. **Describe the series and parallel arrangement of the cardiac chambers, pulmonary circulation, and major organs of the systemic circulation.**
3. **Describe the pathways for the flow of blood through the heart chambers and large vessels associated with the heart.**
4. **Describe, in general terms, the primary functions of the heart and vasculature.**
5. **Explain how the autonomic nerves and kidneys serve as a negative feedback system for the control of arterial blood pressure.**

THE NEED FOR A CIRCULATORY SYSTEM

All living cells require metabolic substrates (e.g., oxygen, amino acids, glucose) and a mechanism by which they can remove by-products of metabolism (e.g., carbon dioxide, lactic acid). Single-cell organisms exchange these substances directly with their environment through diffusion and cellular transport systems. In contrast, most cells of large organisms have limited or no exchange capacity with their environment because their cells are not in contact with the outside environment. Nevertheless, exchange with the outside environment must occur for the cells to function. To accomplish this necessary exchange, large organisms have a sophisticated system of blood vessels that transports metabolic substances between cells and blood, and between blood and environment. The smallest of these blood vessels, capillaries, are in close proximity to all cells in the body, thereby permitting exchange to occur. For example, each cell in skeletal muscle is surrounded by two or more capillaries. This arrangement of capillaries around cells ensures that exchange can occur between blood and surrounding cells.

Exchange between blood and the outside environment occurs in several different organs: lungs, gastrointestinal tract, kidneys and skin. As blood passes through the lungs, oxygen and carbon dioxide are exchanged between the blood in the pulmonary capillaries and the gases found within the lung alveoli. Oxygen-enriched blood is then transported to the organs where the oxygen diffuses from the blood into the surrounding cells. At the same time, carbon dioxide, a metabolic waste product, diffuses from the tissue cells into the blood and is transported to the lungs, where exchange occurs between blood and alveolar gases.

Blood passing through the intestine picks up glucose, amino acids, fatty acids, and other ingested substances that have been transported from the intestinal lumen into the blood in the intestinal wall by the cells lining the intestine. The blood then delivers these substances to organs such as the liver for additional metabolic processing and to cells throughout the body as an energy source. Some of the waste products of these cells are taken up by the blood and transported to other organs for metabolic processing and final elimination through either the gastrointestinal tract or the kidneys.

Cells require a proper balance of water and electrolytes (e.g., sodium, potassium, and calcium) to function. The circulation transports ingested water and electrolytes from the intestine to cells throughout the body, including those of the kidneys, where excessive amounts of water and electrolytes can be eliminated in the urine.

The skin also serves as a site for exchange of water and electrolytes (through sweating), and for exchange of heat, which is a major by-product of cellular metabolism that must be removed from the body. Increasing blood flow through the skin enhances heat loss from the body, while decreasing blood flow diminishes heat loss.

In summary, the ultimate purpose for the cardiovascular system is to facilitate exchange of gases, fluid, electrolytes, large molecules and heat between cells and the outside environment. The heart and vasculature ensure that adequate blood flow is delivered to organs so that this exchange can take place.

THE ARRANGEMENT OF THE CARDIOVASCULAR SYSTEM

The cardiovascular system has two primary components: the heart and blood vessels. A third component, the lymphatic system, does not contain blood, but nonetheless serves an important exchange function in conjunction with blood vessels.

The heart can be viewed functionally as two pumps with the pulmonary and systemic circulations situated between the two pumps (Fig. 1-1). The **pulmonary circulation** is the blood flow within the lungs that is involved in the exchange of gases between the blood and alveoli. The **systemic circulation** is comprised of all the blood vessels within and outside of organs excluding the lungs. The right side of the heart comprises the right atrium and the right ventricle. The **right atrium** receives venous blood from the systemic circulation and the **right**

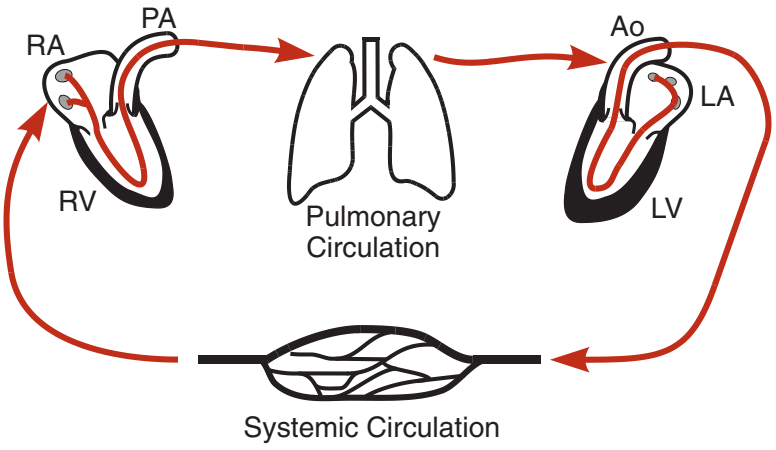

FIGURE 1-1 Overview of the cardiovascular system. The right side of the heart, pulmonary circulation, left side of the heart, and systemic circulation are arranged in series. *RA,* right atrium; *RV,* right ventricle; *PA,* pulmonary artery; *Ao,* aorta; *LA,* left atrium; *LV,* left ventricle.

ventricle pumps it into the pulmonary circulation where oxygen and carbon dioxide are exchanged between the blood and alveolar gases. The left side of the heart comprises the left atrium and the left ventricle. The blood leaving the lungs enters the **left atrium** by way of the pulmonary veins. Blood then flows from the left atrium into the left ventricle. The **left ventricle** ejects the blood into the **aorta,** which then distributes the blood to all the organs via the arterial system. Within the organs, the vasculature branches into smaller and smaller vessels, eventually forming capillaries, which are the primary site of exchange. Blood flow from the capillaries enters veins, which return blood flow to the right atrium via large systemic veins (the superior and inferior vena cava).

As blood flows through organs, some of the fluid, along with electrolytes and small amounts of protein, leaves the circulation and enters the tissue interstitium (a process termed fluid filtration). The **lymphatic vessels,** which are closely associated with small blood vessels within the tissue, collect the excess fluid that filters from the vasculature and transport it back into the venous circulation by way of lymphatic ducts that empty into large veins (subclavian veins) above the right atrium.

It is important to note the overall arrangement of the cardiovascular system. First, the right and left sides of the heart, which are separated by the pulmonary and systemic circulations, are **in series** with each other (see Fig. 1-1). Therefore, all of the blood that is pumped from the right ventricle enters into the pulmonary circulation and then into the left side of the heart from where it is pumped into the systemic circulation before returning to the heart. This in-series relationship of the two sides of the heart and the pulmonary and systemic circulations requires that the output (volume of blood ejected per unit time) of each side of the heart closely matches the output of the other so that there are no major blood volume shifts between the pulmonary and systemic circulations. Second, most of the major organ systems of the body receive their blood from the aorta, and the blood leaving these organs enters into the venous system (superior and inferior vena cava) that returns the blood to the heart. Therefore, the circulations of most major organ systems are **in parallel** as shown in Figure 1-2. One major exception is the liver, which receives a large fraction of its blood supply from the venous circulation of the intestinal tract that drains into the hepatic portal system to supply the liver. The liver also receives blood from the aorta via the hepatic artery. Therefore, most of the liver circulation is in series with the intestinal circulation, while some of the liver circulation is in parallel with the intestinal circulation.

This parallel arrangement has significant hemodynamic implications as described in Chapter 5. Briefly, *the parallel arrangement of*

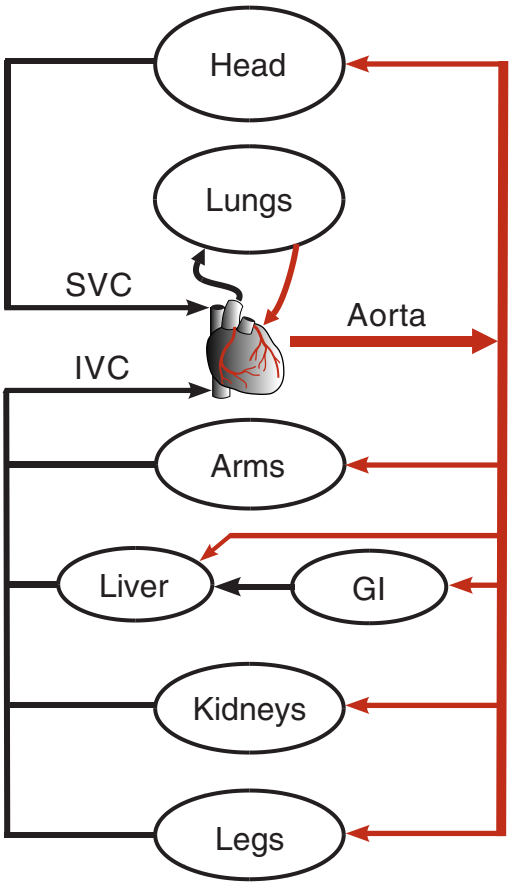

FIGURE 1-2 Parallel arrangement of organs within the body. One major exception is the hepatic (liver) circulation, which is both in series with the gastrointestinal circulation (*GI*) by the hepatic portal circulation and in parallel by the hepatic artery, which supplies part of the hepatic circulation. *SVC,* superior vena cava; *IVC,* inferior vena cava.

major vascular beds prevents blood flow changes in one organ from significantly affecting blood flow in other organs. In contrast, when vascular beds are in series, blood flow changes in one vascular bed significantly alters blood flow to the other vascular bed.

THE FUNCTIONS OF THE HEART AND BLOOD VESSELS

Heart

The heart sometimes is thought of as an organ that pumps blood through the organs of the body. While this is true, it is more accurate to view the heart as a pump that receives blood from venous blood vessels at a low pressure, imparts energy to the blood (raises it to a higher pressure) by contracting around the blood within the cardiac chambers, and then ejects the blood into the arterial blood vessels.

It is important to understand that organ blood flow is not driven by the output of the heart per se, but rather by the pressure generated within the arterial system as the heart pumps blood into the vasculature, which serves as a resistance network. *Organ blood flow is determined by the arterial pressure minus the venous pressure, divided by the vascular resistance of the organ* (see Chapters 5 and 7). Pressures in the cardiovascular system are expressed in millimeters of mercury (mm Hg) above atmospheric pressure. One millimeter of mercury is the pressure exerted by a 1-mm vertical column of mercury (1 mm Hg is the equivalent of 1.36 cm H_2O hydrostatic pressure). Vascular resistance is determined by the size of blood vessels, the arrangement of the vascular network, and the viscosity of the blood flowing within the vasculature.

The right atrium receives systemic venous blood (venous return) at very low pressures (near 0 mm Hg) (Fig. 1-3). This venous return then passes through the right atrium and fills the right ventricle; atrial contraction also contributes to the ventricular filling. Right ventricular contraction ejects blood from the right ventricle into the pulmonary artery. This generates a maximal pressure (systolic pressure) that ranges from 20 to 30 mm Hg within the pulmonary artery. As the blood passes through the pulmonary circulation, the blood pressure falls to about 10 mm Hg. The left atrium receives the pulmonary venous blood, which then flows passively into the left ventricle; atrial contraction provides a small amount of additional filling of the left ventricle. As the left ventricle contracts and ejects blood into the systemic arterial system, a relatively high pressure is generated (100–140 mm Hg maximal or systolic pressure). Therefore, *the left ventricle is a high-pressure pump, in contrast to the right ventricle, which is a low-pressure pump.* Details of the pumping action of the heart are found in Chapter 4.

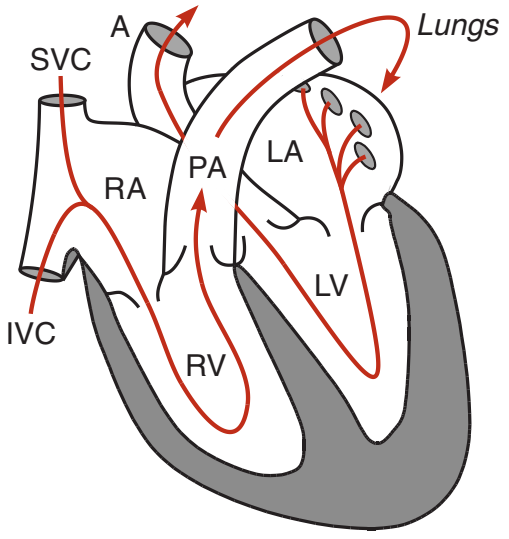

FIGURE 1-3 Blood flow within the heart. Venous blood returns to the right atrium (*RA*) via the superior (*SVC*) and inferior vena cava (*IVC*). Blood passes from the RA into the right ventricle (*RV*), which ejects the blood into the pulmonary artery (*PA*). After passing through the lungs, the blood flows into the left atrium (*LA*) and then fills the left ventricle (*LV*), which ejects the blood into the aorta (*A*) for distribution to the different organs of the body.

The pumping activity of the heart is usually expressed in terms of its cardiac output, which is the amount of blood ejected with each contraction (i.e., stroke volume) multiplied by the heart rate. Any factor that alters heart rate or stroke volume will alter the cardiac output. The heart rate is determined by groups of cells within the heart that act as electrical pacemakers, and their activity is increased or decreased by autonomic nerves and hormones (see Chapter 2). The action potentials generated by these pacemaker cells are conducted throughout the heart and trigger contraction of cardiac myocytes (see Chapter 3). This results in ventricular contraction and ejection of blood. The force of ventricular contraction, and therefore stroke volume, is regulated by mechanisms intrinsic to the heart, by autonomic nerves and hormones (see Chapters 3, 4, and 6).

In recent years, we have learned that the heart has other important functions besides pumping blood. The heart synthesizes several hormones. One of these hormones, atrial natriuretic peptide, plays an important role in the regulation of blood volume and blood pressure (see Chapter 6). Receptors associated with the heart also play a role in regulating the release of antidiuretic hormone from the posterior pituitary, which regulates water loss by the kidneys.

Vascular System

Blood vessels constrict and dilate to regulate arterial blood pressure, alter blood flow within organs, regulate capillary blood pressure, and distribute blood volume within the body. Changes in vascular diameters are brought about by activation of vascular smooth muscle within the vascular wall by autonomic nerves, metabolic and biochemical signals from outside of the blood vessel, and vasoactive substances released by cells that line the blood vessels (i.e., the vascular endothelium; see Chapters 3, 5, and 6).

Blood vessels have another function besides distribution of blood flow and exchange. The endothelial lining of blood vessels produces several substances (e.g., nitric oxide [NO], endothelin-1 [ET-1], and prostacyclin [PGI_2]) that modulate cardiac and vascular function, hemostasis (blood clotting), and inflammatory responses (see Chapter 3).

Interdependence of Circulatory and Organ Function

Cardiovascular function is closely linked to the function of other organs. For example, the brain not only receives blood flow to support its metabolism, but it also acts as a control center for regulating cardiovascular function. A second example of the interdependence between organ function and the circulation is the kidney. The kidneys excrete varying amounts of sodium, water, and other molecules to maintain fluid and electrolyte homeostasis. Blood passing through the kidneys is filtered and the kidneys then modify the composition of the filtrate to form urine. Reduced blood flow to the kidneys can have detrimental effects on kidney function and therefore on

fluid and electrolyte balance in the body. Furthermore, renal dysfunction can lead to large increases in blood volume, which can precipitate cardiovascular changes that sometimes lead to hypertension or exacerbate heart failure. In summary, organ function is dependent on the circulation of blood, and cardiovascular function is dependent on the function of organs.

THE REGULATION OF CARDIAC AND VASCULAR FUNCTION

The cardiovascular system must be able to adapt to changing conditions and demands of the body. For example, when a person exercises, increased metabolic activity of contracting skeletal muscle requires large increases in nutrient supply (particularly oxygen) and enhanced removal of metabolic by-products (e.g., carbon dioxide, lactic acid). To meet this demand, blood vessels within the exercising muscle dilate to increase blood flow; however, blood flow can only be increased if the arterial pressure is maintained. Arterial pressure is maintained by increasing cardiac output and by constricting blood vessels in other organs of the body (see Chapter 9). If these changes were not to occur, arterial blood pressure would fall precipitously during exercise, thereby limiting organ perfusion and exercise capacity. Therefore, a coordinated cardiovascular response is required to permit increased muscle blood flow while a person exercises. Another example of adaptation occurs when a person stands up. Gravitational forces cause blood to pool in the legs when a person assumes an upright body posture (see Chapter 5). In the absence of regulatory mechanisms, this pooling will lead to a fall in cardiac output and arterial pressure, which can cause a person to faint because of reduced blood flow to the brain. To prevent this from happening, coordinated reflex responses increase heart rate and constrict blood vessels to maintain a normal arterial blood pressure when a person stands.

It is important to control arterial blood pressure because it provides the driving force for organ perfusion. As described in Chapter 6, neural and hormonal (neurohumoral) mechanisms regulating cardiovascular function are under the control of pressure sensors located in arteries and veins (i.e., baroreceptors). These **baroreceptors,** through their afferent neural connections to the brain, provide the central nervous system with information regarding the status of blood pressure in the body. A decrease in arterial pressure from its normal operating point elicits a rapid baroreceptor reflex that stimulates the heart to increase cardiac output and constricts blood vessels to restore arterial pressure (a **negative feedback** control mechanism) (Fig. 1-4). These cardiovascular adjustments occur through rapid changes in **autonomic nerve activity** (particularly through sympathetic nerves) to the heart and vasculature.

In addition to altering autonomic nerve activity, a fall in arterial pressure stimulates the release of **hormones** that help to restore arterial pressure by acting on the heart and blood vessels; they also increase arterial pressure by increasing blood volume through their actions on renal function. In contrast to the rapidly acting autonomic mechanisms, hormonal mechanisms acting on the kidneys require hours or days to achieve their full effect

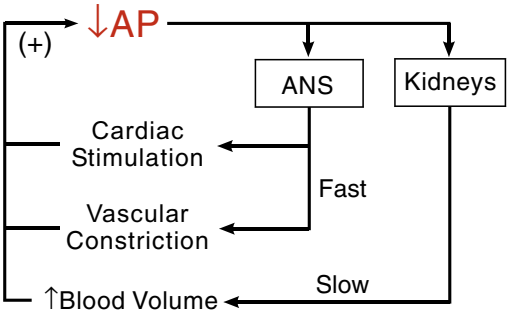

FIGURE 1-4 Feedback control of arterial pressure (*AP*) by the autonomic nervous system (*ANS*) and kidneys. A sudden fall in AP elicits a rapid baroreceptor reflex that activates the ANS to stimulate the heart (increasing cardiac output) and constrict blood vessels to restore AP. The kidneys respond to decreased AP by retaining Na^+ and water to increase blood volume, which helps to restore AP. The (+) indicates the restoration of arterial pressure following the initial fall in pressure (i.e., a negative feedback response).

on blood volume. Hormonal mechanisms include secretion of catecholamines (chiefly epinephrine) by the adrenal glands, release of renin by the kidneys, which triggers the formation of angiotensin II and aldosterone, and release of antidiuretic hormone (vasopressin) by the posterior pituitary. Hormones such as angiotensin II, aldosterone, and vasopressin are particularly important because they act on the kidneys to increase blood volume, which increases cardiac output and arterial pressure. In summary, baroreceptor reflexes are rapid, short-acting mechanisms in contrast to hormones that are slow, long-acting mechanisms that the body uses for achieving blood pressure control.

Autonomic nerves and hormones affect the heart and vasculature by acting through receptor-coupled, signal transduction mechanisms (see Chapter 3). For example, sympathetic autonomic nerves innervating the heart and blood vessels release a neurotransmitter (norepinephrine) that binds to specific receptors located on the cell membrane of the cardiac myocyte or vascular smooth muscle cell. This causes the activation of biochemical pathways within the cell that increases the force of contraction of cardiac myocytes and vascular smooth muscle cells. Hormones such as angiotensin II and vasopressin also bind to specific cell receptors, which activate intracellular mechanisms to produce contraction of vascular smooth muscle cells.

In summary, arterial pressure is monitored by the body and ordinarily is maintained within narrow limits by negative feedback mechanisms that adjust cardiac function, systemic vascular resistance and blood volume. This control is accomplished by changes in autonomic nerve activity to the heart and vasculature, as well as by changes in circulating hormones that influence cardiac, vascular and renal function.

THE CONTENT OF THE FOLLOWING CHAPTERS

This textbook emphasizes our current knowledge of cellular physiology as well as the classical biophysical concepts that have been used for decades to describe cardiac and vascular function. Chapter 2 describes the electrical activity within the heart, both at the cellular and whole organ level. Chapter 3 builds a foundation of cellular physiology by emphasizing intracellular mechanisms that regulate cardiac and vascular smooth muscle contraction. These cellular concepts are reinforced repeatedly in subsequent chapters. Chapter 4 examines cardiac mechanical function. Chapter 5 summarizes concepts of vascular function and the biophysics of blood flow in the context of regulation of arterial and venous blood pressures. Neurohumoral mechanisms regulating cardiac and vascular function are described in Chapter 6. Chapter 7 describes the flow of blood within different organs, with an emphasis on local regulatory mechanisms. Chapter 8 addresses the primary function of the cardiovascular system, that is, the exchange of nutrients, gases, and fluid between the blood and tissues. Finally, Chapter 9 integrates concepts described in earlier chapters by examining how the cardiovascular system responds to altered demands and disease states.

SUMMARY OF IMPORTANT CONCEPTS

- Large organisms require a circulatory system so that metabolic substrates and by-products of cellular metabolism can be efficiently exchanged between cells and the outside environment, as well as transported to distant sites within the body.
- The cardiovascular system is comprised primarily of the heart and blood vessels. Blood returning to the heart via the venous circulation flows into the right atrium and then into the right ventricle. Contraction of the right ventricle pumps the blood into the pulmonary circulation where oxygen and carbon dioxide are exchanged with the gases found within the lung alveoli. Oxygenated blood from the lungs enters into the left atrium, then into the left ventricle, which pumps the blood into the aorta for distribution to various organs via large distributing arteries.

Smaller blood vessels within the organs (primarily capillaries) serve as the primary site of nutrient exchange. Blood leaves the organs and returns to the heart via the venous circulation.

- The venous circulation, the right atrium and ventricle, the pulmonary circulation and the left atrium have relatively low blood pressures. Contraction of the left ventricle and ejection of blood into the aorta generate relatively high blood pressures within the left ventricle and arterial system.
- Most major organ systems are in parallel with each other so that blood flow in one organ has relatively little influence on blood flow in another organ. In contrast, the pulmonary and systemic circulations are in series; therefore, altering blood flow and blood volume in one of these circulations alters the flow and volume in the other.
- Blood flow within organs is determined primarily by the arterial pressure (generated by the pumping action of the heart against a systemic vascular resistance), and by changes in the diameters of blood vessels within the organs brought about by contraction or relaxation of smooth muscle within the walls of the blood vessels.
- Autonomic nerves and circulating hormones regulate cardiac, vascular and renal function to ensure that arterial pressure is adequate for organ perfusion.
- Baroreceptors continuously monitor arterial pressure and adjust the activity of autonomic nerves to maintain arterial pressure within narrow limits.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. The cardiovascular system
    a. Aids in the transfer of heat energy from organs deep within the body to the outside environment.
    b. Is comprised of pulmonary and systemic circulations that are in parallel with each other.
    c. Transports carbon dioxide from the lungs to tissues within organs.
    d. Transports oxygen from individual cells to the lungs.

2. Which of the following statements concerning the heart is true?
    a. The right ventricle receives blood from the pulmonary veins.
    b. The right ventricle generates higher pressures than the left ventricle during contraction.
    c. The right and left ventricles are in parallel.
    d. Cardiac output is the product of ventricular stroke volume and heart rate.

3. Arterial pressure decreases when
    a. A person stands up.
    b. Blood volume increases.
    c. Cardiac output increases.
    d. Plasma concentrations of angiotensin II and aldosterone are elevated.

chapter

2 Electrical Activity of the Heart

CD CONTENTS

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Define and discuss the following terms as they relate to the heart:**
   a. **resting membrane potential**
   b. **depolarization and repolarization**
   c. **threshold potential**
   d. **action potential**
   e. **pacemaker potential**
   f. **automaticity**
   g. **effective refractory period**
   h. **arrhythmias**
2. **Calculate the Nernst equilibrium potential for sodium, potassium, and calcium ions given their intracellular and extracellular concentrations.**
3. **Describe how changing the concentrations of sodium, potassium, and calcium ions inside and outside the cell affect the resting membrane potential in cardiac cells.**
4. **Explain why the resting potential is near the equilibrium potential for potassium and the peak of an action potential approaches the equilibrium potential for sodium.**
5. **Describe how the sarcolemmal Na^+/K^+-adenosine triphosphatase (ATPase) affects the generation and maintenance of cardiac membrane potentials.**
6. **Describe the mechanisms that maintain calcium gradients across the cardiac cell membrane.**
7. **Describe how activation and inactivation gates regulate sodium movement through fast sodium channels.**

8. Contrast cardiac action potentials with those found in nerve and skeletal muscle cells.
9. Contrast the shape, phases, and ionic currents of nonpacemaker and pacemaker (e.g., sinoatrial [SA] node) action potentials.
10. Describe the ionic currents responsible for phase 4, spontaneous depolarization in SA nodal pacemaker cells.
11. Describe how autonomic nerves, circulating catecholamines, extracellular potassium concentrations, thyroid hormone, and hypoxia alter pacemaker activity.
12. Describe how the effective refractory period serves as a protective mechanism in the heart.
13. Describe the role of afterdepolarizations in the generation of tachycardias.
14. Describe the normal pathways for action potential conduction within the heart.
15. Describe the effects of autonomic nerves, circulating catecholamines, cellular hypoxia, and sodium-channel-blocking drugs on conduction velocity within the heart.
16. Describe what each of the following electrocardiogram (ECG) components represents:
    a. P wave
    b. P-R interval
    c. QRS complex
    d. ST segment
    e. Q-T interval
17. Recognize the following from an ECG rhythm strip:
    a. normal sinus rhythm
    b. sinus bradycardia and tachycardia
    c. atrial flutter and fibrillation
    d. atrioventricular (AV) nodal blocks: first, second and third degree
    e. premature ventricular complex
    f. ventricular tachycardia and fibrillation
18. Describe the location for placement of electrodes for each of the following leads: I, II, III, aV_R, aV_L, and aV_F, and precordial V_1-V_6.
19. Draw the axial reference system and show the position (in degrees) for the positive electrode for each of the six limb leads.
20. List the rules for determining the direction of a vector of depolarization and repolarization relative to a given ECG lead.
21. Describe, in terms of vectors, how the QRS complex is generated and why the QRS appears differently when recorded by different electrode leads.
22. Estimate the mean electrical axis for ventricular depolarization from the six limb leads.
23. Describe some changes that can occur in the ECG during cardiac ischemia or hypoxia.

INTRODUCTION

The primary function of cardiac myocytes is to contract. Electrical changes within the myocytes initiate this contraction. This chapter examines (1) the electrical activity of individual myocytes, including resting membrane potentials and action potentials; (2) the way action potentials are conducted throughout the heart to initiate coordinated contraction of the entire heart; and (3) the way electrical activity of the heart is measured using the electrocardiogram (ECG).

CELL MEMBRANE POTENTIALS

Resting Membrane Potentials

Cardiac cells, like all living cells in the body, have an electrical potential across the cell membrane. This potential can be measured by inserting a microelectrode into the cell and

TABLE 2-1 ION CONCENTRATIONS[1] INSIDE AND OUTSIDE OF RESTING MYOCYTES

ION	INSIDE (mM)	OUTSIDE (mM)
Na^+	20	145
K^+	150	4
Ca^{++}	0.0001	2.5
Cl^-	25	140

[1] These concentrations are approximations and are used to illustrate the concepts of chemical gradients and membrane potential. In reality, the free (unbound or ionized) ion concentration and the chemical activity of the ion should be used when evaluating electrochemical gradients.

measuring the electrical potential in millivolts (mV) inside the cell relative to the outside of the cell. By convention, the outside of the cell is considered 0 mV. If measurements are taken with a resting ventricular myocyte, a membrane potential of about –90 mV will be recorded. This **resting membrane potential (Em)** is determined by the concentrations of positively and negatively charged ions across the cell membrane, the relative permeability of the cell membrane to these ions, and the ionic pumps that transport ions across the cell membrane.

Equilibrium Potentials

Of the many different ions present inside and outside of cells, the concentrations of Na^+, K^+, Cl^-, and Ca^{++} are most important in determining the membrane potential across the cell membrane. Table 2-1 shows typical concentrations of these ions. Of the four ions, K^+ is the most important in determining the resting membrane potential. In a cardiac cell, the concentration of K^+ is high inside and low outside the cell. Therefore, a **chemical gradient** (concentration difference) exists for K^+ to diffuse out of the cell (Fig. 2-1). The opposite situation is found for Na^+; its chemical gradient favors an inward diffusion. The concentration differences across the cell membrane for these and other ions are determined by the activity of energy-dependent ionic pumps and the presence of impermeable, negatively charged proteins within the cell that affect the passive distribution of cations and anions.

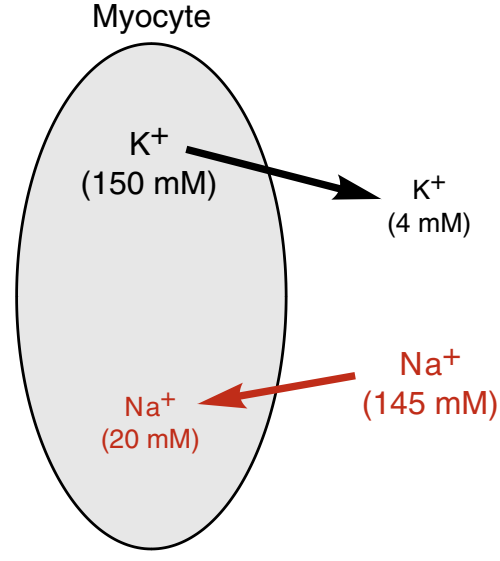

FIGURE 2-1 Concentrations of Na^+ and K^+ inside and outside a cardiac myocyte.

To understand how concentration gradients of ions across a cell membrane affect membrane potential, consider a cell in which K^+ is the only ion across the membrane other than the large negatively charged proteins on the inside of the cell. In this cell, K^+ diffuses down its chemical gradient and out of the cell because its concentration is much higher inside than outside the cell (see Fig. 2-1). As K^+ diffuses out of the cell, it leaves behind negatively charged proteins, thereby creating a separation of charge and a potential difference across the membrane (leaving it negative inside the cell). The membrane potential that is necessary to oppose the movement of K^+

down its concentration gradient is termed the **equilibrium potential for K^+ (E_K;** Nernst potential). The **Nernst potential** for K^+ at 37°C is as follows:

Eq. 2-1 $$E_K = -61 \log \frac{[K^+]_i}{[K^+]_o} = -96\ mV$$

in which the potassium concentration inside $[K^+]_i$ = 150 mM and the potassium concentration outside $[K^+]_o$ = 4 mM. The –61 is derived from RT/zF, in which R is the gas constant, z is the number of ion charges (z = 1 for K^+; z = 2 for divalent ions such as Ca^{++}), F is Faraday's constant, and T is temperature (°K). *The equilibrium potential is the potential difference across the membrane required to maintain the concentration gradient across the membrane.* In other words, the equilibrium potential for K^+ represents the electrical potential necessary to keep K^+ from diffusing down its chemical gradient and out of the cell. If the outside K^+ concentration increased from 4 to 10 mM, the chemical gradient for diffusion out of the cell would be reduced; therefore, the membrane potential required to maintain electrochemical equilibrium would be less negative according to the Nernst relationship.

The Em for a ventricular myocyte is about –90 mV, which is near the equilibrium potential for K^+. Because the equilibrium potential for K^+ is –96 mV and the resting membrane potential is –90 mV, a net driving force (**net electrochemical force**) acts on the K^+, causing it to diffuse out of the cell. In the case of K^+, this net electrochemical driving force is the Em (–90 mV) minus the E_K (–96 mV), resulting in +6 mV. Because the resting cell has a finite permeability to K^+ and a small net outward driving force is acting on K^+, K^+ slowly leaks outward from the cell.

The sodium ions also play a major role in determining the membrane potential. Because the Na^+ concentration is higher outside the cell, this ion would diffuse down its chemical gradient into the cell. To prevent this inward flux of Na^+, a large positive charge is needed inside the cell (relative to the outside) to balance out the chemical diffusion forces. This potential is called the **equilibrium potential for Na^+ (E_{Na})** and is calculated using the Nernst equation, as follows:

Eq. 2-2 $$E_K = -61 \log \frac{[Na^+]_i}{[Na^+]_o} = +52\ mV$$

in which the sodium concentration inside $[Na+]_i$ = 20 mM and the sodium concentration outside $[Na+]_o$ = 145 mM. The calculated equilibrium potential for sodium indicates that to balance the inward diffusion of Na^+ at these intracellular and extracellular concentrations, the cell interior has to be +52 mV to prevent Na^+ from diffusing into the cell.

The net driving or electrochemical force acting on sodium (and each ionic species) has two components. First, the sodium concentration gradient is driving sodium into the cell; according to the Nernst calculation, the electrical force necessary to counterbalance this chemical gradient is +52 mV. Second, because the interior of the resting cell is very negative (–90 mV), a large electrical force is trying to "pull" sodium into the cell. We can derive the net electrochemical force acting on sodium from these two component forces by subtracting the Em minus E_{Na}: –90 mV minus +52 mV equals –142 mV. This large electrochemical force drives sodium into the cell; however, at rest, the permeability of the membrane to Na^+ is so low that only a small amount of Na^+ leaks into the cell.

Ionic Conductances

As explained, the Em in a resting, nonpacemaker cell is very near E_K. This agreement occurs because the membrane is much more permeable to K^+ in the resting state than to other ions such as Na^+ or Ca^{++}. The membrane potential reflects not only the concentration gradients of individual ions (i.e., the equilibrium potentials), but also the relative permeability of the membrane to those ions. If the membrane has a higher permeability to one ion over the others, that ion will have a greater influence in determining the membrane potential.

If the membrane is viewed as a set of parallel electrical circuits (Fig. 2-2), with each ion represented as a voltage source (equilibrium potential, E_X) in series with a variable resis-

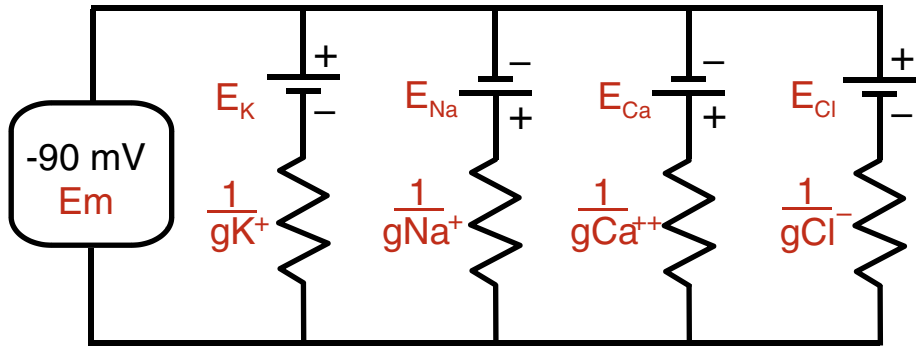

FIGURE 2-2 Resistance model for membrane potential (*Em*). The voltage sources represent the equilibrium potentials (E_X) for potassium (K^+), sodium (Na^+), calcium (Ca^{++}), and chloride (Cl^-) ions. The resistors represent the membrane resistances to the ions. Resistance equals the reciprocal of the ion conductances (i.e., 1/gX).

tance (the inverse of which is conductance), the ion conductance (gX) and its equilibrium potential will contribute to the overall membrane potential. We can represent this model mathematically as follows:

Eq. 2-3

$$Em = \frac{gK^+ (E_K) + gNa^+ (E_{Na}) + gCa^{++} (E_{Ca}) + gCl^- (E_{cl})}{gK^+ + gNa^+ + gCa^{++} + gCl^-}$$

If the equilibrium potential for each ion remains unchanged (i.e., the concentration gradient does not change), then the current flow for each ion will vary as the conductance changes. This variance is a function of membrane permeability for that ion. Permeability and conductance refer to the ease of movement of solutes across membranes (see Ion Permeability and Conductance on CD). If potassium conductance (gK^+) is finite and all other conductances are zero, the membrane potential will equal the equilibrium potential for potassium (approximately –96 mV). However, if sodium conductance (gNa^+) is finite and all other conductances are zero, then the membrane potential will be the equilibrium potential for sodium (approximately +52 mV). According to Equation 2-3, if gK^+ and gNa^+ are equal and the other ion conductances are zero, the membrane potential would lie between the two equilibrium potentials.

The earlier model and equation showed that the membrane potential depends on both the equilibrium potential of the different ions and their conductances. Equation 2-4 simplifies Equation 2-3 by expressing each ion conductance as a relative conductance (g′X). This is the conductance of a single ion divided by the total conductance for all of the ions [e.g., $g'K^+ = gK^+/(gK^+ + gNa^+ + gCa^{++} + gCl^-)$].

Eq. 2-4

$$Em = g'K^+ (E_K) + g'Na^+ (E_{Na}) + g'Ca^{++} (E_{Ca}) + g'Cl^- (E_{Cl})$$

In Equation 2-4, the membrane potential is the sum of the individual equilibrium potentials, each multiplied by the relative membrane conductance for that particular ion. If the equilibrium potential values for K^+, Na^+, Ca^{++} and Cl^- are calculated by incorporating the concentrations found in Table 2-1 in Equation 2-4, this equation can be depicted as follows:

Eq. 2-5

$$Em = g'K^+ (-96mV) + g'Na^+ (+50mV) + g'Ca^{++} (+134mV) + g'Cl^- (-46mV)$$

In a cardiac cell, the individual ion concentration gradients change very little, even when Na^+ enters and K^+ leaves the cell during depolarization. Therefore, *changes in Em primarily result from changes in ionic conductances.* The resting membrane potential is near the equilibrium potential for K^+ because g'K^+ is high relative to all of the other ionic conductances in the resting cell. Therefore, the low relative conductances of Na^+, Ca^{++}, and Cl^-,

multiplied by their equilibrium potential values, causes those ions to contribute little to the resting membrane potential. When g'Na^+ increases and g'K^+ decreases (as occurs during an action potential), the membrane potential becomes more positive (depolarized) because the sodium equilibrium potential has more influence on the overall membrane potential.

In Equation 2-4, ion concentrations (which determine the equilibrium potential) and ion conductances are separate variables. In reality, the conductance of some ion channels is influenced by the concentration of the ion (e.g., K^+-sensitive K^+-channels) or the changes in membrane potential (e.g., voltage-dependent Na^+, K^+, and Ca^{++} ion channels). For example, a decrease in external K^+ concentration (e.g., from 4 to 3 mM) can decrease gK^+ in some cardiac cells and lead to a small depolarization (less negative potential) instead of the hyperpolarization (more negative potential) predicted by the Nernst relationship or Equation 2-4. In some cells, small increases in external K^+ concentration (e.g., from a normal concentration of 4 mM to 6 mM) can cause a small hyperpolarization owing to activation of K^+-channels and an increase in gK^+.

Maintenance of Ionic Gradients

Membrane potential depends on the maintenance of ionic concentration gradients across the membrane. The maintenance of these concentration gradients requires the expenditure of energy (adenosine triphosphate [ATP] hydrolysis) coupled with ionic pumps. Consider the concentration gradients for Na^+ and K^+. Na^+ constantly leaks into the resting cell, and K^+ leaks out. Moreover, whenever an action potential is generated, additional Na^+ enters the cell and additional K^+ leaves. Although the number of ions moving across the sarcolemmal membrane in a single action potential is small relative to the total number of ions, many action potentials can lead to a significant change in the extracellular and intracellular concentration of these ions. To prevent this change from happening (i.e., to maintain the concentration gradients for Na^+ and K^+), an energy (ATP)-dependent pump system (**Na^+/K^+-adenosine triphosphatase [ATPase]**), located on the sarcolemma, pumps Na^+ out and K^+ into the cell (Fig. 2-3). Normal operation of this pump is essential to maintain Na^+ and K^+ concentrations across the membrane. If this pump stops working (such as under hypoxic conditions, when ATP is lost), or if the activity of the pump is inhibited by cardiac glycosides such as digitalis, Na^+ accumulates within the cell and intracellular K^+ falls. This change results in a depolarization of the resting membrane potential. It is important to note that this pump is **electrogenic** because it extrudes three Na^+ for every two K^+ entering the cell. By pumping more positive charges out of the cell than into it, the pump creates a negative potential within the cell. This electrogenic potential may be up to –10 mV. Inhibition of this pump, therefore, causes depolarization resulting from changes in Na^+ and K^+ concentration gradients and from the loss of an electrogenic component of the membrane potential. In addition, because the pump is electrogenic, increases in intracellular Na^+ or extracellular K^+ stimulate the activity of the Na^+/K^+-ATPase pump and produce hyperpolarizing currents.

Because Ca^{++} enters the cell, especially during action potentials, it is necessary to have a mechanism to maintain its concentration gradient. This maintenance is accomplished by Ca^{++} pumps and exchangers on the sarcolemma. Intracellular calcium concentrations in both cardiac and vascular smooth muscle cells range from 10^{-7} M at rest to 10^{-5} M during depolarization. The extracellular concentration of calcium is about 2×10^{-3} M (2 mM), causing a large chemical gradient for calcium to diffuse into the cell. Because cells have a negative resting membrane potential, an electrical force drives calcium into the cell. However, little calcium leaks into the cell except during action potentials when the cell membrane permeability to calcium increases. The calcium that enters the cell during action potentials must be removed from the cell; otherwise, an accumulation of calcium leads to cellular dysfunction.

Two primary mechanisms remove calcium from cells (see Fig. 2-3). The first involves an

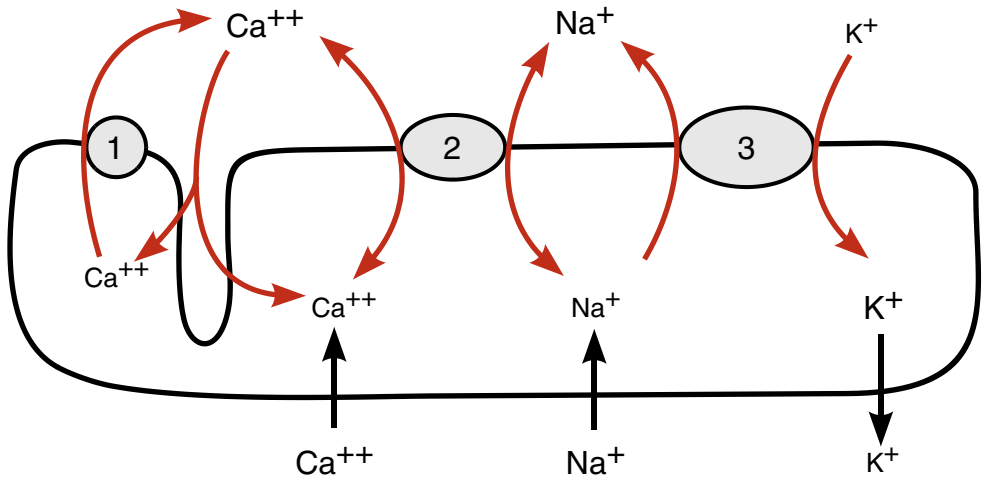

FIGURE 2-3 Sarcolemmal ion pumps and exchangers. These pumps maintain transmembrane ionic gradients for Na^+, K^+, and Ca^{++}. Na^+ and Ca^{++} enter the cell down their electrochemical gradient, especially during action potentials, while K^+ is leaving the cell. Ca^{++} is removed by an adenosine triphosphate (ATP)-dependent Ca^{++} pump (*1*) and by the Na^+/Ca^{++} exchanger (*2*). Na^+ is actively removed from the cell by the Na^+/K^+-ATPase pump, which brings K^+ into the cell; three Na^+ are pumped out for every two K^+; therefore this pump is electrogenic (i.e., it generates a negative potential across the sarcolemma). The Na^+/Ca^{++} exchanger is also electrogenic because it exchanges three Na^+ for every one Ca^{++}. The Ca^{++} pump is electrogenic as well.

ATP-dependent Ca^{++} pump that actively pumps calcium out of the cell and generates a small electrogenic potential. The second mechanism is the **sodium–calcium exchanger.** It is unclear exactly how this exchanger works. It is known, however, that the exchanger can operate in either direction across the sarcolemma. Furthermore, three sodium ions are exchanged for each calcium ion; therefore, the exchanger generates an electrogenic potential. The direction of movement of these ions (either inward or outward) depends upon the membrane potential and the chemical gradient for the ions. We know that an increase in intracellular sodium concentration leads to an increase in intracellular calcium through this exchange mechanism. An example of this is when the activity of the Na^+/K^+-ATPase pump is decreased by cellular hypoxia (which causes ATP levels to fall) or inhibited by chemical inhibitors such as digitalis. When the pump is inhibited, intracellular sodium concentrations increase. Increased intracellular sodium reduces the concentration gradient for Na^+, causing less Na^+ to enter the cell via the Na^+/Ca^{++} exchanger. The result is less Ca^{++} being extruded by the exchanger, leading to an accumulation of intracellular calcium.

Ion Channels

Ion conductance through the sarcolemma occurs because the sarcolemma is permeable to ions. Ions move across the sarcolemma through specialized ion channels, or pores, in the phospholipid bilayer of the cell membrane. These pores are made up of large polypeptide chains that span the membrane and create an opening in the membrane.

PROBLEM 2-1

High concentrations of potassium are added to cardioplegic solutions used to arrest the heart during surgery. Using the Nernst equation, calculate an estimate for the new resting membrane potential (Em) when external potassium concentration is increased from a normal value of 4 mM to 40 mM. Assume that the internal concentration remains at 150 mM and that K^+ and other ion conductances are not altered.

Using Equation 2-1, the membrane potential (actually, the equilibrium potential for potassium) with 4 mM external potassium would be –96 mV. Solving the equation for 40 mM external potassium results in a membrane potential of –35 mV. This is the membrane potential predicted by the Nernst equation assuming that no other ions contribute to the membrane potential (see Equation 2-3). This calculation also neglects any contribution of electrogenic pumps to the membrane potential. Nevertheless, a high concentration of external potassium causes a large depolarization, as predicted by the Nernst equation.

Conformational changes in the ion channel proteins alter the shape of the pore, thereby permitting ions to transverse the membrane channel.

Ion channels are selective for different cations and anions. For example, some ion channels are selective for sodium, potassium, calcium, and chloride ions (Table 2-2). Furthermore, a given ion may have several different types of ion channels responsible for its movement across a cell membrane. For example, several different types of potassium channels exist through which potassium ions move across the cell membrane during cellular depolarization and repolarization.

Two general types of ion channels exist: voltage gated (voltage operated) and receptor gated (receptor operated) channels. **Voltage gated channels** open and close in response to changes in membrane potential. Examples of voltage gated channels include several sodium, potassium, and calcium channels that are involved in cardiac action potentials. **Receptor gated channels** open and close in response to chemical signals operating through membrane receptors. For example, acetylcholine, which is the neurotransmitter released by the vagus nerves innervating the heart, binds to a sarcolemmal receptor that subsequently leads to the opening of special types of potassium channels ($I_{K,\,ACh}$).

Ion channels have both open and closed states. Ions pass through the channel only while it is in the open state. The open and closed states of voltage gated channels are regulated by the membrane potential. Fast sodium channels have been the most extensively studied, and a conceptual model has been developed based upon studies by Hodgkin and Huxley in the 1950s using the squid giant axon. In this model, two gates regulate the movement of sodium through the channel (Fig. 2-4). At a normal resting membrane potential (about –90 mV in cardiac myocytes), the sodium channel is in a resting, closed state. In this configuration, the m-gate (activation gate) is closed and the h-gate (inactivation gate) is open. These gates are polypeptides that are part of the transmembrane protein channel, and they undergo conformational changes in response to changes in voltage. The m-gates rapidly become activated and open when the membrane is rapidly depolarized. This permits sodium, driven by its electrochemical gradient, to enter the cell. As the m-gates open, the h-gates begin to close; however, the m-gates open more rapidly than the h-gates close. The difference in the opening and closing rates of the two gates permits sodium to briefly enter the cell. After a few milliseconds, however, the h-gates close and sodium ceases to enter the cell. The clos-

TABLE 2-2 CARDIAC ION CHANNELS AND CURRENTS

CHANNELS	GATING	CHARACTERISTICS
Sodium		
Fast Na^+ (I_{Na})	Voltage	Phase 0 of myocytes
Slow Na^+ (I_f)	Voltage & Receptor	Contributes to phase 4 pacemaker current in SA and AV nodal cells
Calcium		
L-type (I_{Ca})	Voltage	Slow inward, long-lasting current; phase 2 of myocytes and phases 4 and 0 of SA and AV nodal cells
T-type (I_{Ca})	Voltage	Transient current; contributes to phase 4 pacemaker current in SA and AV nodal cells
Potassium		
Inward rectifier (I_{K1})	Voltage	Maintains negative potential in phase 4; closes with depolarization; its decay contributes to pacemaker currents
Transient outward (I_{to})	Voltage	Contributes to phase 1 in myocytes
Delayed rectifier (I_{Kr})	Voltage	Phase 3 repolarization
ATP-sensitive ($I_{K,\ ATP}$)	Receptor	Inhibited by ATP; opens when ATP decreases
Acetylcholine activated ($I_{K,\ ACh}$)	Receptor	Activated by acetylcholine; Gi-protein coupled

I_x, Name of specific current

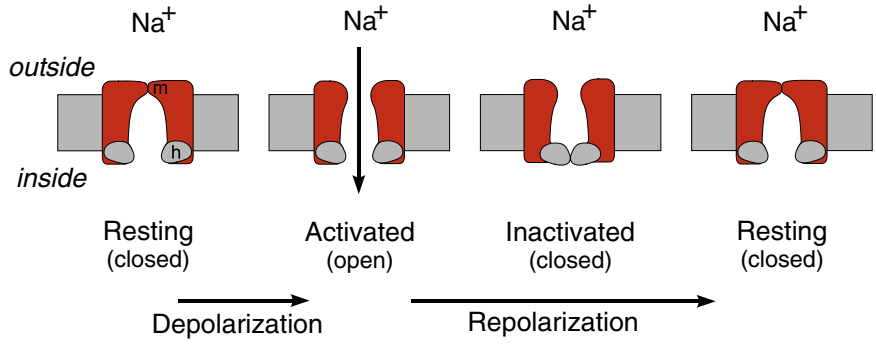

FIGURE 2-4 Open and closed states of fast sodium channels in cardiac myocytes. In the resting (closed) state, the m-gates (activation gates) are closed, although the h-gates (inactivation gates) are open. Rapid depolarization to threshold opens the m-gates (voltage activated), thereby opening the channel and enabling sodium to enter the cell. Shortly thereafter, as the cell begins to repolarize, the h-gates close and the channel becomes inactivated. Toward the end of repolarization, the m-gates again close and the h-gates open. This brings the channel back to its resting state.

ing of the h-gates therefore limits the length of time that sodium can enter the cell. This inactivated, closed state persists throughout the repolarization phase as the membrane potential recovers to its resting level. Near the end of repolarization, the negative membrane potential causes the m-gates to close and the h-gates to open. These changes cause the channel to revert back to its initial resting, closed state. Full recovery of the h-gates can take 100 milliseconds or longer after the resting membrane potential has been restored.

The response of the activation and inactivation gates described above occurs when the resting membrane potential is normal (about –90 mV) and a rapid depolarization of the membrane occurs, as happens when a normal depolarization current spreads from one cardiac cell to another during electrical activation of the heart. The response of the fast sodium channel, however, is different when the resting membrane potential is partially depolarized or the cell is slowly depolarized. For example, when myocytes become hypoxic, the cell depolarizes to a less negative resting membrane potential. This partially depolarized state inactivates sodium channels by closing the h-gates. The more a cell is depolarized, the greater the number of inactivated sodium channels. At a membrane potential of about –55 mV, virtually all fast sodium channels are inactivated. If a myocyte has a normal resting potential, but then undergoes slow depolarization, more time is available for the h-gates to close as the m-gates are opening. This causes the sodium channel to transition directly from the resting (closed) state to the inactivated (closed) state. The result is that there is no activated, open state for sodium to pass through the channel, effectively abolishing fast sodium currents through these channels. As long as the partial depolarized state persists, the channel will not resume its resting, closed state. As described later in this chapter, these changes significantly alter myocyte action potentials by abolishing fast sodium currents during action potentials.

A single cardiac cell has many sodium channels; each channel has a slightly different voltage activation threshold and duration of its open, activated state. The amount of sodium (the sodium current) that passes through sodium channels when a cardiac cell undergoes depolarization depends upon the number of sodium channels, the duration of time the channels are in the open state, and the electrochemical gradient driving the sodium into the cell.

The open and closed states described for sodium channels are also found in other ion channels. For example, slow calcium channels have activation and inactivation gates (although they have different letter designations than fast sodium channels). Although this conceptual model is useful to help understand how ions transverse the membrane, many of the details of how this actually occurs at the molecular level are still unknown. Nevertheless, recent research is helping to show which regions of ion channel proteins act as voltage sensors and which regions undergo conformational changes analogous to the gates described in the conceptual model.

Action Potentials

Action potentials occur when the membrane potential suddenly depolarizes and then repolarizes back to its resting state. The two general types of cardiac action potentials include nonpacemaker and pacemaker action potentials. Nonpacemaker action potentials are triggered by depolarizing currents from adjacent cells, whereas pacemaker cells are capable of spontaneous action potential generation. Both types of action potentials in the heart differ considerably from the action potentials found in neural and skeletal muscle cells (Fig. 2-5). One major difference is the duration of the action potentials. In a typical nerve, the action potential duration is about 1 millisecond. In skeletal muscle cells, the action potential duration is approximately 2-5 milliseconds. In contrast, the duration of ventricular action potentials ranges from 200 to 400 milliseconds. These differences among nerve, skeletal muscle, and cardiac myocyte action potentials relate to differences in the ionic conductances responsible for generating the changes in membrane potential.

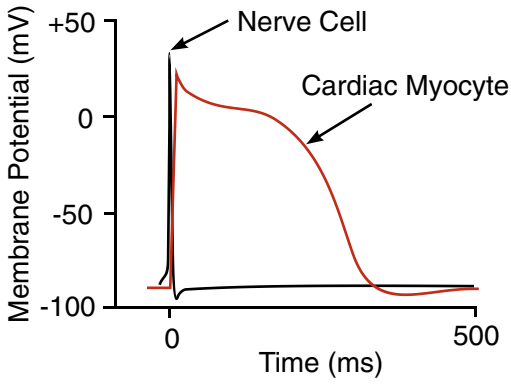

FIGURE 2-5 Comparison of action potentials from a nerve cell and a nonpacemaker cardiac myocyte. Cardiac action potentials are much longer in duration than nerve cell action potentials.

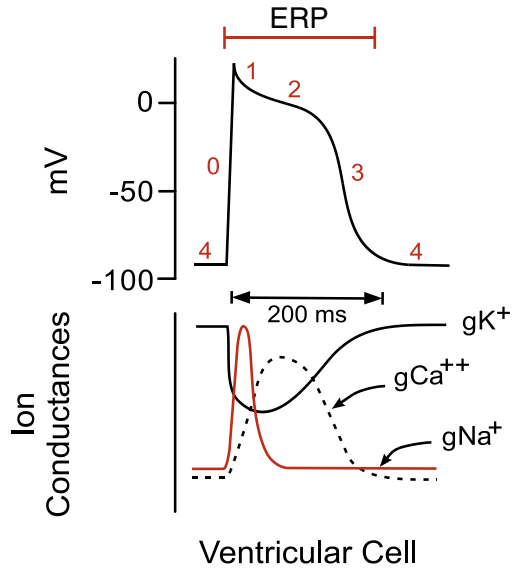

FIGURE 2-6 Changes in ion conductances associated with a ventricular myocyte action potential. Phase 0 (depolarization) primarily is due to the rapid increase in sodium conductance (gNa^+) accompanied by a fall in potassium conductance (gK^+); the initial repolarization of phase 1 is due to opening of special potassium channels (I_{to}); phase 2 (plateau) primarily is due to an increase in slow inward calcium conductance (gCa^{++}) through L-type Ca^{++} channels; phase 3 (repolarization) results from an increase in gK^+ and a decrease in gCa^{++}. Phase 4 is a true resting potential that primarily reflects a high gK^+. *ERP,* effective refractory period.

Nonpacemaker Action Potentials

Figure 2-6 shows the ionic mechanisms responsible for the generation of nonpacemaker action potentials. By convention, the action potential is divided into five numbered phases. Nonpacemaker cells, such as atrial and ventricular myocytes and Purkinje cells, have a true resting membrane potential (**phase 4**) that remains near the equilibrium potential for K^+. At the resting membrane potential, gK^+, through inward rectifying potassium channels (see Table 2-2), is high relative to gNa^+ and gCa^{++}. When these cells are rapidly depolarized from –90 mV to a threshold voltage of about –70 mV (owing to, for example, an action potential conducted by an adjacent cell), a rapid **depolarization** (**phase 0**) is initiated by a transient increase in fast Na^+-channel conductance. At the same time, gK^+ falls. These two conductance changes move the membrane potential away from the potassium equilibrium potential and closer to the sodium equilibrium potential (see Equation 2-4). **Phase 1** represents an **initial repolarization** caused by the opening of a special type of K^+ channel (transient outward) and the inactivation of the Na^+ channel. However, because of the large increase in slow inward gCa^{++}, the repolarization is delayed and the action potential reaches a **plateau phase** (**phase 2**). This inward calcium movement is through long-lasting (L-type) calcium channels that open when the membrane potential depolarizes to about –40 mV. L-type calcium channels are the major calcium channels in cardiac and vascular smooth muscle. They are opened by membrane depolarization (they are voltage-operated) and remain open for a relatively long duration. These channels are blocked by classical L-type calcium channel blockers (verapamil, diltiazem, and dihydropyridines such as nifedipine). **Repolarization** (**phase 3**) occurs when gK^+ increases through delayed rectifier potassium channels and gCa^{++} decreases. Therefore, changes in Na^+, Ca^{++}, and K^+ conductances primarily determine the action potential in nonpacemaker cells.

During phases 0, 1, 2, and part of phase 3, the cell is refractory (i.e., unexcitable) to the initiation of new action potentials. This is the **effective refractory period** (ERP) (see Fig.

2-6). During the ERP, stimulation of the cell does not produce new, propagated action potentials because the h-gates are still closed. The ERP acts as a protective mechanism in the heart by limiting the frequency of action potentials (and therefore contractions) that the heart can generate. This enables the heart to have adequate time to fill and eject blood. The long ERP also prevents the heart from developing sustained, tetanic contractions like those that occur in skeletal muscle. At the end of the ERP, the cell is in its **relative refractory period.** Early in this period, suprathreshold depolarization stimuli are required to elicit actions potentials. Because not all the sodium channels have recovered to their resting state by this time, action potentials generated during the relative refractory period have a decreased phase 0 slope and lower amplitude. When the sodium channels are fully recovered, the cell becomes fully excitable and normal depolarization stimuli can elicit new, rapid action potentials.

Nonpacemaker action potentials are also called "fast response" action potentials because of their rapid phase 0 depolarization. If the fast sodium channels that are responsible for the rapid phase 0 are blocked pharmacologically or inactivated by slow depolarization, the slope of phase 0 is significantly depressed, and the amplitude of the action potential is reduced. The depolarization phase of the action potential under these conditions is brought about by slow inward calcium currents carried through L-type calcium channels. These action potentials are called "slow response" action potentials and resemble action potentials found in pacemaker cells.

Pacemaker Action Potentials

Pacemaker cells have no true resting potential, but instead generate regular, spontaneous action potentials. Unlike most other cells that exhibit action potentials (e.g., nerve cells, and muscle cells), the depolarizing current of the action potential is carried primarily by relatively slow, inward Ca^{++} currents (through L-type calcium channels) instead of by fast Na^{+} currents. Fast Na^{+} channels are inactivated in nodal cells because of their more depolarized state, which closes the h-gates.

Cells within the **sinoatrial (SA) node,** located within the posterior wall of the right atrium, constitute the primary pacemaker site within the heart. Other pacemaker cells exist within the atrioventricular node and ventricular conduction system, but their firing rates are driven by the higher rate of the SA node because the intrinsic pacemaker activity of the secondary pacemakers is suppressed by a mechanism termed **overdrive suppression.** This mechanism causes the secondary pacemaker to become hyperpolarized when driven at a rate above its intrinsic rate. Hyperpolarization occurs because the increased action potential frequency stimulates the activity of the electrogenic Na^{+}/K^{+}-ATPase pump as a result of enhanced entry of sodium per unit time into these cells. If the SA node becomes depressed, or its action potentials fail to reach

PROBLEM 2-2

A drug is found to partially inactivate fast sodium channels. How would this drug alter the action potential in a ventricular myocyte? How would the drug alter conduction velocity within the ventricle?

Because phase 0 of myocyte action potentials is generated by activation of fast sodium channels, partial inactivation of these channels would decrease the upstroke velocity of phase 0 (decrease the slope of phase 0). Partial inactivation also would decrease the maximal degree of depolarization. These changes in phase 0 would reduce the conduction velocity within the ventricle. Blockade of fast sodium channels is the primary mechanism of action of Class I antiarrhythmic drugs such as quinidine and lidocaine.

secondary pacemakers, overdrive suppression ceases, which permits a secondary site to take over as the pacemaker for the heart. When this occurs, the new pacemaker is called an **ectopic foci.**

SA nodal action potentials are divided into three phases: phase 0, upstroke of the action potential; phase 3, the period of repolarization; and phase 4, the period of spontaneous depolarization that leads to subsequent generation of a new action potential (Fig. 2-7).

Phase 0 depolarization primarily is due to increased gCa^{++} through L-type calcium channels. These voltage-operated channels open when the membrane is depolarized to a threshold voltage of about –40 mV. Because the movement of Ca^{++} through calcium channels is not rapid (hence, the term "slow calcium channels"), the rate of depolarization (the slope of phase 0) is much slower than that found in other cardiac cells (e.g., in Purkinje cells). As the calcium channels open and the membrane potential moves toward the calcium equilibrium potential, a transient decrease in gK^+ occurs, which contributes to the depolarization as shown in the following equation:

$$Em = g'K\ (-96mV) + g'Ca\ (+134mV)$$

Depolarization causes voltage-operated, delayed rectifier potassium channels to open, and the increased gK^+ repolarizes the cell toward the equilibrium potential for K^+ (**phase 3**). At the same time, the slow inward Ca^{++} channels that opened during phase 0 become inactivated, thereby decreasing gCa^{++} and contributing to the repolarization. Phase 3 ends when the membrane potential reaches about –65 mV. The phase of repolarization is self-limited because the potassium channels begin to close again as the cell becomes repolarized.

The ionic mechanisms responsible for the spontaneous depolarization of the pacemaker potential (**phase 4**) are not entirely clear, but probably involve several different ionic currents. First, early in phase 4, gK^+ is still declining. This fall in gK^+ contributes to depolarization. Second, in the repolarized state, a **pacemaker current (I_f),** or "funny" current, has been identified. This current may involve a slow inward movement of Na^+. Third, in the second half of phase 4, there is a small increase in gCa^{++} through T-type calcium channels. T-type ("transient") calcium channels differ from L-type calcium channels in that they open briefly only at very negative voltages (–50 mV) and are not blocked by the classical L-type calcium channel blockers. Fourth, as the depolarization begins to reach threshold, the L-type calcium channels begin to open, causing a further increase in gCa^{++} until threshold is reached and phase 0 is initiated.

To summarize, the action potential in SA nodal cells primarily depends on changes in gCa^{++} and gK^+ conductances, with slow Na^+ currents (I_f) and changes in gCa^{++} and gK^+ conductances playing a role in the spontaneous depolarization.

The SA node displays intrinsic automaticity at a rate of 100 to 110 depolarizations per minute. Heart rate, however, can vary between low resting values of about 60 beats/min to over 200 beats/min. These changes in

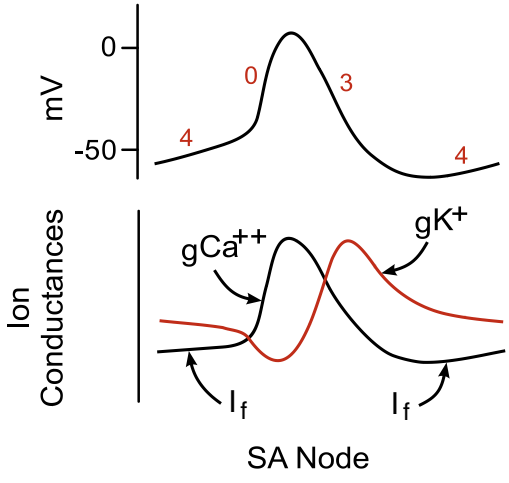

FIGURE 2-7 Changes in ion conductances associated with a sinoatrial (*SA*) nodal action potential. Phase 0 (depolarization) primarily is due to an increase in calcium conductance (gCa^{++}) through L-type Ca^{++} channels accompanied by a fall in potassium conductance (gK^+); phase 3 (repolarization) results from an increase in gK^+ and a decrease in gCa^{++}. Phase 4 undergoes a spontaneous depolarization owing to a pacemaker current (I_f) carried in part by Na^+; decreased gK^+ and increased gCa^{++} also contribute to the spontaneous depolarization.

rate primarily are controlled by autonomic nerves acting on the SA node. At resting heart rates, vagal influences are dominant over sympathetic influences. This is termed **vagal tone.** Autonomic nerves increase SA nodal firing rate by both decreasing vagal tone and increasing sympathetic activity on the SA node in a reciprocal manner. An increase in heart rate is a positive chronotropic response (or **positive chronotropy**), whereas a reduction in heart rate is a negative chronotropic response (or **negative chronotropy**).

Autonomic influences alter the rate of pacemaker firing through the following mechanisms: (1) changing the slope of phase 4; (2) altering the threshold for triggering phase 0; and (3) altering the degree of hyperpolarization at the end of phase 3. Any of these three mechanisms will either increase or decrease the time to reach threshold. Sympathetic activation of the SA node increases the slope of phase 4 (Fig. 2-8) and lowers the threshold, thereby increasing pacemaker frequency (positive chronotropy). In this mechanism, norepinephrine binds to β_1-adrenoceptors coupled to a stimulatory G-protein (Gs-protein), which activates adenylyl cyclase and increases cyclic adenosine monophosphate (cAMP; see Chapter 3). This effect leads to an increased opening of L-type calcium channels and an increase in I_f, both of which increase the rate of depolarization. Vagal stimulation releases acetylcholine at the SA node, which decreases the slope of phase 4, hyperpolarizes the cell, and increases threshold. All of these effects cause the pacemaker potential to take longer to reach threshold, thereby slowing the rate (negative chronotropy). Acetylcholine binds to muscarinic receptors (M_2) and decreases cAMP via the inhibitory G-protein (Gi-protein), the opposite effect of sympathetic activation (see Chapter 3). Acetylcholine may also increase cyclic guanosine monophosphate (cGMP) through the nitric oxide (NO)–cGMP pathway, which inactivates L-type calcium channels. Finally, acetylcholine, acting through the Gi-protein, activates a special type of potassium channel (K_{ACh} channel) that hyperpolarizes the cell by increasing potassium conductance.

Nonneural mechanisms also alter pacemaker activity (Table 2-3). For example, circulating catecholamines (epinephrine and norepinephrine) cause tachycardia by a mechanism similar to norepinephrine released by sympathetic nerves. Hyperthyroidism induces tachycardia, and hypothyroidism induces bradycardia. Changes in the serum concentration of ions, particularly potassium, can cause changes in SA node firing rate. Hyperkalemia induces bradycardia or can even stop SA nodal firing, whereas hypokalemia increases the rate of phase 4 depolarization and causes tachycardia, apparently by decreasing potassium conduc-

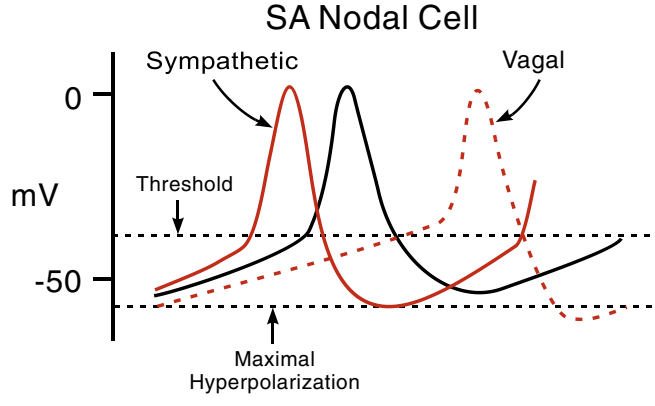

FIGURE 2-8 Effects of sympathetic and parasympathetic (vagal) stimulation on sinoatrial (*SA*) nodal pacemaker activity. Sympathetic stimulation increases the firing rate by increasing the slope of phase 4 and lowering the threshold for the action potential. Vagal stimulation has the opposite effects, and it hyperpolarizes the cell.

TABLE 2-3 FACTORS INCREASING OR DECREASING THE SINOATRIAL NODE FIRING RATE

INCREASING	DECREASING
Sympathetic stimulation	Parasympathetic stimulation
Muscarinic receptor antagonist	Muscarinic receptor agonists
β-Adrenoceptor agonists	β-Blockers
Circulating catecholamines	Ischemia/hypoxia
Hypokalemia	Hyperkalemia
Hyperthyroidism	Sodium and calcium channel blockers

tance during phase 4. Cellular hypoxia depolarizes the membrane potential, causing bradycardia and abolition of pacemaker activity.

Various drugs used to treat abnormal heart rhythm (i.e., antiarrhythmic drugs) also affect SA nodal rhythm. Calcium channel blockers, for example, cause bradycardia by inhibiting L-type calcium channels and slow inward Ca^{++} currents during phase 4 and phase 0. Drugs affecting autonomic control or autonomic receptors (e.g., β-blockers and M_2 receptor antagonists; β-adrenoceptor agonists) alter pacemaker activity. Digitalis causes bradycardia by increasing parasympathetic activity and inhibiting the sarcolemmal Na^+/K^+-ATPase, which leads to depolarization.

Abnormal Action Potentials

By mechanisms not fully clear, nonpacemaker cells may undergo spontaneous depolarizations either during phase 3 or early in phase 4, triggering abnormal action potentials. These spontaneous depolarizations (termed **afterdepolarizations**), if of sufficient magnitude, can trigger self-sustaining action potentials resulting in tachycardia (Fig. 2-9). **Early afterdepolarizations** occur during phase 3 and are more likely to occur when action potential durations are prolonged. Because these afterdepolarizations occur at a time when fast Na^+ channels are still inactivated, slow inward Ca^{++} carries the depolarizing current. Another type of afterdepolarization, **delayed afterdepolarization,** occurs at the end of phase 3 or early in phase 4. It, too, can lead to self-sustaining action potentials and tachycardia. This form of triggered activity appears to be associated with elevations in intracellular calcium, as occurs during ischemia, digitalis toxicity, and excessive catecholamine stimulation.

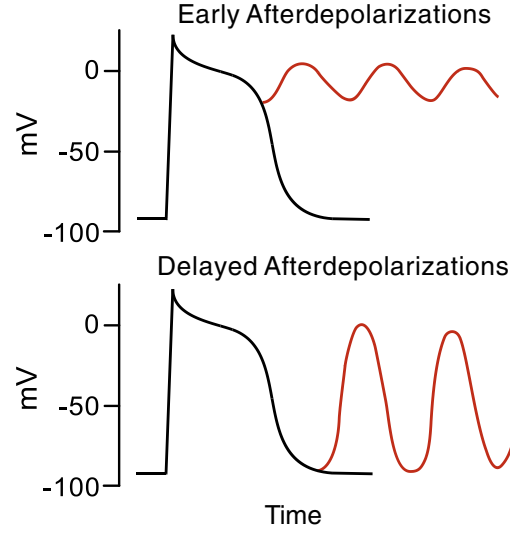

FIGURE 2-9 Early (*top panel*) and delayed (*bottom panel*) afterdepolarizations. If the magnitude of spontaneous depolarization is sufficient, it can trigger self-sustaining action potentials.

CONDUCTION OF ACTION POTENTIALS WITHIN THE HEART

Electrical Conduction within the Heart

The action potentials generated by the SA node spread throughout the atria primarily through cell-to-cell conduction (Fig. 2-10).

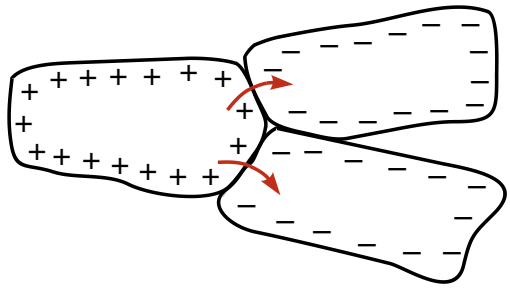

FIGURE 2-10 Cell-to-cell conduction. Cardiac cells are connected together by low-resistance gap junctions between the cells, forming a functional syncytium. When one cell depolarizes, depolarizing currents can pass through the gap junctions and depolarize adjacent cells, resulting in a cell-to-cell propagation of action potentials.

When a single myocyte depolarizes, positive charges accumulate just inside the sarcolemma. Because individual myocytes are joined together by low-resistance **gap junctions** located at the **intercalated disks,** ionic currents can flow between two adjoining cells. When these ionic intercellular currents are sufficient to depolarize the adjoining cell to its threshold potential, an action potential is elicited in the second cell. Through this current spread or conduction between adjacent cells, action potentials are propagated throughout the atria. Action potentials in the atrial muscle have a conduction velocity of about 0.5 m/sec, which is similar to that of ventricular muscle (Fig. 2-11). Although the conduction of action potentials within the atria is primarily between myocytes, some functional evidence (although controversial) points to the existence of specialized conducting pathways within the atria, termed internodal tracts. As each wave of action potentials originating from the SA node spreads across and depolarizes the atrial muscle, it initiates excitation–contraction coupling (see Chapter 3).

Nonconducting connective tissue separates the atria from the ventricles. Action potentials normally have only one pathway available to enter the ventricles, a specialized region of cells called the **atrioventricular (AV) node.** The AV node, located in the inferior–posterior region of the interatrial septum, is a highly specialized conducting tissue (cardiac, not neural in origin) that slows the impulse con-

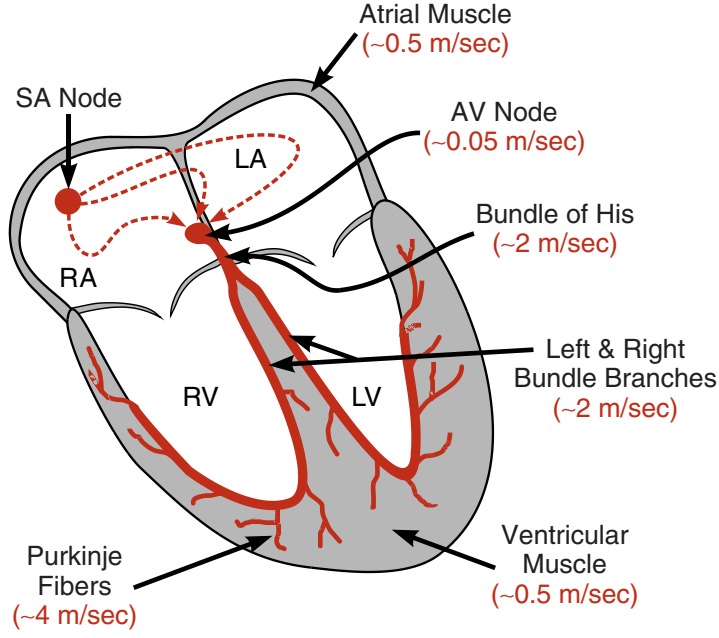

FIGURE 2-11 Conduction system within the heart. Conduction velocities of different regions are noted in parentheses. Note that Purkinje fibers have the highest conduction velocity and the atrioventricular (*AV*) node has the lowest conduction velocity. *SA,* sinoatrial.

duction velocity to about 0.05 m/sec. This is one-tenth the velocity found in atrial or ventricular myocytes (see Fig. 2-11).

The delay in conduction between the atria and ventricles at the AV node is important. First, it allows sufficient time for complete atrial depolarization, contraction, and emptying of atrial blood into the ventricles prior to ventricular depolarization and contraction (see Chapter 4). Second, the low conduction velocity helps to limit the frequency of impulses traveling through the AV node and activating the ventricle. This is important in atrial flutter and fibrillation, in which excessively high atrial rates, if transmitted to the ventricles, lead to severe ventricular tachycardia and reduced cardiac output caused by inadequate time for ventricular filling.

Action potentials leaving the AV node enter the base of the ventricle at the **bundle of His** and then follow the left and right **bundle branches** along the interventricular septum. These specialized bundle branch fibers conduct action potentials at a high velocity (about 2 m/sec). The bundle branches divide into an extensive system of **Purkinje fibers** that conduct the impulses at high velocity (about 4 m/sec) throughout the ventricles. The Purkinje fiber cells connect with ventricular myocytes, which become the final pathway for cell-to-cell conduction within the heart.

The conduction system within the heart is important because it permits rapid, organized, near-synchronous depolarization and contraction of ventricular myocytes, which is essential to generate pressure efficiently during ventricular contraction. If the conduction system becomes damaged or dysfunctional, as can occur during ischemic conditions or myocardial infarction, this change can lead to altered pathways of conduction and decreased conduction velocity within the heart. The functional consequence is that it diminishes the ability of the ventricles to generate pressure. Furthermore, damage to the conducting system can precipitate arrhythmias.

Regulation of Conduction Velocity

The rate of cell-to-cell conduction is determined by several intrinsic and extrinsic factors. Intrinsic factors include the electrical resistance between cells and the nature of the action potential, particularly in the initial rate of depolarization (phase 0). As discussed earlier in this chapter, fast sodium channels are responsible for the rapid upstroke velocity of nonpacemaker action potentials. Increasing the number of activated fast sodium channels increases the rate of depolarization. The more rapidly one cell depolarizes, the more quickly an adjoining cell depolarizes. Therefore, conditions that decrease the availability of fast sodium channels (e.g., depolarization caused by cellular hypoxia), decrease the rate and magnitude of phase 0, thereby decreasing conduction velocity within the heart. In AV nodal tissue in which slow inward calcium primarily determines phase 0 of the action potential, alterations in calcium conductance alter the rate of depolarization and therefore the rate of conduction between AV nodal cells.

Extrinsic factors can influence conduction velocity, including autonomic nerves, circulating hormones (particularly catecholamines), and various drugs (Table 2-4). Autonomic

TABLE 2-4 EXTRINSIC FACTORS INCREASING OR DECREASING CONDUCTION VELOCITY WITHIN THE HEART

INCREASING	DECREASING
Sympathetic stimulation	Parasympathetic stimulation
Muscarinic receptor antagonists	Muscarinic receptor agonists
β_1-Adrenoceptor agonists	Beta-blockers
Circulating catecholamines	Ischemia/hypoxia
Hyperthyroidism	Sodium and calcium channel blockers

nerve activity significantly influences the conduction of electrical impulses throughout the heart, particularly in the specialized conduction system. An increase in sympathetic firing (or increased circulating catecholamines) increases conduction velocity via norepinephrine binding to β_1-adrenoceptors. The activation of parasympathetic (vagal) nerves decreases conduction velocity via the action of acetylcholine on M_2 receptors. The signal transduction mechanisms coupled to β_1-adrenoceptors and M_2 receptors (Gs- and Gi-proteins) are the same as described in Chapter 3 (see Fig. 3-6) for the regulation of cardiac contraction. A number of drugs can affect conduction velocity by altering autonomic influences or directly altering intercellular conduction. For example, antiarrhythmic drugs that block fast sodium channels decrease conduction velocity; digitalis compounds activate vagal influences on the conduction system; and β-adrenoceptor agonists or antagonists can increase or decrease conduction velocity, respectively.

Abnormal Conduction

When electrical activation of the heart does not follow the normal pathways outlined earlier, ventricular contraction efficiency may be reduced and arrhythmias may be precipitated. For example, if the AV node becomes completely blocked by ischemic damage or excessive vagal stimulation, impulses cannot travel from the atria into the ventricles. Fortunately, latent pacemakers within the ventricular conduction system usually take over to activate the ventricles; however, the lower firing rate of these pacemakers results in ventricular bradycardia and decreased cardiac output. As another example, if one of the bundle branches is blocked, ventricular depolarization still occurs, but the depolarization pathways will be altered leading to a delay in ventricular activation and reduced contraction efficiency. An ectopic beat originating within the ventricle can cause altered pathways of conduction as well. When this occurs outside of the normal fast conducting system, it alters the pathway of depolarization, and ventricular depolarization has to rely on the relatively slow cell-to-cell conduction between myocytes.

In addition, abnormal conduction can arise from accessory conduction pathways, such as may be found between the atria and ventricles. These accessory pathways alter the route and sequence of ventricular depolarization and often result in arrhythmias (e.g., supraventricular tachycardias), which occur as a result of **reentry mechanisms** (see Reentry Mechanisms on CD).

THE ELECTROCARDIOGRAM (ECG)

The ECG is a crucial diagnostic tool in clinical practice. It is especially useful in diagnosing rhythm disturbances, changes in electrical conduction, and myocardial ischemia and infarction. The remaining sections of this chapter describe how the ECG is generated and how it can be used to examine changes in cardiac electrical activity. For more in-depth information about this topic, particularly how to interpret abnormal ECGs, consult detailed clinical textbooks such as those listed at the end of this chapter.

ECG Tracing

As cardiac cells depolarize and repolarize, electrical currents spread throughout the body because the tissues surrounding the heart are able to conduct electrical currents generated by the heart. When these electrical currents are measured by an array of electrodes placed at specific locations on the body surface, the recorded tracing is called an ECG (Fig. 2-12). The repeating waves of the ECG represent the sequence of depolarization and repolarization of the atria and ventricles. The ECG does not measure absolute voltages, but voltage changes from a baseline (isoelectric) voltage. ECGs are generally recorded on paper at a speed of 25 mm/sec and with a vertical calibration of 1 mV/cm.

By convention, the first wave of the ECG is the **P wave.** It represents the wave of depolarization that spreads from the SA node throughout the atria; it is usually 0.08 to 0.1 seconds

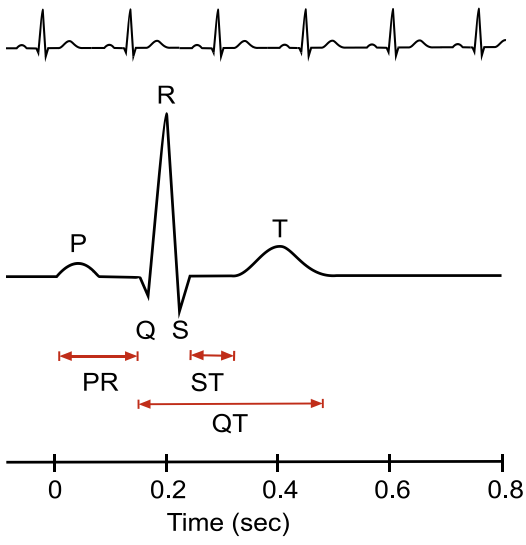

FIGURE 2-12 Components of the ECG trace. A rhythm strip at the top shows a typical ECG recording. An enlargement of one of the repeating waveform units shows the P wave, QRS complex, and T wave, which represent atrial depolarization, ventricular depolarization, and ventricular repolarization, respectively. The P-R interval represents the time required for the depolarization wave to transverse the atria and the atrioventricular node; the Q-T interval represents the period of ventricular depolarization and repolarization; and the ST segment is the isoelectric period when the entire ventricle is depolarized.

(80-100 m/sec) in duration (Table 2-5). No distinctly visible wave represents atrial repolarization in the ECG because it occurs during ventricular depolarization and is of relatively small amplitude. The brief isoelectric (zero voltage) period after the P wave represents the time in which the atrial cells are depolarized and the impulse is traveling within the AV node, where conduction velocity is greatly reduced. The period of time from the onset of the P wave to the beginning of the QRS complex, the **P-R interval,** normally ranges from 0.12 to 0.20 seconds. This interval represents the time between the onset of atrial depolarization and the onset of ventricular depolarization. If the P-R interval is greater than 0.2 seconds, a conduction defect (usually within the AV node) is present (e.g., first-degree heart block).

The **QRS complex** represents ventricular depolarization. The duration of the QRS complex is normally 0.06 to 0.1 seconds, indicating that ventricular depolarization occurs rapidly. If the QRS complex is prolonged (greater than 0.1 seconds), conduction is impaired within the ventricles. Impairment can occur with defects (e.g., bundle branch blocks) or aberrant conduction, or it can occur when an ectopic ventricular pacemaker drives ventricular depolarization. Such ectopic foci nearly always cause impulses to be conducted over slower pathways within the heart, thereby increasing the time for depolarization and the duration of the QRS complex.

The isoelectric period (**ST segment**) following the QRS is the period at which the entire ventricle is depolarized and roughly corresponds to the plateau phase of the ventricular action potential. The ST segment is important in the diagnosis of ventricular

TABLE 2-5 SUMMARY OF ECG WAVES, INTERVALS, AND SEGMENTS

ECG COMPONENT	REPRESENTS	NORMAL DURATION (SEC)
P wave	Atrial depolarization	0.08 – 0.10
QRS complex	Ventricular depolarization	0.06 – 0.10
T wave	Ventricular repolarization	[1]
P-R interval	Atrial depolarization plus AV nodal delay	0.12 – 0.20
ST segment	Isoelectric period of depolarized ventricles	[1]
Q-T interval	Length of depolarization plus repolarization – corresponds to action potential duration	0.20 – 0.40 [2]

[1] Duration not normally measured. [2] High heart rates reduce the action potential duration and therefore the Q-T interval.

ischemia, in which the ST segment can become either depressed or elevated, indicating nonuniform membrane potentials in ventricular cells. The **T wave** represents ventricular repolarization (phase 3 of the action potential) and lasts longer than depolarization.

During the **Q-T interval,** both ventricular depolarization and repolarization occur. This interval roughly estimates the duration of ventricular action potentials. The Q-T interval can range from 0.2 to 0.4 seconds depending on heart rate. At high heart rates, ventricular action potentials are shorter, decreasing the Q-T interval. Because prolonged Q-T intervals can be diagnostic for susceptibility to certain types of arrhythmias, it is important to determine if a given Q-T interval is excessively long. In practice, the Q-T interval is expressed as a corrected Q-T (Q-Tc) interval by taking the Q-T interval and dividing it by the square root of the R-R interval (the interval between ventricular depolarizations). This calculation allows the Q-T interval to be assessed independent of heart rate. Normal corrected Q-Tc intervals are less than 0.44 seconds.

Interpretation of Normal and Abnormal Cardiac Rhythms from the ECG

One important use of the ECG is that it lets a physician evaluate abnormally slow, rapid, or irregular cardiac rhythm. Atrial and ventricular rates of depolarization can be determined from the frequency of P waves and QRS complexes by recording a **rhythm strip.** A rhythm strip is usually generated from a single electrocardiogram lead (often lead II). In a normal ECG, a consistent, one-to-one correspondence exists between P waves and the QRS complex; i.e., each P wave is followed by a QRS complex. This correspondence, when found, indicates that ventricular depolarization is being triggered by atrial depolarization. Under these normal conditions, the heart is said to be in **sinus rhythm,** because the SA node is controlling the cardiac rhythm. Normal sinus rhythm can range from 60–100 beats/min. Although the term "beats" is being used here, strictly speaking, the electrocardiogram gives information only about the frequency of electrical depolarizations. However, a depolarization usually results in contraction and therefore a "beat."

Abnormal rhythms (arrhythmias) can be caused by abnormal formation of action potentials. A sinus rate less than 60 beats/min is termed **sinus bradycardia.** The resting sinus rhythm, as previously described, is highly dependent on vagal tone. Some people, especially highly conditioned athletes, may have normal resting heart rates that are significantly less than 60 beats/min. In other individuals, sinus bradycardia may result from depressed SA nodal function. A sinus rate of 100–180 beats/min, **sinus tachycardia,** is an abnormal condition for a person at rest; however, it is a normal response when a person exercises or becomes excited.

In a normal ECG, a QRS complex follows each P wave. Conditions exist, however, when the frequency of P waves and QRS complexes may be different (Fig. 2-13). For example, atrial rate may become so high in **atrial flutter** (250-350 beats/min) that not all of the impulses are conducted through the AV node; therefore, the ventricular rate (as determined by the frequency of QRS complexes) may be only half of the atrial rate. In **atrial fibrillation,** the SA node does not trigger the atrial depolarizations. Instead, depolarization currents arise from many sites throughout the atria, leading to uncoordinated, low-voltage, high-frequency depolarizations with no discernable P waves. In this condition, the ventricular rate is irregular and usually rapid. Atrial fibrillation illustrates an important function of the AV node; it limits the frequency of impulses that it conducts, thereby limiting ventricular rate. This feature is mechanically consequential because when ventricular rates become very high (e.g., greater than 200 beats/min), cardiac output falls owing to inadequate time for ventricular filling between contractions.

Atrial rate is greater than ventricular rate in some forms of **AV nodal blockade** (see Fig. 2-13). This is an example of an arrhythmia caused by abnormal (depressed) impulse conduction. With AV nodal blockade, atrial

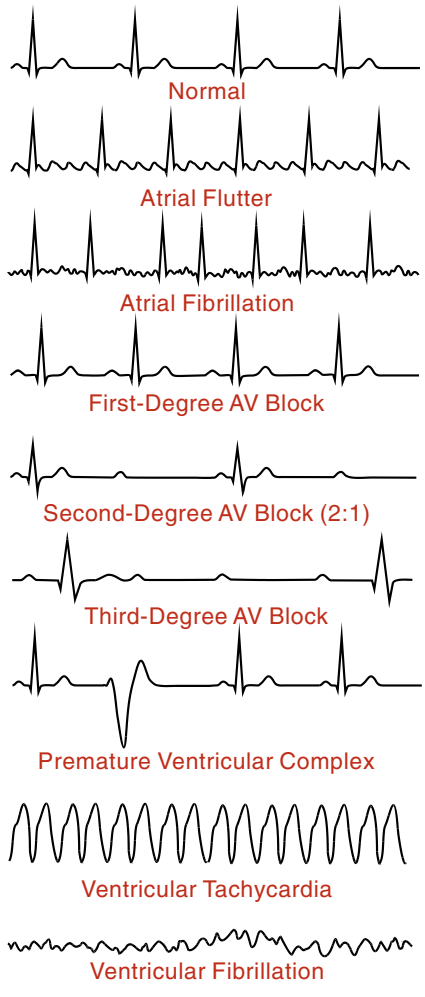

FIGURE 2-13 ECG examples of abnormal rhythms. *AV,* atrioventricular.

rate is normal, but every atrial depolarization may not be followed by a ventricular depolarization. A **second-degree AV nodal block** may have two or three P waves preceding each QRS complex because the AV node does not successfully conduct every impulse. In a less severe form of AV nodal blockade, the conduction through the AV node is delayed, but the impulse is still able to pass through the AV node and excite the ventricles. With this condition, termed **first-degree AV nodal block,** a consistent one-to-one correspondence remains between the P waves and QRS complexes; however, the P-R interval is found to be greater than 0.2 seconds. In an extreme form of AV nodal blockade, **third-degree AV nodal block,** no atrial depolarizations are conducted through the AV node, and P waves and QRS complexes are completely dissociated. The ventricles still undergo depolarization because of the expression of secondary pacemaker sites (e.g., at the AV nodal junction or from some ectopic foci within the ventricles); however, the ventricular rate is generally slow (less than 40 beats/min). Bradycardia occurs because the intrinsic firing rate of secondary, latent pacemakers is much slower than in the SA node. For example, pacemaker cells within the AV node and bundle of His have rates of 50–60 beats/min, whereas those in the Purkinje system have rates of only 30–40 beats/min. If the ectopic foci is located within the ventricle, the QRS complex will have an abnormal shape and be wider than normal because depolarization does not follow the normal conduction pathways.

A condition can arise in which ventricular rate is greater than atrial rate; i.e., the frequency of QRS complexes is greater than the frequency of P waves (see Fig. 2-13). This condition is termed **ventricular tachycardia** (100–200 beats/min) or **ventricular flutter** (greater than 200 beats/min). The most common causes of ventricular arrhythmias are reentry circuits caused by abnormal impulse conduction within the ventricles or rapidly firing ectopic pacemaker sites within the ventricles (which may be caused by afterdepolarizations). With ventricular arrhythmias, there is a complete dissociation between atrial and ventricular rates. Both ventricular tachycardia and ventricular flutter are serious clinical conditions because they compromise ventricular mechanical function and can lead to **ventricular fibrillation.** This latter condition is seen in the ECG as rapid, low-voltage, uncoordinated depolarizations (having no discernable QRS complexes), which results in cardiac output going to zero. This lethal condition can sometimes be reverted to a sinus rhythm by applying strong but brief electrical currents to the heart by placing electrodes on the chest (electrical defibrillation).

CASE 2-1

A patient is being treated for hypertension with a β-blocker (a drug that blocks to β-adrenoceptors in the heart) in addition to a diuretic. A routine ECG reveals that the patient's P-R interval is 0.24 seconds (first-degree AV nodal block). Explain how removal of the β-blocker might improve AV nodal conduction.

Sympathetic nerve activity increases conduction velocity within the AV node (positive dromotropic effect). This effect on the AV node is mediated by norepinephrine binding to β-adrenoceptors within the nodal tissue. A β-blocker would remove this sympathetic influence and slow conduction within the AV node, which might prolong the P-R interval. Therefore, taking the patient off the β-blocker might improve AV nodal conduction and thereby decrease the P-R interval to within the normal range (0.12 to 0.20 seconds).

The ECG can reveal another type of arrhythmia, **premature depolarizations** (see Fig. 2-13). These depolarizations can occur within either the atria (premature atrial complex) or the ventricles (premature ventricular complex). They are usually caused by ectopic pacemaker sites within these cardiac regions and appear as extra (and early) P waves or QRS-complexes. These premature depolarizations are often abnormally shaped, particularly in ventricles, because the impulses generated by the ectopic site are not conducted through normal pathways.

Volume Conductor Principles and ECG Rules of Interpretation

The previous section defined the components of the ECG trace and what they represent in terms of electrical events within the heart. This section examines in more detail how the recorded ECG waveform depends on (1) location of recording electrodes on the body surface; (2) conduction pathways and speed of conduction; and (3) changes in muscle mass. To interpret the significance of changes in the appearance of the ECG, we must first understand the basic principles of how the ECG is generated and recorded.

Recording Depolarization and Repolarization using External Electrodes

Figure 2-14 depicts a piece of living ventricular muscle placed into a bath containing a conducting, physiologic salt solution. Electrodes are located on either side of the muscle to measure potential differences. Initially, no potential difference exists between the two electrodes (i.e., an **isoelectric** voltage), because all of the cells are completely polarized (i.e., at rest). The reason for isoelectric voltage is that the outside of all of the cells is positive relative to the inside (see Fig. 2-14, panel A). Normally in cell physiology, the inside of the cell is considered negative relative to the outside (which is zero by convention); however, for this model, assume that the outside is positive relative to the inside so that a separation of charges can be displayed on the surface of the model. Because the entire surface is positive, no current is flowing along the surface of the muscle. If the left side of the muscle was suddenly depolarized to generate action potentials, a wave of depolarization would sweep across the muscle from left to right as action potentials were propagated by cell-to-cell conduction. Midway through this depolarization process, depolarized cells on the left would be negative on the outside relative to the inside, whereas nondepolarized cells on the right side of the muscle would be still polarized (positive on the outside) (see Fig. 2-14, panel B). A potential difference between the positive and negative electrodes would now exist owing to a separation of charges (i.e., an **electrical dipole**). By convention, *a wave of depolarization heading toward the positive electrode is recorded as a positive voltage* (an upward deflection in the recording). Immediately after the wave of depolarization sweeps across the

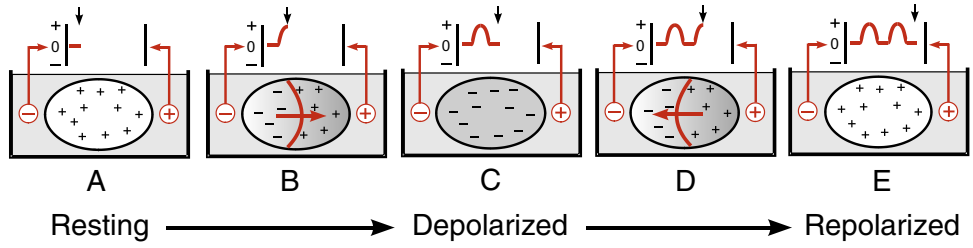

FIGURE 2-14 A model of the way depolarization and repolarization of ventricular muscle results in voltage changes recorded by external electrodes. Ventricular muscle is placed in a conducting solution, and electrodes are located on either side of the muscle to record potential differences. (*A*) Resting (polarized) muscle has the same potential across the surface, as indicated by positive charges outside of the cells (relative to the negative cell interior; see text); therefore, the electrodes record no potential difference between them (0 voltage; i.e., isoelectric). (*B*) Muscle depolarizes beginning at the left side, and a wave of depolarization (*arrow*) travels from left to right across the muscle. The separation of charges in the partially depolarized muscle results in a positive voltage recording (analogous to the QRS complex). (*C*) All of the muscle is depolarized (all cells negative on the outside), so that there is no separation of charge and therefore no potential difference (isoelectric; analogous to the ST segment). (*D*) Partially repolarized muscle; the last cells to depolarize are the first to repolarize, resulting in a wave of repolarization (*arrow*) moving from right to left. The separation of charges results in a positive voltage recording (analogous to the T wave). (*E*) Muscle fully repolarized as in *A*.

entire muscle mass, all of the cells on the outside are negative, and once again, no potential difference exists between the two electrodes (i.e., isoelectric voltage) (Fig. 2-14, panel C). Because the movement of the wave of depolarization is time dependent, we initially see zero voltage (panel A) followed by a transient positive voltage deflection (panel B), ending once again at zero voltage (panel C). This pattern depicts in simplistic terms the process of atrial and ventricular depolarizations, and the way the P wave and QRS complex, respectively, are generated.

All of the cells are depolarized for only a brief period of time, after which they undergo repolarization. For this model, assuming that the last cells to depolarize are the first to repolarize, a wave of repolarization would move from right-to-left (panel D). As repolarization occurs, cells on the right (nearest to the positive electrode) are the first to become positive again on the outside. This event results in a potential difference between the electrodes, with the positive electrode "seeing" a positive polarity and therefore recording a positive voltage. After the wave of repolarization sweeps across the entire mass and all the cells become repolarized, the entire surface is once again positive and no potential difference exists between the electrodes (i.e., isoelectric voltage) (Fig. 2-14, panel E). By convention, *a wave of repolarization moving away from a positive electrode produces a positive voltage difference.* This repolarization direction is what happens in the ventricle and explains why the T wave, which represents ventricular repolarization, is normally positive. If the wave of repolarization were to begin with the first cells that depolarized, the wave would travel toward the positive electrode, and a negative voltage deflection would be recorded. Therefore, by convention, *a wave of repolarization moving toward a positive electrode produces a negative voltage deflection* in the ECG. This repolarization direction is what happens in the atria. If atrial repolarization could be seen in the ECG, the waveform would have a negative voltage deflection.

Vectors and Mean Electrical Axis

The simplified model presented in Figure 2-14 depicts single waves of depolarization and repolarization. In reality, there is no single wave of electrical activity through the muscle. As illustrated for the atria in Figure 2-15, when the SA node fires, many separate depolarization waves emerge from the SA node and travel throughout the atria. These separate waves can be depicted as arrows representing individual **electrical vectors.** At any

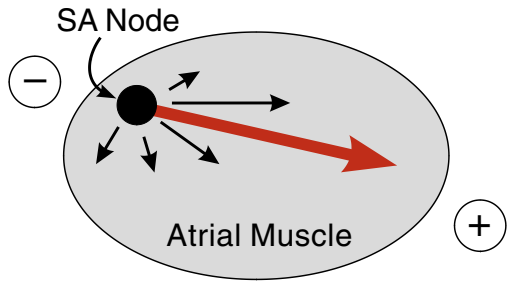

FIGURE 2-15 Electrical vectors. Instantaneous individual vectors of depolarization (*black arrows*) spread across the atria after the sinoatrial (SA) node fires. The mean electrical vector (*red arrow*) represents the sum of the individual vectors at a given instant in time.

given instant, many individual vectors exist; each one represents action potential conduction in a different direction. A **mean electrical vector** can be derived at that instant by summing the individual vectors.

The direction of the mean electrical vector relative to the axis between the recording electrodes determines the polarity and magnitude of the recorded voltage (Fig. 2-16). If the mean electrical vector is pointing toward the positive electrode, the ECG displays a positive deflection (positive voltage). If at some other instant the mean electrical vector is pointing away from the positive electrode, there is a negative deflection (negative voltage). If the mean electrical vector is oriented perpendicular to the axis between the positive and negative electrodes, there is no net change in voltage.

The preceding discussion describes a mean electrical vector determined at a specific point in time (i.e., an **instantaneous mean vector**). If a series of instantaneous mean vectors is determined over time, it is possible to derive an average mean vector that represents all of the individual vectors over time. Figure 2-17 depicts the sequence of depolarization within the ventricles by showing four different mean vectors representing different times during depolarization. This model shows the septum and free walls of the left and right ventricles; each of the four vectors is depicted as originating from the AV node. The size of the vector arrow is related to the mass of tissue undergoing depolarization. The larger the arrow (and tissue mass), the greater the measured voltage. The electrode placement represents lead II (see the next section, ECG Leads). Early during ventricular activation, the interventricular septum depolarizes from left to right as depicted by mean electrical vector 1. This small vector is heading away from the positive electrode (to the right of a line perpendicular to the lead axis) and therefore records a small negative deflection (the Q

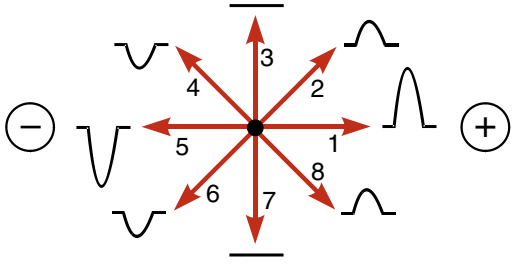

FIGURE 2-16 Recording of electrical vectors. Orientation of the mean electrical vector of depolarization relative to the recording electrodes determines the polarity of the recording. *Arrow 1,* which is heading directly toward the positive electrode, gives the greatest positive deflection. As the vector moves around the axis to the left, and therefore moves away from the positive electrode, the recorded voltage becomes less positive, and then negative as the vector heads away from the positive electrode. No net voltage is present when the vector is perpendicular to the axis between the two electrodes.

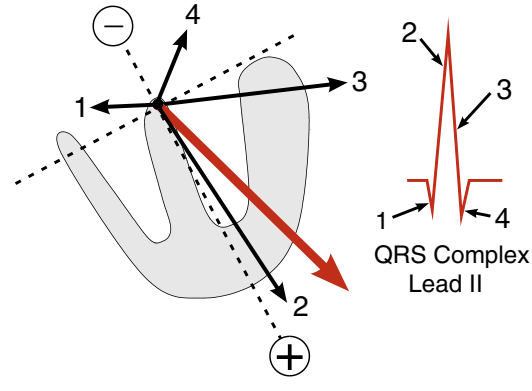

FIGURE 2-17 Generation of QRS complex from vectors representing ventricular depolarization. *Arrows 1-4* represent the time-dependent sequence of ventricular depolarization and the way these time-dependent vectors generate the QRS complex. The relationship of the positive and negative recording electrodes relative to the ventricle depicts lead II. See the text for more details.

wave of the QRS). About 20 milliseconds later, the mean electrical vector points downward toward the apex (vector 2), and heads toward the positive electrode. This direction gives a very tall, positive deflection (the R wave of the QRS). After another 20 milliseconds, the mean vector is directed toward the left arm and anterior chest as the free wall of the ventricle depolarizes from the endocardial (inside) to epicardial (outside) surface (vector 3). This vector still records a small positive voltage in lead II and corresponds to a voltage point between the R and S waves. Finally, the last regions to depolarize result in vector 4, which causes a slight negative deflection (the S wave) of the QRS because it is pointed away from the positive electrode. If the four vectors in Figure 2-15 are summed, the resultant vector (red arrow) is the **mean electrical axis.** The mean electrical axis is the average ventricular depolarization vector over time; therefore, it is the average of all of the instantaneous mean electrical vectors occurring sequentially during ventricular depolarization. The determination of mean electrical axis is particularly significant for the ventricles. It is used diagnostically to identify left and right axis deviations, which can be caused by a number of factors, including conduction blocks in a bundle branch and ventricular hypertrophy.

It is important to note that the shape of the QRS complex can change considerably depending on the placement of the recording electrodes. For example, if the polarity of the electrodes were reversed in Figure 2-17, the QRS complex would be inverted: a small positive deflection, followed by a large negative deflection, and ending with a small positive deflection.

Based on the previous discussion, the following rules can be used in interpreting the ECG:

1. **A wave of depolarization traveling toward a positive electrode results in a positive deflection in the ECG trace.** [Corollary: A wave of depolarization traveling away from a positive electrode results in a negative deflection.]
2. **A wave of repolarization traveling toward a positive electrode results in a negative deflection.** [Corollary: A wave of repolarization traveling away from a positive electrode results in a positive deflection.]
3. **A wave of depolarization or repolarization oriented perpendicular to an electrode axis has no net deflection.**
4. **The instantaneous amplitude of the measured potentials depends upon the orientation of the positive electrode relative to the mean electrical vector.**
5. **Voltage amplitude (positive or negative) is directly related to the mass of tissue undergoing depolarization or repolarization.**

The first three rules are derived from the volume conductor models described earlier. The fourth rule takes into consideration that, at any given point in time during depolarization in the atria or ventricles, many separate waves of depolarization are traveling in different directions relative to the positive electrode. The recording by the electrode reflects the average, instantaneous direction and magnitude (i.e., the mean electrical vector) for all of the individual depolarization waves. The fifth rule states that the amplitude of the wave recorded by the ECG is directly related to the mass of the muscle undergoing depolarization or repolarization. For example, when the mass of the left ventricle is increased (i.e., ventricular hypertrophy), the amplitude of the QRS complex, which largely represents left ventricular depolarization, is sometimes increased (depending on the degree of hypertrophy).

ECG Leads: Placement of Recording Electrodes

The ECG is recorded by placing an array of electrodes at specific locations on the body surface. Conventionally, electrodes are placed on each arm and leg, and six electrodes are placed at defined locations on the chest. Three basic types of ECG leads are recorded by these electrodes: standard limb leads, augmented limb leads, and chest leads. These

electrode leads are connected to a device that measures potential differences between selected electrodes to produce the characteristic ECG tracings. The limb leads are sometimes referred to as **bipolar** leads because each lead uses a single pair of positive and negative electrodes. The augmented leads and chest leads are **unipolar** leads because they have a single positive electrode with the other electrodes coupled together electrically to serve as a common negative electrode.

ECG Limb Leads

Standard limb leads are shown in Figure 2-18. **Lead I** has the positive electrode on the left arm and the negative electrode on the right arm, therefore measuring the potential difference across the chest between the two arms. In this and the other two limb leads, an electrode on the right leg is a reference electrode for recording purposes. In the **lead II** configuration, the positive electrode is on the left leg and the negative electrode is on the right arm. **Lead III** has the positive electrode on the left leg and the negative electrode on the left arm. These three limb leads roughly form an equilateral triangle (with the heart at the center), called **Einthoven's triangle** in honor of Willem Einthoven who developed the ECG in 1901. Whether the limb leads are attached to the end of the limb (wrists and ankles) or at the origin of the limbs (shoulder and upper thigh) makes virtually no difference in the recording because the limb can be viewed as a wire conductor originating from a point on the trunk of the body. The electrode located on the right leg is used as a ground.

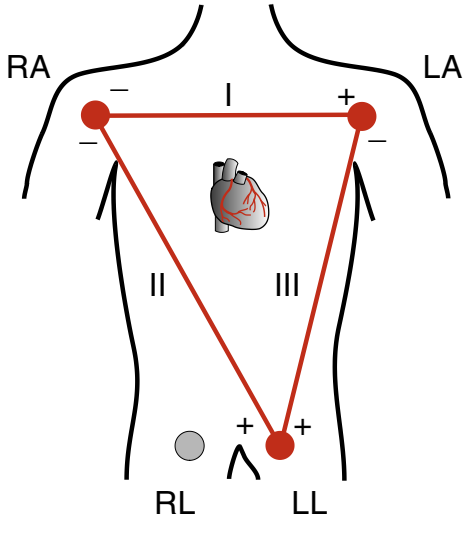

FIGURE 2-18 Placement of the standard ECG limb leads (leads I, II, and III) and the location of the positive and negative recording electrodes for each of the three leads. *RA,* right arm; *LA,* left arm; *RL,* right leg; *LL,* left leg.

When using the ECG rules described in the previous section, it is clear that a wave of depolarization heading toward the left arm gives a positive deflection in lead I because the positive electrode is on the left arm. Maximal positive deflection of the tracing occurs in lead I when a wave of depolarization travels parallel to the axis between the right and left arms. If a wave of depolarization heads away from the left arm, the deflection is negative. In addition, a wave of repolarization moving away from the left arm is seen as a positive deflection.

Similar statements can be made for leads II and III, with which the positive electrode is located on the left leg. For example, a wave of depolarization traveling toward the left leg gives a positive deflection in both leads II and III because the positive electrode for both leads is on the left leg. A maximal positive deflection is obtained in lead II when the depolarization wave travels parallel to the axis between the right arm and left leg. Similarly, a maximal positive deflection is obtained in lead II when the depolarization wave travels parallel to the axis between the left arm and left leg.

If the three limbs of Einthoven's triangle (assumed to be equilateral) are broken apart, collapsed, and superimposed over the heart (Fig. 2-19), the positive electrode for lead I is defined as being at zero degrees relative to the heart (along the horizontal axis; see Figure 2-19). Similarly, the positive electrode for lead II is +60° relative to the heart, and the positive electrode for lead III is +120° relative to the heart, as shown in Figure 2-19. This new construction of the electrical axis is called the **axial reference system**. Although the designation of lead I as being 0°, lead II as being

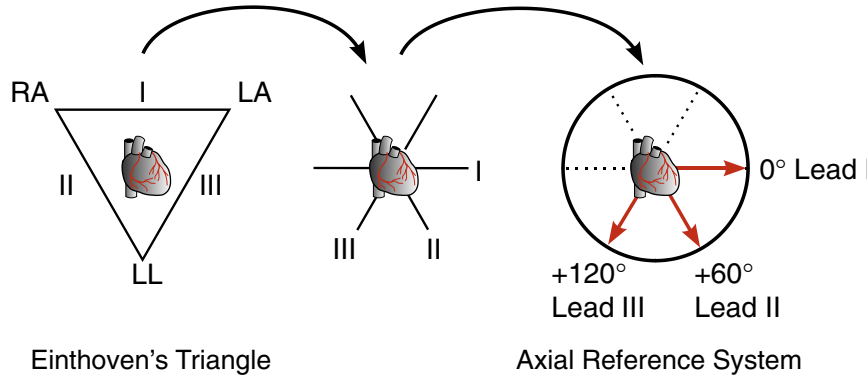

FIGURE 2-19 Transformation of leads I, II, and III from Einthoven's triangle into the axial reference system. Leads I, II, and III correspond to 0°, 60°, and 120° in the axial reference system. *RA,* right arm; *LA,* left arm; *LL,* left leg.

+60°, and so forth is arbitrary, it is the accepted convention. With this axial reference system, a wave of depolarization oriented at +60° produces the greatest positive deflection in lead II. A wave of depolarization oriented +90° relative to the heart produces equally positive deflections in both leads II and III. In the latter case, lead I shows no net deflection because the wave of depolarization is heading perpendicular to the 0°, or lead I, axis (see ECG rules).

Three **augmented limb leads** exist in addition to the three bipolar limb leads described. Each of these leads has a single positive electrode that is referenced against a combination of the other limb electrodes. The positive electrodes for these augmented leads are located on the left arm (aV_L), the right arm (aV_R), and the left leg (aV_F; the "F" stands for "foot"). In practice, these are the same positive electrodes used for leads I, II, and III. (The ECG machine does the actual switching and rearranging of the electrode designations.) The axial reference system in Figure 2-20 shows that the aV_L lead is at –30° relative to the lead I axis; aV_R is at –150°, and aV_F is at +90°. It is critical to learn which lead is associated with each axis.

The three augmented leads, coupled with the three standard limb leads, constitute the six limb leads of the ECG. These leads record electrical activity along a single plane, the frontal plane relative to the heart. The direction of an electrical vector can be determined

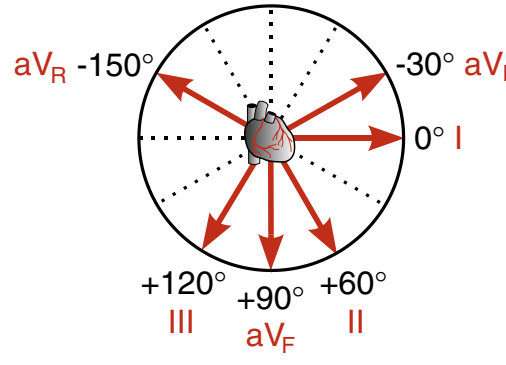

FIGURE 2-20 The axial reference system showing the location within the axis of the positive electrode for all six limb leads.

at any given instant using the axial reference system and these six leads. If a wave of depolarization is spreading from right to left along the 0° axis (heading toward 0°), lead I shows the greatest positive amplitude. Likewise, if the direction of the electrical vector for depolarization is directed downward (+90°), aV_F shows the greatest positive deflection.

Determining the Mean Electrical Axis from the Six Limb Leads

The mean electrical axis for the ventricle can be estimated by using the six limb leads and the axial reference system. The mean electrical axis corresponds to the axis that is perpendicular to the lead axis with the smallest net QRS amplitude (net amplitude = positive minus negative deflection voltages of the QRS

complex). If, for example, lead III has the smallest net amplitude (a biphasic ECG with equal positive and negative deflections) and leads I and II are equally positive, the mean electrical axis is perpendicular to lead III, which is 120° minus 90°, or +30° (see Figure 2-20). In this example, lead aV_R has the greatest negative deflection.

It is often important to determine if there is a significant deviation in the mean electrical axis from a normal range, which is between –30° and +90° (some authors define the normal range as between 0° and +90°). Less than –30° is considered a **left axis deviation,** and greater than +90° is considered a **right axis deviation.** Axis deviations can occur because of the physical position of the heart within the chest or changes in the sequence of ventricular activation (e.g., conduction defects). Axis deviations also can occur if ventricular regions are incapable of being activated (e.g., infarcted tissue). Ventricular hypertrophy can display axis deviation (a left shift for left ventricular hypertrophy and a right shift for right ventricular hypertrophy).

ECG Chest Leads

The last ECG leads to consider are the unipolar, precordial **chest leads.** These six positive electrodes are placed on the surface of the chest over the heart to record electrical activity in a horizontal plane perpendicular to the frontal plane (Fig. 2-21). The six leads are named V_1–V_6. V_1 is located to the right of the sternum over the fourth intercostal space, whereas V_6 is located laterally (midaxillary line) on the chest over the fifth intercostal space. With this electrode placement, V_1 overlies the right ventricular free wall, and V_6 overlies the left ventricular lateral wall. The rules of interpretation are the same as for the limb leads. For example, a wave of depolariza-

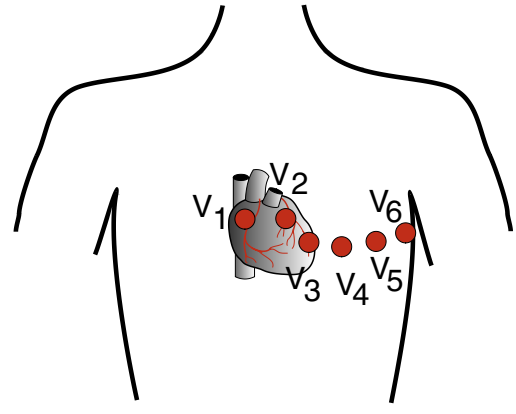

FIGURE 2-21 Placement of the six precordial chest leads. These electrodes record electrical activity in the horizontal plane, which is perpendicular to the frontal plane of the limb leads.

CASE 2-2

A patient's ECG recording shows that the net QRS deflection is zero (equally positive and negative deflections) in lead I, and that leads II and III are equally positive. What is the mean electrical axis? How would leads aV_L and aV_R appear in terms of net negative or net positive deflections?

The QRS complex has no net deflection in lead I (i.e., equally positive and negative deflections), which indicates that the mean electrical axis is perpendicular (90°) to lead I (see Rule 3); therefore, it is either at –90° or +90° because the axis for lead I is 0° by definition. Because the QRS is positive in leads II and III, the mean electrical axis must be oriented toward the positive electrode on the left leg, which is used for leads II and III. Therefore, the mean electrical axis cannot be –90°, but is instead +90°. Both aV_L and aV_R leads would have net negative deflections because the direction of the mean electrical axis is away from these two leads, which are oriented at –30° and –150°, respectively (see Figure 2-20). Furthermore, the net negative deflections in these two augmented leads would be of equal magnitude because each lead axis differs from the mean electrical axis by the same number of degrees.

tion traveling toward a particular electrode on the chest surface elicits a positive deflection. Normal electrical activation of the ventricles results in a net negative deflection in V_1 and a net positive deflection in V_6.

ELECTROPHYSIOLOGICAL CHANGES DURING CARDIAC ISCHEMIA

The ECG is a key tool for diagnosing myocardial ischemia and infarction. When the heart becomes ischemic (i.e., when oxygen delivery is inadequate relative to oxygen demand), electrophysiological changes occur that can alter both rhythm and conduction. The ECG can identify the extent, location, and progress of damage to the heart following ischemic injury. This assessment is made by evaluating changes in the electrical activity of the heart by using the 12-lead ECG recording. For example, altered conduction can result in exaggerated Q waves in specific leads following some types of myocardial infarction. Ischemia can also damage conduction pathways, leading to arrhythmias or changes in the shape of the QRS complex. Furthermore, ischemia can produce injury currents flowing from the depolarized ischemic regions to normal regions that can shift the isoelectric portions of the ECG, resulting in upward or downward shifts in the ST segment. The mechanisms by which ischemia and infarction alter the ECG are complex and not fully understood. We do know, however, that tissue hypoxia caused by ischemia results in membrane depolarization. As ATP levels decline during hypoxia, there is a net loss of K^+ as it leaks out of cells through K_{ATP} channels (normally inhibited by ATP) and as a result of decreased activity of the Na^+/K^+-ATPase pump. Increased extracellular K^+, coupled with decreased intracellular K^+, causes membrane depolarization. This depolarization inactivates fast sodium channels as previously described, thereby decreasing action potential upstroke velocity. One result is decreased conduction velocity. Changes in refractory period and conduction velocity can lead to reentry currents and tachycardia. Membrane depolarization also alters pacemaker activity and can cause latent pacemakers to be active, leading to changes in rhythm and ectopic beats. Finally, cellular hypoxia results in the accumulation of intracellular calcium, which can lead to afterdepolarizations and tachycardia.

SUMMARY OF IMPORTANT CONCEPTS

- The membrane potential is determined primarily by the concentration differences of ions, particularly sodium, potassium, and calcium, across the cell membrane and by the relative conductances of the membrane to these ions.
- The resting membrane potential is very close to the potassium equilibrium potential (calculated from Nernst equation) because the relative conductance of potassium is much higher than the relative conductances of sodium and calcium in the resting cell.
- Ions move across the cell membrane through ion selective channels, which have open (activated) and closed (inactivated) states that are regulated by either membrane voltage or by receptor-coupled signal transduction mechanisms.
- Concentrations of sodium, potassium, and calcium across the cell membrane are maintained by the Na^+/K^+-ATPase pump, the Na^+/Ca^{++} exchanger, and the Ca^{++}-ATPase pump. These ion transport systems are electrogenic and therefore contribute several millivolts to the negative membrane potential.
- Nonpacemaker cardiac action potentials are characterized as having very negative resting potentials (approximately –90 mV), a rapid phase 0 depolarization produced primarily by a transient increase in sodium conductance, and a prolonged plateau phase (phase 2) generated primarily by inward calcium currents through L-type calcium channels; increased potassium conductance repolarizes the cells during phase 3.
- Pacemaker action potentials (e.g., those found in SA nodal cells) have no true resting potential. Instead, these cells spontaneously depolarize from about –65 mV to a

threshold voltage of about –40 mV (phase 4) owing in part to special pacemaker currents (I_f). Upon reaching the threshold for action potential generation, calcium conductance increases as L-type calcium channels become activated (fast sodium channels are inactivated in pacemaker cells), which causes depolarization (phase 0). As the calcium channels close, potassium conductance increases and the cell repolarizes.

- Pacemaker activity is regulated by sympathetic and parasympathetic (vagal) nerves as well as circulating hormones. At rest, SA nodal activity is strongly influenced by vagal activity (vagal tone), which significantly reduces the intrinsic SA nodal firing rate to approximately 60 to 80 beats/minute. Pacemaker activity, and therefore heart rate (chronotropy), is increased by sympathetic activation and vagal inhibition.
- Conduction of action potentials within the heart is primarily cell-to-cell, although specialized conduction pathways (e.g., bundle of His, bundle branches, Purkinje fibers) exist within the heart that ensure rapid distribution of the conducted action potentials. Conduction velocity (dromotropy) is increased by activation of sympathetic nerves and decreased by parasympathetic activation.
- The AV node, which is normally the only electrical bridge between the atria and ventricles, decreases the conduction velocity between the atria and ventricles, thereby allowing sufficient time for atrial contraction to contribute to ventricular filling.
- Although the SA node is the primary pacemaker within the heart, cells located within the AV node and ventricular conducting system can also serve as pacemakers if the SA node fails or conduction is blocked between the atria and ventricles (AV nodal block).
- The ECG measures electrical activity of the heart through an array of electrodes placed on the arms, legs, and chest (12-lead ECG). The ECG evaluates rhythm and conduction by examining the appearance (amplitude, duration, and shape) of specific waveforms that represent atrial depolarization (P wave), ventricular depolarization (QRS complex), and ventricular repolarization (T wave).
- Different ECG leads view the electrical activity of the heart from different angles. Each limb lead (I, II, III, aV_R, aV_L, and aV_F) can be represented by an electrical axis on a frontal plane from which the direction of depolarization and repolarization vectors within the heart can be determined using standard rules of interpretation (e.g., a wave of depolarization traveling toward a positive electrode produces a positive voltage in the ECG). Chest leads (V_1-V_6) measure the electrical activity in a horizontal plane that is perpendicular to the frontal plane.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. Which one of the following depolarizes the resting membrane potential in a cardiac myocyte?
   a. Decreased calcium conductance
   b. Decreased sodium conductance
   c. Increased potassium conductance
   d. Inhibition of the sarcolemmal Na^+/K^+-ATPase

2. Fast sodium channels are inactivated
   a. During phase 0 of a ventricular action potential.
   b. When the h-gates open.
   c. By slow depolarization of the cell.
   d. More slowly than L-type calcium channels are inactivated.

3. The relative potassium conductance is highest during which of the following phases of a ventricular action potential?
   a. Phase 0
   b. Phase 2
   c. Early phase 3
   d. Phase 4

4. In sinoatrial (SA) nodal action potentials,
   a. β_1-adrenoceptor activation increases pacemaker current (I_f).

b. Fast sodium channels are responsible for phase 0.
c. Potassium conductance is highest during phase 0.
d. Vagal stimulation increases the slope of phase 4.

5. The normal sequence of conduction within the heart is
   a. SA node → atrioventricular (AV) node → bundle of His → bundle branches → Purkinje fibers
   b. SA node → bundle of His → AV node →bundle branches → Purkinje fibers
   c. AV node → SA node → bundle of His → bundle branches → Purkinje fibers
   d. SA node → AV node → bundle of His → Purkinje fibers → bundle branches

6. Conduction velocity within the AV node is increased by
   a. Blocking β_1-adrenoceptors.
   b. Blocking muscarinic (M_2) receptors.
   c. Depolarizing the AV node.
   d. Blocking L-type calcium channels.

7. In a normal ECG,
   a. The P-R interval is greater than 0.2 seconds.
   b. The ST segment represents the duration of the ventricular action potential.
   c. The T wave represents ventricular repolarization.
   d. The duration of the QRS is greater than 0.2 seconds.

8. Which one of the following ECG leads has the positive electrode on the left arm?
   a. Lead I
   b. Lead II
   c. aV_R
   d. aV_F

9. What is the approximate mean electrical axis for ventricular depolarization when the QRS is equally biphasic in lead II (no net deflection), and aV_L has the most positive deflection?
   a. –30°
   b. 0°
   c. +60°
   d. +120°

10. An ECG rhythm strip shows a complete dissociation between P waves and QRS complexes. The atrial rate is 95 beats/min and regular, and the ventricular rate is about 60 beats/min and regular. The QRS complexes are of normal shape and duration. This ECG represents
    a. First-degree AV nodal block.
    b. Second-degree AV nodal block.
    c. Third-degree AV nodal block.
    d. Premature ventricular complexes.

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chapter

3

Cellular Structure and Function

CD CONTENTS

1. Formation and Physiologic Actions of Nitric Oxide
2. Formation and Physiologic Actions of Endothelin-1
3. Formation and Physiologic Actions of Metabolites of Arachidonic Acid

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Describe the function of the following cellular components of cardiac myocytes: sarcolemma, intercalated disks, transverse (T)-tubules, myofibrils, myofilaments, sarcomeres, sarcoplasmic reticulum, and terminal cisternae.**
2. **Describe the composition of thick and thin myofilaments in cardiac myocytes.**
3. **Describe the significance of a functional syncytium within the heart.**
4. **Describe the steps of excitation–contraction coupling, including the role of T tubules, L-type calcium channels, trigger calcium, terminal cisternae, ryanodine receptors (calcium-release channels), troponin-C (TN-C), troponin-I (TN-I), troponin-T (TN-T), actin, myosin heads, adenosine triphosphate (ATP) hydrolysis, and sarco-endoplasmic reticulum calcium adenosine triphosphatase (SERCA) pump.**
5. **List several mechanisms involved in the regulation of cardiac inotropy and lusitropy.**
6. **List in order of preference the metabolic substrates used by the heart, and summarize the importance of oxidative metabolism relative to anaerobic metabolism.**
7. **Draw the cross section of a muscular artery, label the three layers, and list the major components of each layer.**
8. **Contrast the organization of actin and myosin in vascular smooth muscle with the organization of these myofilaments in cardiac myocytes.**
9. **Describe the mechanism of vascular smooth muscle contraction and include descriptions of the roles of calcium, calmodulin, and myosin light chain kinase.**
10. **Compare the effects of inositol triphosphate (IP_3) and cyclic adenosine monophosphate (cAMP) signal transduction pathways on the contraction of cardiac muscle and vascular smooth muscle.**

11. List the major agonists that are associated with the following guanine nucleotide-binding regulatory protein (G-protein) coupled systems: inhibitory G-protein (Gi-protein), stimulatory G-protein (Gs-protein), and phospholipase C-coupled Gq-protein. Describe the effects of these agonists on cardiac and smooth muscle contraction.

12. Describe the vascular effects of endothelial-derived nitric oxide (NO), prostacyclin (PGI_2), and endothelin-1 (ET-1).

INTRODUCTION

Many different cell types are associated with the cardiovascular system. This chapter examines the structure and function of three major types of structural cells that serve important roles in cardiovascular function: cardiac myocytes, vascular smooth muscle, and vascular endothelium.

CARDIAC CELL STRUCTURE AND FUNCTION

Myocytes and Sarcomeres

Cardiac myocytes represent a type of striated muscle, so-called because crossbands or cross striations are observed microscopically. Although cardiac muscle shares some structural and functional similarities with skeletal muscle, it has several important differences. Cardiac myocytes are generally single nucleated and have a diameter of approximately 25 μm and a length of about 100 μm. In contrast, although some types of skeletal muscle myocytes may have a similar diameter, their cell lengths run the entire length of the muscle and therefore can be many centimeters long. Cardiac myocytes form a branching network of cells that is sometimes referred to as a functional **syncytium,** which results from a fusion of cells. Individual myocytes connect to each other by way of specialized cell membranes called **intercalated disks. Gap junctions** within these intercellular regions serve as low-resistance pathways between cells, permitting cell-to-cell conduction of electrical (ionic) currents. Therefore, if one cardiac myocyte is electrically stimulated, cell-to-cell conduction ensures that the electrical impulse will travel to all of the interconnected myocytes. This arrangement allows the heart to contract as a unit (i.e., as a syncytium). In contrast, individual skeletal muscle cells are innervated by motor neurons, which utilize neuromuscular transmission to activate individual muscle fibers to contract. No cell-to-cell electrical conduction occurs in skeletal muscle.

The cardiac myocyte is composed of bundles of myofibrils that contain myofilaments (Fig. 3-1). When myocytes are viewed microscopically, distinct repeating lines and bands can be seen, each of which represents different myofilament components. The segment between two **Z-lines** represents the basic contractile unit of the myocyte, the **sarcomere.** The length of each sarcomere under physiologic conditions ranges from about 1.6 to 2.2 μm in human hearts. As described later and in Chapter 4, the length of the sarcomere is an important determinant of the force of myocyte contraction.

The sarcomere contains **thick** and **thin filaments,** which represent about 50% of the cell volume (see Fig. 3-1). Thick filaments are comprised of myosin, whereas thin filaments contain actin and other associated proteins. Chemical interactions between the actin and myosin filaments during the process of excitation–contraction coupling (see the next section) cause the sarcomere to shorten as the myosin and actin filaments slide past each other, thereby shortening the distance between the Z-lines. Within the sarcomere, a large, filamentous protein called **titin** exists. It connects the myosin filament to the Z-lines, which helps to keep the thick filament centered within the sarcomere. Because of its elastic properties, titin plays an important role in the passive mechanical properties of the heart (see Chapter 4). In addition to titin, myosin, and actin, a number of other proteins form the cytoskeleton of myocytes, connecting the internal and external cell components.

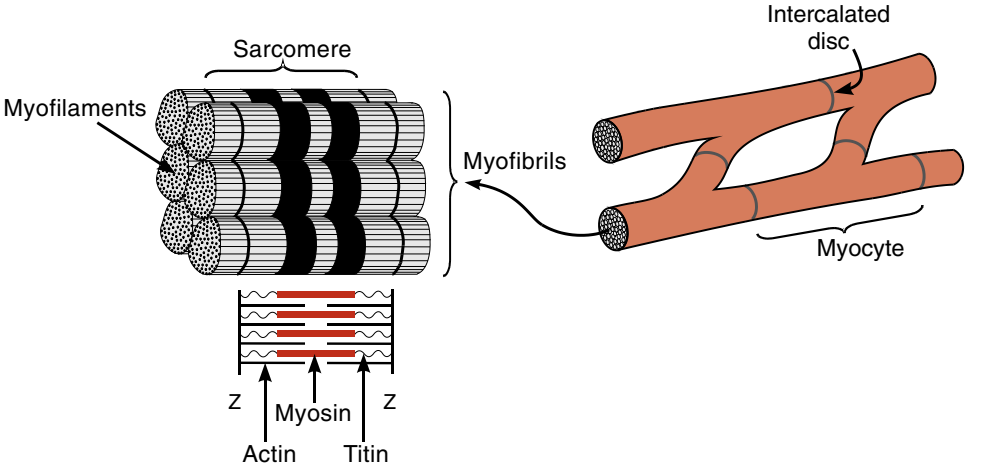

FIGURE 3-1 Structure of cardiac myocytes. The myocytes are joined together by intercalated discs to form a functional syncytium (right side of the figure). Myocytes are composed of myofibrils, each of which contains myofilaments that are composed largely of actin (thin filaments) and myosin (thick filaments) (left side of the figure). Myosin is anchored to the Z-line by the protein titin. The sarcomere, or basic contractile unit, lies between two Z-lines.

Myosin is a large molecular weight protein. Within each sarcomere, myosin molecules are bundled together so that there are about 300 molecules of myosin per thick filament. Each myosin molecule contains two heads, which serve as the site of myosin adenosine triphosphatase **(myosin ATPase),** an enzyme that hydrolyzes adenosine triphosphate (ATP). ATP is required for the cross-bridge formation between the thick and thin filaments. The molecule's heads interact with a binding site on actin (Fig. 3-2). Regulatory subunits (myosin light chains) that can alter the ATPase activity when phosphorylated are associated with each myosin head.

Each thick filament is surrounded by a hexagonal arrangement of six thin filaments. The thin filaments are composed of actin, tropomyosin, and troponin (Fig. 3-2). Actin is a globular protein arranged as a chain of repeating globular units, forming two helical strands. Interdigitated between the actin strands are rod-shaped proteins called tropomyosin. Each tropomyosin molecule is associated with seven actin molecules. Attached to the tropomyosin at regular intervals is the troponin regulatory complex, made up of three subunits: **troponin-T** (TN-T), which attaches to the tropomyosin; **troponin-C** (TN-C), which serves as a binding site for

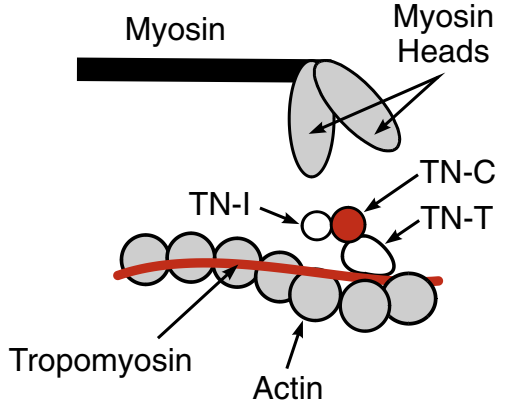

FIGURE 3-2 Composition of cardiac thick and thin myofilaments. The thick filaments are composed of myosin molecules, with each molecule having two myosin heads, which serve as the site of the myosin ATPase. Thin filaments are composed of actin, tropomyosin, and regulatory proteins (troponin complex, TN) having three subunits: TN-T (binds to tropomyosin), TN-C (binds to calcium ions), and TN-I (inhibitory troponin, which binds to actin). Calcium binding to TN-C produces a conformation change in the troponin-tropomyosin complex that exposes a myosin binding site on the actin, leading to ATP hydrolysis. For simplicity, this figure shows only one actin strand and its associated tropomyosin filament.

Ca^{++} during excitation–contraction coupling; and **troponin-I** (TN-I), which binds to actin. The troponin complex holds tropomyosin in position to prevent binding of myosin heads to actin. When Ca^{++} binds to TN-C, a confor-

mational change occurs in the troponin complex such that the troponin–tropomyosin complex moves away from the myosin-binding site on the actin, thereby making the actin accessible to the myosin head for binding. When Ca^{++} is removed from the TN-C, the troponin–tropomyosin complex resumes its inactivated position, thereby inhibiting myosin-actin binding. As a clinical aside, both TN-I and TN-T are used as diagnostic markers for myocardial infarction because of their release into the circulation when myocytes die.

Excitation–Contraction Coupling

Transverse Tubules and the Sarcoplasmic Reticulum

The coupling between myocyte action potentials and contraction is called excitation–contraction coupling. To understand this process, the internal structure of the myocyte needs to be examined in more detail. The sarcolemmal membrane of the myocyte surrounds the bundle of myofibrils and has deep invaginations called **transverse (T) tubules** (Fig. 3-3). The T tubules, being a part of the external sarcolemma, are open to the external environment of the cell. This permits ionic exchanges between extracellular and intracellular compartments to occur deep within the myocyte during electrical depolarization and repolarization of the myocyte. Within the cell, and in close association with the T tubules, is an extensive, branching tubular network called the **sarcoplasmic reticulum. Terminal cisternae** are end pouches of the sarcoplasmic reticulum that are adjacent to the T tubules. Between the terminal cisternae and the T tubules are electron-dense regions called **feet** that are believed to sense calcium between the T tubules and the terminal cisternae. Closely associated with the sarcoplasmic reticulum are large numbers of mitochondria, which provide the energy necessary for myocyte contraction.

Calcium Cycling and the Function of Regulatory Proteins

When an action potential causes depolarization of a myocyte (see Chapter 2), it initiates excitation–contraction coupling. When the myocyte is depolarized, calcium ions enter the cell during the action potential through long-lasting (L-type) calcium channels located on

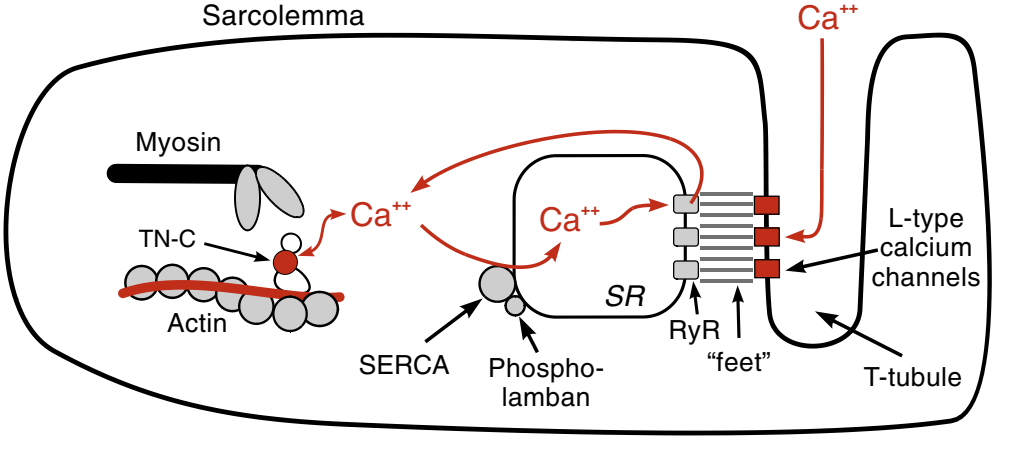

FIGURE 3-3 Role of calcium (*Ca++*) in cardiac excitation-contraction coupling. During action potentials, Ca^{++} enters cell through L-type Ca^{++} channels. This so-called trigger Ca^{++} is sensed by the "feet" of the calcium release channel (ryanodine receptor, *RyR*) of the sarcoplasmic reticulum (*SR*), which releases Ca^{++} into the cytoplasm. This Ca^{++} binds to troponin-C (*TN-C*), inducing a conformational change in the troponin-tropomyosin complex so that movement of the troponin-tropomyosin complex exposes a myosin binding site on actin, leading to ATP hydrolysis and movement of actin relative to myosin. Ca^{++} is resequestered into the SR by an ATP-dependent Ca^{++} pump, sarco-endoplasmic reticulum calcium ATPase (*SERCA*) that is inhibited by phospholamban. Not shown are Ca^{++} pumps that remove Ca^{++} from the cell. *TN-1,* troponin-I.

the external sarcolemma and T tubules (see Fig. 3-3). It is important to note that a relatively small amount of calcium enters the cell during depolarization. By itself, this calcium influx does not significantly increase intracellular calcium concentrations except in local regions just inside the sarcolemma. This calcium is sensed by the "feet" of the calcium release channels (**ryanodine receptors,** or ryanodine-sensitive calcium-release channels) associated with the terminal cisternae. This triggers the subsequent release of large quantities of calcium stored in the terminal cisternae through the calcium-release channels, which increases intracellular calcium concentrations a hundred-fold, from about 10^{-7} to 10^{-5} M. Therefore, the calcium that enters the cell during depolarization is sometimes referred to as **"trigger calcium."**

The free calcium binds to TN-C in a concentration-dependent manner. This induces a conformational change in the regulatory complex such that the troponin–tropomyosin complex moves away from and exposes a myosin binding site on the actin molecule. The binding of the myosin head to the actin results in ATP hydrolysis, which supplies energy so that a conformational change can occur in the actin–myosin complex. This results in a movement ("ratcheting") between the myosin heads and the actin. The actin and myosin filaments slide past each other, thereby shortening the sarcomere length (this is referred to as the **sliding filament theory** of muscle contraction) (Fig. 3-4). Ratcheting cycles will occur as long as the cytosolic calcium remains elevated. Toward the end of the myocyte action potential, calcium entry into the cell diminishes and the sarcoplasmic reticulum sequesters calcium by an ATP-dependent calcium pump, sarco-endoplasmic reticulum calcium ATPase (**SERCA;** see Fig. 3-3). As intracellular calcium concentration declines, calcium dissociates from TN-C, which causes a conformational change in the troponin–tropomyosin complex; this again leads to troponin–tropomyosin inhibition of the actin-binding site. At the end of the cycle, a new ATP binds to the myosin head, displacing the adenosine diphosphate (ADP), and the initial sarcomere length is restored. Thus, ATP is required both for providing the energy of contraction and for relaxation. In the absence of sufficient ATP as occurs during cellular hypoxia, cardiac muscle contraction and relaxation will be impaired. The events associated

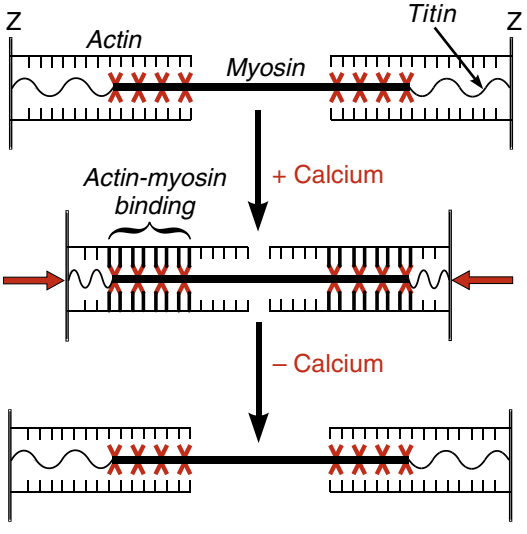

FIGURE 3-4 Sarcomere shortening and the sliding filament theory. Calcium binding to TN-C permits actin-myosin binding (cross-bridge formation) and ATP hydrolysis. This results in the thin filaments sliding over the myosin during cross-bridge cycling, thereby shortening the sarcomere (distance between Z-lines). Removal of calcium from the TN-C inhibits actin-myosin binding so that cross-bridge cycling ceases and the sarcomere resumes its relaxed length.

with excitation–contraction coupling are summarized in Table 3-1.

Regulation of Contraction (Inotropy)

Several cellular mechanisms regulate contraction (Fig. 3-5). Most of these mechanisms ultimately affect calcium handling by the cell. Changes in contraction resulting from altered calcium handling and myosin ATPase activity are referred to as inotropic changes (**inotropy**). Inotropy is modulated by 1) calcium entry into the cell through L-type calcium channels; 2) calcium release by the sarcoplasmic reticulum; 3) calcium binding to TN-C; 4) myosin phosphorylation; 5) SERCA activity; and 6) calcium efflux across the sarcolemma.

Calcium Entry into Myocytes

The amount of calcium that enters the cell during depolarization (Fig. 3-5, site 1) is regulated largely by phosphorylation of the L-type calcium channel. The primary mechanism for

TABLE 3-1 SUMMARY OF EXCITATION–CONTRACTION COUPLING.

1. Ca^{++} enters cell during depolarization and triggers release of Ca^{++} by terminal cisternae.
2. Ca^{++} binds to TN-C, inducing a conformational change in the troponin complex.
3. Myosin heads bind to actin, leading to cross-bridge movement (requires ATP hydrolysis) and reduction in sarcomere length.
4. Ca^{++} is resequestered by sarcoplasmic reticulum by the SERCA pump.
5. Ca^{++} is removed from TN-C, and myosin unbinds from actin (requires ATP); this allows the sarcomere to resume its original, relaxed length.

ATP, adenosine triphosphate; SERCA, sarco-endoplasmic reticulum calcium ATPase; TN-C, troponin-C.

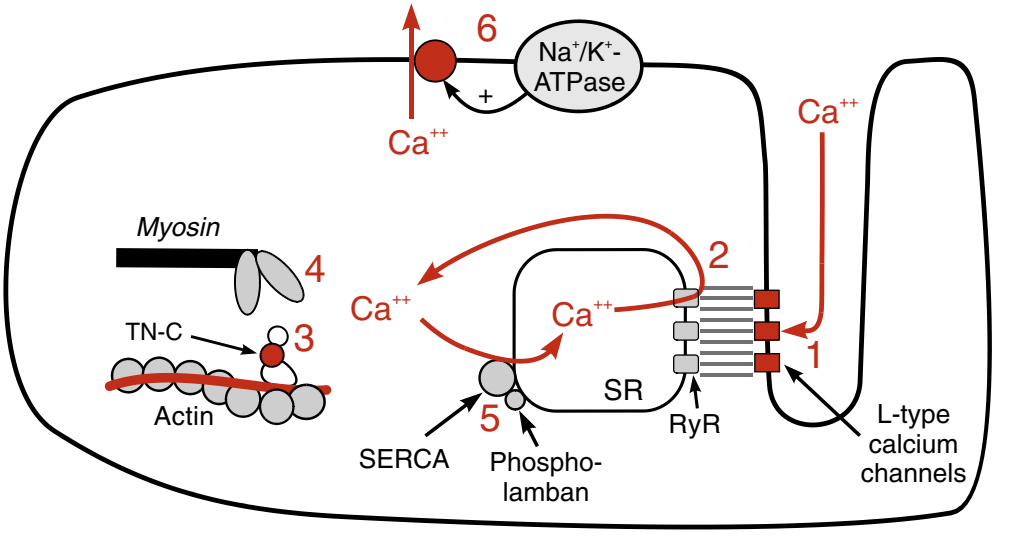

FIGURE 3-5 Intracellular mechanisms regulating inotropy. Inotropy can be increased by increasing Ca^{++} influx through L-type Ca^{++} channels (site 1); increasing release of Ca^{++} by the sarcoplasmic reticulum (*SR*) (site 2); increasing troponin-C (*TN-C*) affinity for Ca^{++} (site 3); increasing myosin-ATPase activity through phosphorylation of myosin heads (site 4); increasing sarco-endoplasmic reticulum calcium ATPase (*SERCA*) activity by phosphorylation of phospholamban (site 5); or inhibiting Ca^{++} efflux across the sarcolemma (site 6), which can occur secondarily to inhibition of the Na^+/K^+-ATPase.

this regulation involves cyclic adenosine monophosphate (**cAMP),** the formation of which is coupled to β-adrenoceptors (Fig. 3-6). Norepinephrine released by sympathetic nerves, or circulating epinephrine released by the adrenal glands, binds primarily to β_1-adrenoceptors located on the sarcolemma. This receptor is coupled to a specific guanine nucleotide-binding regulatory protein (**stimulatory G-protein;** Gs-protein), that activates adenylyl cyclase, which in turn hydrolyzes ATP to cAMP. The cAMP acts as a second messenger to activate **protein kinase A** (cAMP-dependent protein kinase, PK-A), which is capable of phosphorylating different sites within the cell. One important site of phosphorylation is the L-type calcium channel. Phosphorylation increases the permeability of the channel to calcium, thereby increasing calcium influx during action potentials. This increase in trigger calcium enhances calcium release by the sarcoplasmic reticulum, thereby increasing inotropy. Therefore, norepinephrine and epinephrine are positive inotropic agents.

Another G-protein, the **inhibitory G-protein** (Gi-protein), inhibits adenylyl cyclase and decreases intracellular cAMP. Therefore, activation of this pathway decreases inotropy. This pathway is coupled to muscarinic receptors (M_2) that bind acetylcholine released by parasympathetic (vagal) nerves within the heart. Adenosine receptors (A_1) also are coupled to the Gi-protein. Therefore, acetylcholine and adenosine are negative inotropic agents.

Calcium Release by the Sarcoplasmic Reticulum

Enhanced calcium release by the sarcoplasmic reticulum also can increase inotropy (Fig. 3-5, site 2). During β-adrenoceptor and cAMP activation, PK-A phosphorylates sites on the sarcoplasmic reticulum, leading to an increase in calcium release.

Besides the cAMP pathway, a second pathway within myocytes can affect calcium

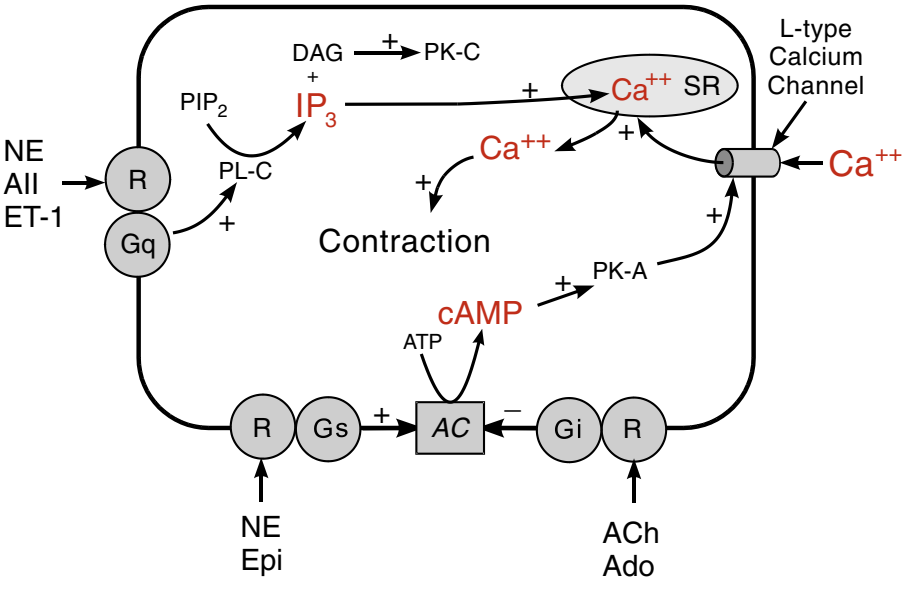

FIGURE 3-6 Signal transduction pathways regulating cardiac myocyte contraction. The two major pathways involve formation of either cyclic adenosine monophosphate (*cAMP*) or inositol 1,4,5-triphosphate (IP_3), both of which affect Ca^{++} release by sarcoplasmic reticulum and therefore affect contraction. *R,* receptor; *Gs,* stimulatory G-protein; *Gi,* inhibitory G-protein; *Gq,* phospholipase C-coupled G-protein; *AC,* adenylyl cyclase; *PL-C,* phospholipase C; PIP_2, phosphatidylinositol 4,5-bisphosphate; *DAG,* diacylglycerol; *PK-C,* protein kinase C; *PK-A,* protein kinase A; *SR,* sarcoplasmic reticulum; *ATP,* adenosine triphosphate; *NE,* norepinephrine; *AII,* angiotensin II; *ET-1,* endothelin-1; *Epi,* epinephrine; *ACh,* acetylcholine; *Ado,* adenosine.

release by the sarcoplasmic reticulum, although this pathway appears to be less important physiologically than the cAMP/PK-A pathway. This second pathway involves a class of G-proteins (**Gq-proteins**) that are associated with α_1-adrenoceptors (binds norepinephrine), angiotensin II receptors (AT_1), and endothelin-1 receptors (ET_A; see Fig. 3-6). Activation of these receptors stimulates **phospholipase-C** to form inositol triphosphate (**IP_3**) from phosphatidylinositol 4,5-bisphosphate (PIP_2), which stimulates calcium release by the sarcoplasmic reticulum.

Calcium Binding to TN-C

Another mechanism by which inotropy can be modulated is by altered binding of calcium to TN-C (Fig. 3-5, site 3). The binding of calcium to TN-C is determined by the free intracellular concentration of calcium and the binding affinity of TN-C to calcium. The greater the intracellular calcium concentration, the more calcium that is bound to TN-C, and the more force that is generated between actin and myosin. Increasing the affinity of TN-C for calcium increases binding at any given calcium concentration, thereby increasing force generation. Acidosis, which occurs during myocardial hypoxia, has been shown to decrease TN-C affinity for calcium. This may be one mechanism by which acidosis decreases the force of contraction.

Changes in calcium sensitivity may explain in part how increases in sarcomere length (also known as preload; see Chapter 4) leads to an increase in force generation. It appears that increased preload increases calcium sensitivity of TN-C, thereby increasing calcium binding. The mechanism by which changes in length increase calcium affinity by TN-C is unknown.

Myosin ATPase Activity

The myosin heads have sites (myosin light chains) that can be phosphorylated by the enzyme myosin light chain kinase (Fig. 3-5, site 4). Increased cAMP is known to be associated with increased phosphorylation of the myosin heads, which may increase inotropy. The physiologic significance of this mechanism, however, is uncertain.

Calcium Uptake by Sarcoplasmic Reticulum

In addition to influencing relaxation, increasing calcium transport into the sarcoplasmic reticulum by the SERCA pump can indirectly increase the amount of calcium released by the sarcoplasmic reticulum (Fig. 3-5, site 5). PK-A phosphorylation of phospholamban, which removes the inhibitory effect of phospholamban on SERCA, increases the rate of calcium transport into the sarcoplasmic reticulum. SERCA activity can also be stimulated by increased intracellular calcium caused by increased calcium entry into the cell or decreased cellular efflux. Enhanced sequestering of calcium by the sarcoplasmic reticulum increases subsequent release of calcium by the sarcoplasmic reticulum, thereby increasing inotropy.

Regulation of Calcium Efflux from the Myocyte

The final mechanisms that can modulate inotropy are the sarcolemmal Na^+/Ca^{++} exchange pump and the ATP-dependent calcium pump (Fig. 3-5, site 6). As described in Chapter 2, these pumps transport calcium out of the cell, thereby preventing the cell from becoming overloaded with calcium. If calcium extrusion is inhibited, the rise in intracellular calcium can increase inotropy because more calcium is available to TN-C.

Digitalis and related cardiac glycosides inhibit the Na^+/K^+-ATPase, which increases intracellular Na^+(see Chapter 2). This leads to an increase in intracellular Ca^{++} through the Na^+/Ca^{++} exchange pump, leading to enhanced inotropy.

Regulation of Relaxation (Lusitropy)

The rate of myocyte relaxation (**lusitropy**) is determined by the ability of the cell to rapidly reduce the intracellular concentration of calcium following its release by the sarcoplasmic reticulum. This reduction in intracellular calcium causes calcium that is bound to troponin-C to be released, thereby permitting the troponin-tropomyosin complex to resume its resting, inactivated conformation.

Several intracellular mechanisms help to regulate lusitropy, most of which influence intracellular calcium concentrations.

1. The rate that calcium enters the cell at rest and during action potentials influences intracellular concentrations. Under some pathologic conditions (e.g., myocardial ischemia), the cell becomes more permeable to calcium, leading to "calcium overload," which impairs relaxation.
2. The rate with which calcium leaves the cell through the sarcolemmal calcium ATPase pump and the Na^+/Ca^{++} exchange pump (see Chapter 2) affects intracellular concentrations. Inhibiting these transport systems can cause intracellular calcium concentrations to increase to a point at which relaxation is impaired.
3. The activity of the SERCA pump, which pumps calcium back into the sarcoplasmic reticulum, has a major role in determining intracellular calcium concentrations. Lusitropy can be increased by increasing SERCA activity through phosphorylation of phospholamban, a regulatory protein associated with SERCA. Phosphorylation of phospholamban removes its inhibitory effect on SERCA. This is a normal physiologic mechanism in response to β-adrenoceptor stimulation, which increases cAMP and PK-A, the latter of which phosphorylates phospholamban. The impairment of the activity of the SERCA pump, as occurs in some forms of heart failure, causes intracellular calcium concentrations to rise, leading to impaired relaxation.
4. The binding affinity of troponin-C for calcium also influences lusitropy. Calcium binding to troponin-C can be modulated by PK-A phosphorylation of troponin-I. This increases calcium dissociation from troponin-C, thereby increasing relaxation. The increased lusitropy caused by β-adrenoceptor stimulation may be partly related to troponin-I phosphorylation. Some drugs used to increase the force of contraction (inotropic drugs) do so by increasing troponin-C affinity for calcium. Although this may increase inotropy, it also may lead

PROBLEM 3-1

Describe the mechanisms by which norepinephrine, after being released by sympathetic nerve activation, increases myocardial inotropy and lusitropy. Note that norepinephrine primarily binds to b_1-adrenoceptors, although it also can bind to α_1-adrenoceptors.

Sympathetic nerve stimulation releases norepinephrine, which binds to β_1-adrenoceptors and α_1-adrenoceptors found on cardiac myocytes. β_1-adrenoceptor activation stimulates cAMP production through the Gs-protein. cAMP production activates protein kinase A (PK-A), which can phosphorylate L-type calcium channels, leading to an increase in calcium influx during the action potential. Increased calcium influx triggers increased calcium release by the sarcoplasmic reticulum, leading to increased calcium binding by TN-C. Calcium binding increases myosin ATPase activity and forces generation. PK-A also phosphorylates phospholamban and removes its inhibition of SERCA, which leads to increased calcium reuptake by the sarcoplasmic reticulum and increases the rate of relaxation, or lusitropy. Increased calcium within the sarcoplasmic reticulum subsequently enhances the release of calcium from the sarcoplasmic reticulum. In addition, PK-A may phosphorylate sites on the sarcoplasmic reticulum to enhance calcium release. PK-A phosphorylation of TN-I also may contribute to enhanced lusitropy by altering TN-C affinity for calcium. Although physiologically less important than the β_1-adrenoceptor-Gs protein pathway, norepinephrine binding to α_1-adrenoceptors increases the formation of IP_3 via Gq-protein and phospholipase C activation, which stimulates the release of calcium from the sarcoplasmic reticulum.

to reduced lusitropy because the calcium is more tightly bound to the troponin-C.

Cardiac Myocyte Metabolism

The maintenance of ionic pumps and other transport systems in living cells requires significant amounts of energy, primarily in the form of ATP. Cardiac myocytes have an exceptionally high metabolic rate because their primary function is to contract repetitively. Unlike skeletal muscle, in which contraction is often intermittent and relatively short, cardiac muscle contracts one to three times per second throughout life. Repetitive cycles of contraction and relaxation require an enormous amount of ATP, which the heart must produce aerobically. This is why cardiac myocytes contain such large numbers of mitochondria. In the absence of oxygen, myocytes can contract for no more than a minute. Unlike some types of skeletal muscle fibers (e.g., fast twitch, glycolytic), cardiac myocytes have only a limited anaerobic capacity for meeting ATP requirements. This limited anaerobic capacity coupled with a high use of ATP explains why cellular ATP concentrations fall and contractions weaken so rapidly under hypoxic conditions.

Unlike many other cells in the body, cardiac myocytes can use a variety of substrates to regenerate ATP oxidatively. For example, in an overnight fasted state, the heart uses primarily fatty acids (~60%) and carbohydrates (~40%). Following a high-carbohydrate meal, the heart can adapt to using carbohydrates (primarily glucose) almost exclusively. Lactate can be used in place of glucose, and it becomes an important substrate during exercise when circulating concentrations of lactate increase. The heart also can use amino acids and ketones (e.g., acetoacetate) instead of fatty acids.

Myocyte ATP use and oxygen consumption increase dramatically when the frequency of contraction (i.e., heart rate) and the force of contraction are increased. Under these conditions, more oxygen must be delivered to the heart by the coronary circulation to support myocyte metabolic demands. As Chapter 8 discusses, biochemical signals from the myocytes dilate the coronary blood vessels to supply additional blood flow and oxygen to meet greater oxygen demands. This ensures that the heart is able to generate ATP by aerobic mechanisms.

VASCULAR STRUCTURE AND FUNCTION

Large blood vessels, both arterial and venous, are composed of three layers – intima, media, and adventitia (Fig. 3-7). The **intima,** or innermost layer, is composed of a single layer of thin endothelial cells, which are separated from the media by a basal lamina. In larger vessels, a region of connective tissue also exists between the endothelial cells and the basal lamina. The **media** contains smooth muscle cells, imbedded in a matrix of collagen, elastin, and various glycoproteins.

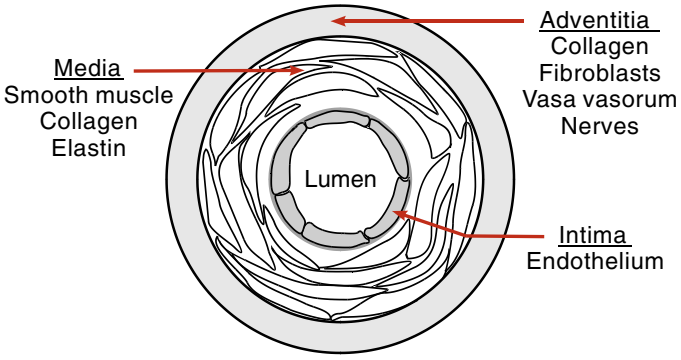

FIGURE 3-7 Blood vessel components. Blood vessels, except capillaries and small postcapillary venules, are composed of three layers: intima, media, and adventitia. Capillaries and small postcapillary venules do not have media and adventitia. The primary components are given for each layer.

Depending on the size of the vessel, there may be several layers of smooth muscle cells, some arranged circumferentially and others arranged helically along the longitudinal axis of the vessel. The smooth muscles cells are organized so that their contraction reduces the vessel diameter. The ratio of smooth muscle, collagen, and elastin, each of which has different elastic properties, determines the overall mechanical properties of the vessel. For example, the aorta has a large amount of elastin, which enables it to passively expand and contract as blood is pumped into it from the heart. This mechanism enables the aorta to dampen the arterial pulse pressure (see Chapter 5). In contrast, smaller arteries and arterioles have a relatively large amount of smooth muscle, which is required for these vessels to contract and thereby regulate arterial blood pressure and organ blood flow. The outermost layer, or **adventitia,** is separated from the media by the external elastic lamina. The adventitia contains collagen, fibroblasts, blood vessels (vasa vasorum found in large vessels), lymphatics, and autonomic nerves (primarily sympathetic adrenergic). The smallest vessels, capillaries, are composed of endothelial cells and a basal lamina; they are devoid of smooth muscle.

Vascular Smooth Muscle Cells

Cellular Structure of Vascular Smooth Muscle

Vascular smooth muscle cells are typically 5–10 μm in diameter and vary from 50–200 μm in length. Numerous small invaginations (**caveolae**) found in the cell membrane significantly increase the surface area of the cell (Fig. 3-8). The sarcoplasmic reticulum is poorly developed compared with the sarcoplasmic reticulum found in cardiac myocytes. Contractile proteins (actin and myosin) are present; however, the actin and myosin in smooth muscle are not organized into distinct bands of repeating units as they are in cardiac and skeletal muscle. Instead, bands of actin filaments are joined together and anchored by **dense bodies** within the cell or **dense bands** on the inner surface of the sarcolemma, which function like Z-lines in cardiac myocytes. Each myosin filament is surrounded by several actin filaments. Similar to cardiac myocytes, vascular smooth muscle cells are electrically connected by **gap junctions.** These low-resistance intercellular connections allow propagated responses along the length of the blood vessels. For example, electrical depolarization and contraction of a local site on

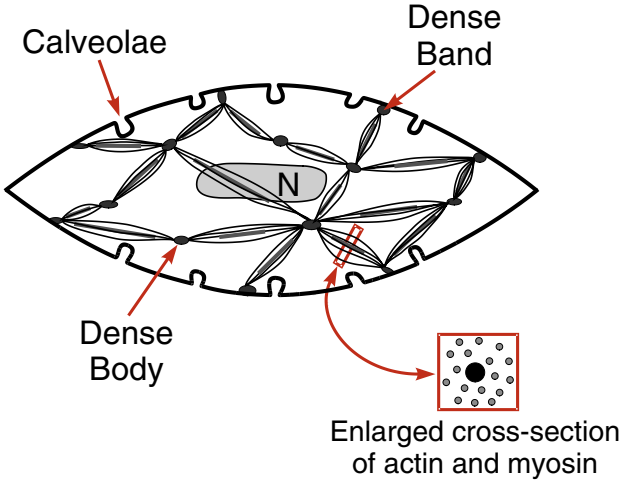

FIGURE 3-8 Vascular smooth muscle cell structure. Actin and myosin filaments are connected by dense bodies and dense bands. Each myosin filament is surrounded by several actin filaments. *N,* nucleus.

an arteriole can result in depolarization at a distant site along the same vessel, indicating cell-to-cell propagation of the depolarizing currents.

Vascular Smooth Muscle Contraction

Contractile characteristics and the mechanisms responsible for contraction differ considerably between vascular smooth muscle and cardiac myocytes. Vascular smooth muscle tonic contractions are slow and sustained, whereas cardiac muscle contractions are rapid and relatively short (a few hundred milliseconds). In blood vessels, the smooth muscle is normally in a partially contracted state, which determines the resting tone or diameter of the vessel. This tonic contraction is determined by a number of stimulatory and inhibitory influences acting on the vessel (see Chapter 5, Fig. 5-9, and Chapters 6 and 7); the most important of these are sympathetic adrenergic nerves, circulating hormones (e.g., epinephrine, angiotensin II), substances released by the endothelium lining the vessel, and vasoactive substances released by the tissue surrounding the blood vessel.

Vascular smooth muscle contraction can be initiated by electrical, chemical, and mechanical stimuli. Electrical depolarization of the vascular smooth muscle cell membrane elicits contraction primarily by opening voltage-dependent calcium channels (L-type calcium channels), which causes an increase in the intracellular concentration of calcium. Electrical depolarization occurs through changes in ion concentrations (e.g., depolarization induced by increased extracellular potassium) or by the receptor-coupled opening of ion channels, particularly calcium channels.

Many different chemical stimuli, such as norepinephrine, epinephrine, angiotensin II, vasopressin, endothelin-1, and thromboxane A_2 can elicit contraction. Each of these substances binds to specific receptors on the vascular smooth muscle cell. Different signal transduction pathways converge to increase intracellular calcium, thereby eliciting contraction.

Mechanical stimuli in the form of passive stretching of smooth muscle in some arteries can cause a contraction that originates from the smooth muscle itself and is therefore termed a **myogenic response.** This probably results from stretch-induced activation of ionic channels that leads to calcium influx.

Figure 3-9 illustrates the mechanism by which an increase in intracellular calcium

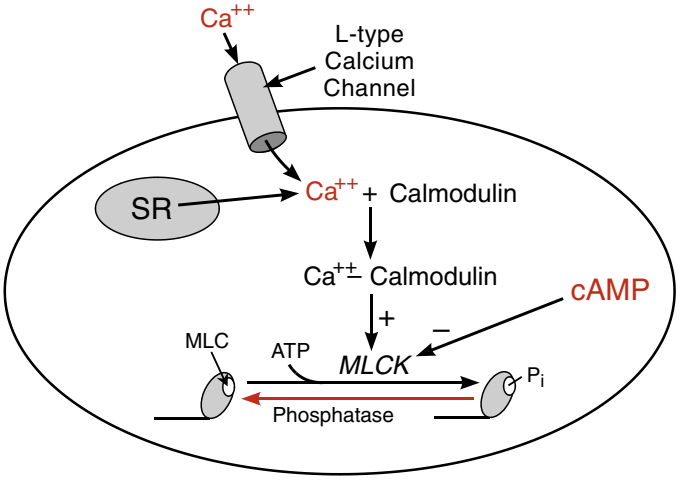

FIGURE 3-9 Regulation of vascular smooth muscle contraction by myosin light chain kinase (*MLCK*). Increased intracellular calcium, by either increased entry into the cell (through L-type Ca^{++} channels) or release from the sarcoplasmic reticulum (*SR*), forms a complex with calmodulin, activating MLCK, which phosphorylates myosin light chains (*MLC*), causing contraction. Cyclic adenosine monophosphate (*cAMP*) inhibits MLCK, thereby causing relaxation. *ATP,* adenosine triphosphate; *P_i,* phosphate group.

stimulates vascular smooth muscle contraction. An increase in free intracellular calcium can result from either increased entry of calcium into the cell through L-type calcium channels or release of calcium from internal stores (e.g., sarcoplasmic reticulum). The free calcium binds to a special calcium-binding protein called **calmodulin.** The calcium-calmodulin complex activates **myosin light chain kinase,** an enzyme that phosphorylates **myosin light chains** in the presence of ATP. Myosin light chains are regulatory subunits found on the myosin heads. Myosin light chain phosphorylation leads to cross-bridge formation between the myosin heads and the actin filaments, thus leading to smooth muscle contraction.

Intracellular calcium concentrations, therefore, are very important in regulating smooth muscle contraction. The concentration of intracellular calcium depends on the balance between the calcium that enters the cells, the calcium that is released by intracellular storage sites, and the movement of calcium either back into intracellular storage sites or out of the cell. Calcium is resequestered by the sarcoplasmic reticulum by an ATP-dependent calcium pump similar to the SERCA pump found in cardiac myocytes. Calcium is removed from the cell to the external environment by either an ATP-dependent calcium pump or the sodium–calcium exchanger, as in cardiac muscle (see Chapter 2).

Several signal transduction mechanisms modulate intracellular calcium concentration and therefore the state of vascular tone. This section describes three different pathways: (1) IP_3 via Gq-protein activation of phospholipase C; (2) cAMP via Gs-protein activation of adenylyl cyclase; and (3) cyclic guanosine monophosphate (cGMP) via nitric oxide (NO) activation of guanylyl cyclase (Fig. 3-10).

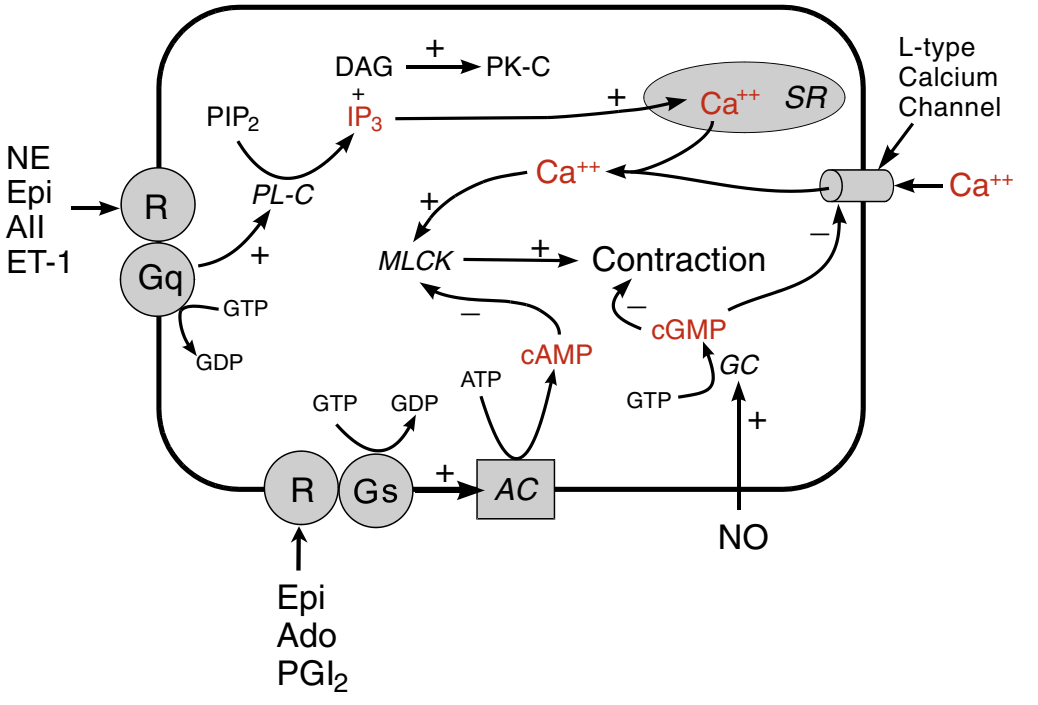

FIGURE 3-10 Receptors and signal transduction pathways that regulate vascular smooth muscle contraction. *R,* receptor; *Gs,* stimulatory G-protein; *Gq,* phospholipase C-coupled G-protein; *AC,* adenylyl cyclase; *PL-C,* phospholipase C; *PIP_2,* phosphatidylinositol 4,5-bisphosphate; *IP_3,* inositol triphosphate; *DAG,* diacylglycerol; *PK-C,* protein kinase C; *SR,* sarcoplasmic reticulum; *MLCK,* myosin light chain kinase; *Ado,* adenosine; *PGI_2,* prostacyclin; *Epi,* epinephrine; *NO,* nitric oxide; *GC,* guanylyl cyclase; *AII,* angiotensin receptor agonist; *ET-1,* endothelin-1; *NE,* norepinephrine; *ACh,* acetylcholine; *GDP,* guanosine diphosphate; *GTP,* guanosine triphosphate; *ATP,* adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate.

The IP_3 pathway in vascular smooth muscle is similar to that found in the heart. Norepinephrine and epinephrine (via α_1-adrenoceptors), angiotensin II (via AT_1 receptors), endothelin-I (via ET_A receptors), and acetylcholine (via M_3 receptors) activate phospholipase C through the Gq-protein, causing the formation of IP_3 from PIP_2. IP_3 then directly stimulates the sarcoplasmic reticulum to release calcium. The formation of diacylglycerol from PIP_2 activates protein kinase C, which can modulate vascular smooth muscle contraction as well via protein phosphorylation.

Receptors coupled to the Gs-protein stimulate adenylyl cyclase, which catalyzes the formation of cAMP. In vascular smooth muscle, unlike cardiac myocytes, an increase in cAMP by a β_2-adrenoceptor agonist such as isoproterenol causes relaxation. The mechanism for this process is cAMP inhibition of myosin light chain kinase (see Fig. 3-9), which decreases myosin light chain phosphorylation, thereby inhibiting the interactions between actin and myosin. Adenosine and prostacyclin (PGI_2) also activate Gs-protein through their receptors, leading to an increase in cAMP and smooth muscle relaxation. Epinephrine binding to β_2-adrenoceptors relaxes vascular smooth muscle through the Gs-protein.

A third important mechanism for regulating vascular smooth muscle contraction is the nitric oxide (NO)–cGMP system. Many endothelial-dependent vasodilator substances (e.g., acetylcholine, bradykinin, substance P), when bound to their respective endothelial receptors, stimulate the conversion of L-arginine to NO by activating NO synthase. The NO diffuses from the endothelial cell to the vascular smooth muscle cells, where it activates guanylyl cyclase, increases cGMP formation, and causes smooth muscle relaxation. The precise mechanisms by which cGMP relaxes vascular smooth muscle are unclear; however, cGMP can activate a cGMP-dependent protein kinase, inhibit calcium entry into the vascular smooth muscle, activate K^+ channels causing cellular hyperpolarization, and decrease IP_3.

Vascular Endothelial Cells

The vascular endothelium is a thin layer of cells that line all blood vessels. Endothelial cells are flat, single-nucleated, elongated cells that are 0.2–2.0 μm thick and 1-20 μm across (varying by vessel type). Depending on the type of vessel (e.g., arteriole versus capillary) and tissue location (e.g., renal glomerular versus skeletal muscle capillaries), endothelial cells are joined together by different types of intercellular junctions. Some of these junctions are very tight (e.g., all arteries and skeletal muscle capillaries), whereas others have

PROBLEM 3-2

cAMP is degraded by a phosphodiesterase. Milrinone, a drug sometimes used in the treatment of acute heart failure, is a phosphodiesterase inhibitor that increases cardiac inotropy and relaxes blood vessels by inhibiting the degradation of cAMP. Explain why an increase in cAMP in cardiac muscle increases the force of contraction, whereas an increase in cAMP in vascular smooth muscle cells diminishes the force of contraction.

Increasing cAMP in the heart activates protein kinase A, which phosphorylates different sites within the cells (see the answer to Problem 3-1). Phosphorylation enhances calcium influx into the cell and calcium release by the sarcoplasmic reticulum, leading to an increase in inotropy. In vascular smooth muscle, myosin light chain kinase, when activated by calcium-calmodulin, phosphorylates myosin light chains to stimulate smooth muscle contraction. cAMP inhibits myosin light chain kinase; therefore, an increase in cAMP by a phosphodiesterase inhibitor such as milrinone further inhibits the myosin light chain kinase, thereby reducing smooth muscle contraction.

gaps between the cells (e.g., capillaries in spleen and bone marrow) that enable blood cells to move in and out of the capillary easily. See Chapter 8 for information about different types of capillaries and endothelium.

Endothelial cells have several important functions, including:

1. Serving as a barrier for the exchange of fluid, electrolytes, macromolecules, and cells between the intravascular and extravascular space (see Chapter 8);
2. Regulating smooth muscle function through the synthesis of several different vasoactive substances, the most important of which are NO, PGI_2, and endothelin-1;
3. Modulating platelet aggregation primarily through biosynthesis of NO and PGI_2;
4. Modulating leukocyte adhesion and transendothelial migration through the biosynthesis of NO and the expression of surface adhesion molecules.

Vascular endothelial cells continuously produce NO by the enzyme NO synthase, which converts L-arginine to NO. This basal NO production can be enhanced by (1) specific agonists (e.g., acetylcholine, bradykinin) binding to endothelial receptors; (2) increased shearing forces acting on the endothelial surface (e.g., as occurs with increased blood flow); and (3) cytokines such as tumor necrosis factor and interleukins, which are released by leukocytes during inflammation and infection. NO, although very labile, rapidly diffuses out of endothelial cells to cause smooth muscle relaxation or inhibit platelet aggregation in the blood. Both of these actions of NO result from increased cGMP formation, which occurs in response to NO activation of guanylyl cyclase (see Fig. 3-10). Increased NO within the endothelium stimulates endothelial cGMP production, which inhibits the expression of adhesion molecules involved in attaching leukocytes to the endothelial surface. Therefore, endothelial-derived NO relaxes smooth muscle, inhibits platelet function, and inhibits inflamma tory responses (Fig. 3-11). (See Formation and Physiologic Actions of Nitric Oxide on CD.)

In addition, endothelial cells synthesize endothelin-1 (ET-1), a powerful vasoconstrictor (see Fig. 3-11). Synthesis is stimulated by angiotensin II, vasopressin, thrombin, cytokines, and shearing forces, and it is inhibited by NO and PGI_2. ET-1 leaves the endothelial cell and can bind to receptors (ET_A) on vascular smooth muscle, which causes calcium mobilization and smooth muscle contraction. The smooth muscle actions of ET-1 occur through activation of the IP_3 signaling pathway (see Fig. 3-10). (See Formation and Physiologic Actions of Endothelin-1 on CD.)

PGI_2 is a product of arachidonic acid metabolism within endothelial cells. (See Formation and Physiologic Actions of Metabolites of Arachidonic Acid on CD.) The two primary roles of PGI_2 formed by endothelial cells are smooth muscle relaxation and inhibition of platelet aggregation (see Fig. 3-11), both of which are induced by the formation of cAMP (see Fig. 3-10).

The importance of normal endothelial function is made clear from examining how endothelial dysfunction contributes to disease states. For example, endothelial damage and dysfunction occurs in atherosclerosis, hypertension, diabetes, and hypercholesterolemia. Endothelial dysfunction results in less NO and PGI_2 production, causing vaso-

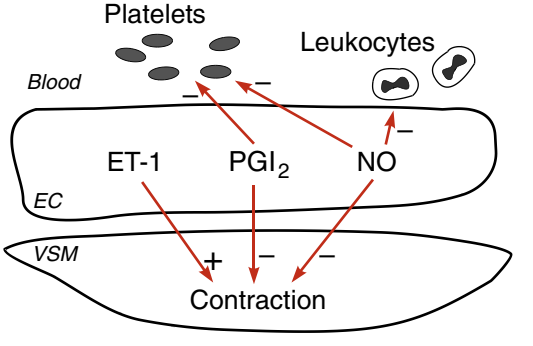

FIGURE 3-11 Endothelial cell (*EC*) production of nitric oxide (*NO*), prostacyclin (*PGI_2*), and endothelin-1 (*ET-1*) stimulates (+) or inhibits (-) vascular smooth muscle (*VSM*) contraction, platelet aggregation and adhesion, and leukocyte-endothelial cell adhesion.

PROBLEM 3-3

When acetylcholine is infused into normal coronary arteries, the vessels dilate; however, if the vessel is diseased and the endothelium damaged, acetylcholine can cause vasoconstriction. Explain why acetylcholine can have opposite effects on vascular function depending on the integrity of the vascular endothelium.

Acetylcholine has two effects on blood vessels. When acetylcholine binds to M_2 receptors on the vascular endothelium, it stimulates the formation of nitric oxide (NO) by constitutive NO synthase. The NO can then diffuse from the endothelial cell into the adjacent smooth muscle cells, where it activates guanylyl cyclase to form cGMP. Increased cGMP within the smooth muscle cell inhibits calcium entry into the cell, which leads to relaxation. Acetylcholine, however, also can bind to M_3 receptors located on the smooth muscle. This activates the IP_3 pathway and stimulates calcium release by the sarcoplasmic reticulum, which leads to increased smooth muscle contraction. If the endothelium is intact, stimulation of the NO–cGMP pathway dominates over the actions of the IP_3 pathway; therefore, acetylcholine will cause vasodilation.

constriction, loss of vasodilatory capacity, thrombosis, and vascular inflammation. Evidence exists that enhanced ET-1 production contributes to hypertension and other vascular disorders. Damage to the endothelium at the capillary level increases capillary permeability (see Chapter 8), which leads to increased capillary fluid filtration and tissue edema.

SUMMARY OF IMPORTANT CONCEPTS

- The basic contractile unit of a cardiac myocyte is the sarcomere, which contains thick filaments (myosin) and thin filaments (actin, troponin, and tropomyosin). During myocyte contraction, the sarcomere shortens as the thick and thin filaments slide past each other (the sliding filament theory of muscle contraction).
- The process of excitation–contraction coupling is initiated by depolarization of the cardiac myocyte, which causes calcium to enter the cell across the sarcolemmal membrane, particularly in the T-tubules. This entering calcium triggers the release of calcium through calcium-release channels associated with the terminal cisternae of the sarcoplasmic reticulum, which increases intracellular calcium concentration. Calcium then binds to TN-C, which induces a conformation change in the troponin-tropomyosin complex and exposes a myosin binding site on the actin. Hydrolysis of ATP occurs during actin and myosin binding; it provides the energy for the subsequent movement of the thin filament across the thick filament. Relaxation (also requiring ATP) occurs when calcium is removed from the TN-C and is resequestered by the sarcoplasmic reticulum by means of the SERCA pump.
- Calcium serves as the primary regulator of the force of contraction (inotropy). Increased calcium entry into the cell, increased release of calcium by the sarcoplasmic reticulum, and enhanced binding of calcium by TN-C are major mechanisms controlling inotropy. Phosphorylation of myosin light chains may also play a role in modulating inotropy.
- Relaxation of cardiac myocytes (lusitropy) is primarily regulated by the reuptake of calcium by the sarcoplasmic reticulum by the SERCA pump. Phospholamban, a regulatory protein associated with SERCA, regulates the activity of SERCA.
- The contractile function of cardiac myocytes requires large amounts of ATP, which is generated primarily by oxidative metabo-

lism of fatty acids and carbohydrates, although the heart is flexible in its use of substrates and can also metabolize amino acids, ketones, and lactate.

- Arteries and veins are arranged as three layers: adventitia, media, and intima. Autonomic nerves and small blood vessels (vasa vasorum in large vessels) are found in the adventitia; vascular smooth muscle is found in the media; and the intima is lined by the endothelium. The relative proportions of elastin and collagen in the adventitia and media influence the elastic properties of blood vessels.
- Vascular smooth muscle contains actin and myosin; however, these components are not arranged in the same repetitive pattern as that found in cardiac myocytes. Vascular smooth muscle contraction is slow and tonic, in contrast to the contraction of cardiac myocytes, which is fast and phasic. Vascular smooth muscle contraction is regulated by calcium and the phosphorylation of myosin light chains by myosin light chain kinase.
- Cardiac muscle and vascular smooth muscle contraction is regulated by G-proteins coupled to membrane receptors. Activation of stimulatory Gs-proteins through β-adrenoceptor stimulation (e.g., by norepinephrine) increases intracellular cAMP, whereas activation of inhibitory Gi-proteins through specific muscarinic or adenosine receptors decreases intracellular cAMP. Increased cAMP in cardiac myocytes increases the force of contraction, whereas increased cAMP in vascular smooth muscle causes relaxation. Activation of the Gq-protein through angiotensin II receptors, endothelin-1 receptors, or α_1-adrenoceptors stimulates the activity of phospholipase C, which causes the formation of inositol triphosphate (IP_3). Increased IP_3 enhances calcium release by the sarcoplasmic reticulum and increased contraction in both cardiac muscle and vascular smooth muscle.
- The vascular endothelium synthesizes nitric oxide and prostacyclin, both of which relax vascular smooth muscle. Endothelin-1, which is also synthesized by the endothelium, contracts vascular smooth muscle.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. Which of the following is common to both cardiac myocytes and vascular smooth muscle cells?
   a. Dense bodies
   b. Myosin light chain kinase
   c. Terminal cisternae
   d. T tubules

2. Thick filaments within cardiac myocytes contain
   a. Actin
   b. Myosin
   c. Tropomyosin
   d. Troponin

3. During excitation–contraction coupling in cardiac myocytes,
   a. Calcium binds to myosin causing ATP hydrolysis.
   b. Calcium binds to troponin-I.
   c. Myosin heads bind to actin.
   d. SERCA pumps calcium out of the sarcoplasmic reticulum.

4. Cardiac inotropy is enhanced by
   a. Agonists coupled to Gi-protein.
   b. Decreased calcium binding to troponin-C.
   c. Decreased release of calcium by terminal cisternae.
   d. Protein kinase A phosphorylation of L-type calcium channels.

5. β_2-adrenoceptor activation in vascular smooth muscle leads to
   a. Activation of myosin light chain kinase.
   b. Contraction.
   c. Decreased intracellular cAMP.
   d. Dephosphorylation of myosin light chains.

6. Angiotensin II causes contraction of vascular smooth muscle by
    a. Activating Gs-protein.
    b. Increasing cAMP.
    c. Increasing IP3.
    d. Inhibiting release of calcium by sarcoplasmic reticulum.
7. Vascular smooth muscle contraction is stimulated by
    a. cGMP.
    b. Endothelin-1.
    c. Nitric oxide.
    d. Prostacyclin.

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chapter

4

Cardiac Function

CD CONTENTS

1. Compliance
2. Energetics of Flowing Blood
3. Valve Disease
4. Ventricular Hypertrophy
5. Ventricular Stroke Work

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Describe the basic anatomy of the heart, including the names of venous and arterial vessels entering and leaving the heart, cardiac chambers, and heart valves; trace the flow of blood through the heart.**
2. **Describe how each of the following changes during the cardiac cycle:**
   a. **electrocardiogram**
   b. **left ventricular pressure and volume**
   c. **aortic pressure**
   d. **aortic flow**
   e. **left atrial pressure**
   f. **jugular pulse waves**
3. **Describe the origin of the four heart sounds and show when they occur during the cardiac cycle.**
4. **Know normal values for end-diastolic and end-systolic left ventricular volumes, atrial and ventricular pressures, and systolic and diastolic aortic and pulmonary arterial pressures.**
5. **Draw and label ventricular pressure-volume loops derived from ventricular pressure and volume changes during the cardiac cycle.**
6. **Calculate stroke volume, cardiac output, and ejection fraction from ventricular end-diastolic and end-systolic volumes and heart rate.**
7. **Describe how an increase in heart rate affects ventricular filling time, ventricular end-diastolic volume, and stroke volume.**

8. Define preload, afterload, and inotropy.
9. List factors that determine or modify preload, afterload, and inotropy.
10. Describe the Frank-Starling mechanism and discuss its importance in regulating cardiac output.
11. Describe the biophysical basis for the Frank-Starling mechanism using the length-tension diagram for cardiac muscle.
12. Show how changes in preload, afterload, and inotropic state affect ventricular end-diastolic volume, end-systolic volume, and stroke volume by using Frank-Starling curves (plotting stroke volume versus preload) and ventricular pressure-volume loops.
13. Describe how changes in preload, afterload, and inotropy alter the force-velocity relationship for cardiac muscle, and explain how changes in this relationship affect ventricular stroke volume.
14. Describe mechanisms that have been proposed to account for the way preload and inotropy affect force generation by myocytes.
15. Calculate myocardial oxygen consumption given coronary blood flow, and coronary arterial and venous oxygen contents.
16. Explain why a given percentage increase in stroke volume in response to an increase in venous return increases myocardial oxygen consumption less than the same percentage increase in aortic pressure.

INTRODUCTION

The heart is a specialized muscular organ that rhythmically contracts and pumps blood from the low-pressure venous side to the high-pressure arterial side of the circulation. Efficient pumping occurs because of the orderly contraction sequence of the different heart chambers, and the presence of valves within the heart that ensure a unidirectional flow of blood. This chapter describes the basic anatomy of the heart—its chambers, valves, and vessels entering and leaving the heart—and the sequence of electrical and mechanical events that occur during a cycle of contraction and relaxation. It then describes the mechanisms that regulate cardiac output, particularly those mechanisms that influence the amount of blood ejected into the aorta with each contraction of the left ventricle. The last section of this chapter discusses the relationship between myocardial oxygen consumption and the mechanical activity of the heart.

CARDIAC ANATOMY

Functional Anatomy of the Heart

The heart consists of four chambers: right atrium, right ventricle, left atrium, and left ventricle (Fig. 4-1). The **right atrium** receives blood from the **superior and inferior vena cavae**, which carry blood returning from the systemic circulation. The right atrium is a highly distensible chamber that can easily expand to accommodate the venous return at a low pressure (0-4 mm Hg). Blood flows from the right atrium, across the **tricuspid valve**, and into the right ventricle. The free wall of the **right ventricle** wraps around part of the larger and thicker left ventricle. The outflow tract of the right ventricle is the **pulmonary artery,** which is separated from the ventricle by the semilunar **pulmonic valve.** Blood returns to the heart from the lungs via four **pulmonary veins** that enter the **left atrium.** The pressure within the left atrium normally ranges from 8–12 mm Hg. Blood flows from the left atrium, across the **mitral valve** (left atrioventricular valve), and into the left ventricle. The **left ventricle** has a thick muscular wall that allows it to generate high pressures during contraction. The left ventricle ejects blood across the **aortic valve** and into the **aorta**.

The tricuspid and mitral valves (also called right and left atrioventricular, or AV valves, respectively) have fibrous strands (**chordae tendineae**) on their leaflets that attach to

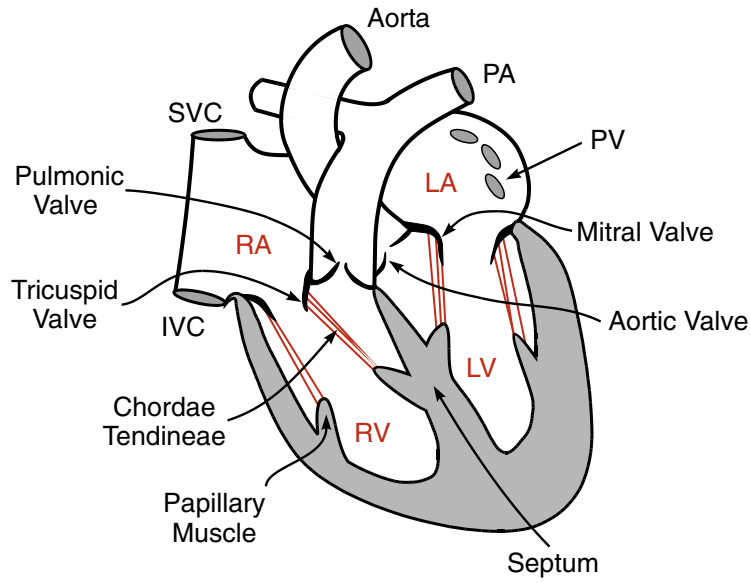


FIGURE 4-1 Anatomy of the heart. *SVC,* superior vena cava; *RA,* right atrium; *IVC,* inferior vena cava; *PA,* pulmonary artery; *PV,* pulmonary veins; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

papillary muscles located on the respective ventricular walls. The papillary muscles contract when the ventricles contract. This generates tension on the valve leaflets via the chordae tendineae, preventing the AV valves from bulging back and leaking blood into the atria (i.e., preventing regurgitation) as the ventricles develop pressure. The semilunar valves (pulmonic and aortic) do not have analogous attachments.

Autonomic Innervation

Autonomic innervation of the heart plays an important role in regulating cardiac function. The heart is innervated by parasympathetic (vagal) and sympathetic efferent fibers. (See Chapter 6 for details on the origin of these autonomic nerves.) The right vagus nerve preferentially innervates the sinoatrial (SA) node, whereas the left vagus nerve innervates the AV node; however, significant overlap can occur in the anatomical distribution. Atrial muscle is also innervated by vagal efferents; the ventricular myocardium is only sparsely innervated by vagal efferents. Sympathetic efferent nerves are present throughout the atria (especially in the SA node) and ventricles and in the conduction system of the heart.

Vagal activation of the heart decreases heart rate (negative **chronotropy**), decreases conduction velocity (negative **dromotropy**), and decreases contractility (negative **inotropy**) of the heart. Vagal-mediated inotropic influences are moderate in the atria and relatively weak in the ventricles. Activation of the sympathetic nerves to the heart increases heart rate, conduction velocity, and inotropy. Sympathetic influences are pronounced in both the atria and ventricles.

As Chapter 6 describes in more detail, the heart also contains vagal and sympathetic afferent nerve fibers that relay information from stretch and pain receptors. The stretch receptors involve feedback regulation of blood volume and arterial pressure, whereas the pain receptors produce chest pain when activated during myocardial ischemia.

THE CARDIAC CYCLE

Cardiac Cycle Diagram

To understand how cardiac function is regulated, one must know the sequence of mechanical events during a complete cardiac cycle and how these mechanical events relate to the electrical activity of the heart. The cardiac

cycle diagram in Figure 4-2 depicts changes in the left side of the heart (left ventricular pressure and volume, left atrial pressure, and aortic pressure) as a function of time. Pressure and volume changes in the right side of the heart (right atrium and ventricle and pulmonary artery) are qualitatively similar to those in the left side. Furthermore, the timing of mechanical events in the right side of the heart is very similar to that of the left side. The main difference is that the pressures in the right side of the heart are much lower than those found in the left side.

A catheter can be placed in the ascending aorta and left ventricle to obtain the pressure and volume information shown in the cardiac cycle diagram and to measure simultaneous changes in aortic and intraventricular pressure as the heart beats. This catheter can also be used to inject a radiopaque contrast agent into

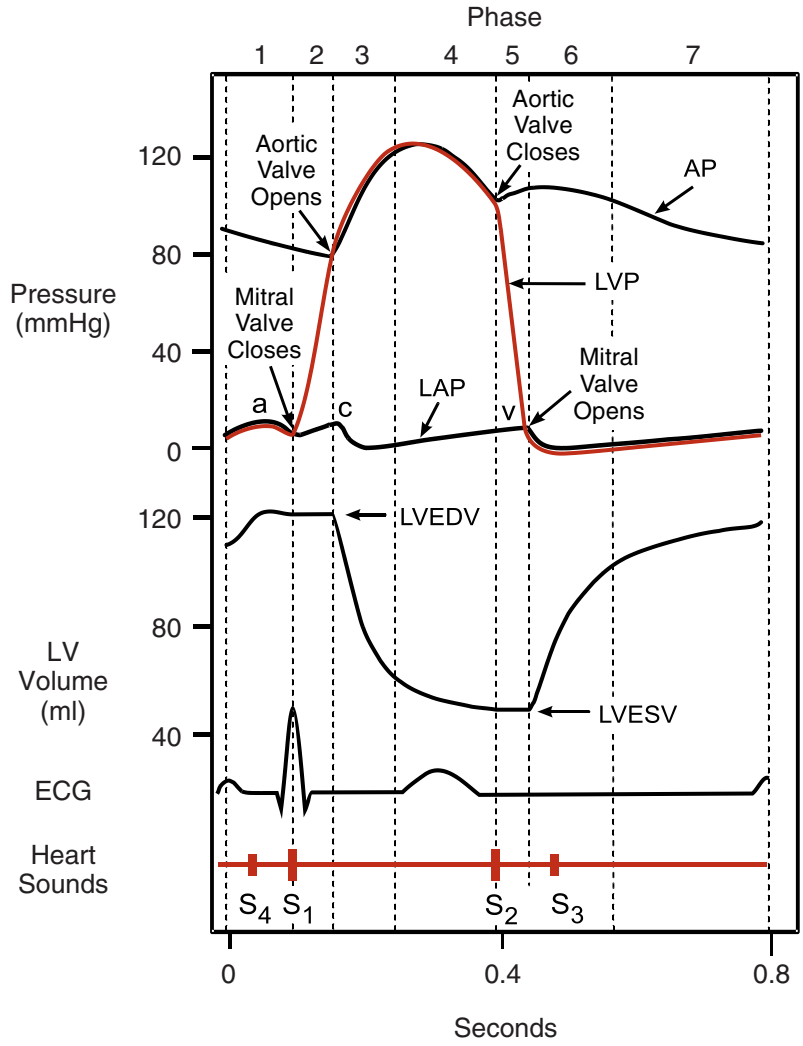


FIGURE 4-2 Cardiac cycle. The seven phases of the cardiac cycle are (*1*) atrial systole; (*2*) isovolumetric contraction; (*3*) rapid ejection; (*4*) reduced ejection; (*5*), isovolumetric relaxation; (*6*) rapid filling; and (*7*) reduced filling. *LV* , left ventricle; *ECG,* electrocardiogram; *a,* a-wave; *c,* c-wave; *v,* v-wave; *AP,* aortic pressure; *LVP,* left ventricular pressure; *LAP,* left atrial pressure; *LVEDV,* left ventricular end-diastolic volume; *LVESV,* left ventricular end-systolic volume, S_1-S_4, four heart sounds.

the left ventricular chamber. This permits fluoroscopic imaging (contrast ventriculography) of the ventricular chamber, from which estimates of ventricular volume can be obtained; however, real time echocardiography and nuclear imaging of the heart are more commonly used to obtain clinical assessment of volume and function.

In the following discussion, a complete cardiac cycle is defined as the cardiac events initiated by the P wave in the electrocardiogram (ECG) and continuing until the next P wave. The cardiac cycle is divided into two general categories: systole and diastole. **Systole** refers to events associated with ventricular contraction and ejection. **Diastole** refers to the rest of the cardiac cycle, including ventricular relaxation and filling. The cardiac cycle is further divided into seven phases, beginning when the P wave appears. These phases are atrial systole, isovolumetric contraction, rapid ejection, reduced ejection, isovolumetric relaxation, rapid filling, and reduced filling. The events associated with each of these phases are described below.

PHASE 1. ATRIAL SYSTOLE: AV VALVES OPEN; AORTIC AND PULMONIC VALVES CLOSED

The P wave of the ECG represents electrical depolarization of the atria, which initiates contraction of the atrial musculature. As the atria contract, the pressures within the atrial chambers increase; this drives blood from the atria, across the open AV valves, and into the ventricles. Retrograde atrial flow back into the vena cava and pulmonary veins is impeded by the inertial effect of venous return and by the wave of contraction throughout the atria, which has a "milking effect." However, atrial contraction produces a small increase in proximal venous pressure (i.e., within the pulmonary veins and vena cava). On the right side of the heart, this produces the **"a-wave"** of the jugular pulse, which can be observed when a person is recumbent and the jugular vein in the neck expands with blood.

Atrial contraction normally accounts for only about 10% of left ventricular filling when a person is at rest and the heart rate is low, because most of the ventricular filling occurs before the atria contract. Therefore, ventricular filling is mostly passive and depends on the venous return. However, at high heart rates (e.g., during exercise), the period of diastolic filling is shortened considerably (because overall cycle length is decreased), and the amount of blood that enters the ventricle by passive filling is reduced. Under these conditions, the relative contribution of atrial contraction to ventricular filling increases greatly and may account for up to 40% of ventricular filling. In addition, atrial contribution to ventricular filling is enhanced by an increase in the force of atrial contraction caused by sympathetic nerve activation. Enhanced ventricular filling owing to increased atrial contraction is sometimes referred to as the "atrial kick." During atrial fibrillation (see Chapter 2), the contribution of atrial contraction to ventricular filling is lost. This leads to inadequate ventricular filling, particularly when ventricular rates increase during physical activity.

After atrial contraction is complete, the atrial pressure begins to fall, which causes a slight pressure gradient reversal across the AV valves. This fall in atrial pressure following the peak of the a-wave is termed the **"x-descent."** As the pressures within the atria fall, the AV valves float upward (pre-position) before closure.

At the end of this phase, the ventricular volumes are maximal (**end-diastolic volume, EDV**). The left ventricular end-diastolic volume (typically about 120 mL) is associated with end-diastolic pressures of 8–12 mm Hg. The right ventricular end-diastolic pressure typically ranges from 3–6 mm Hg.

A heart sound is sometimes heard during atrial contraction (**Fourth Heart Sound, S_4**). The sound is caused by vibration of the ventricular wall during atrial contraction. This sound generally is noted when the ventricle compliance is reduced (i.e., "stiff" ventricle), as occurs in ventricular hypertrophy (see Ventricular Hypertrophy on CD. The sound is commonly present as a normal finding in older individuals.

PHASE 2. ISOVOLUMETRIC CONTRACTION: ALL VALVES CLOSED

This phase of the cardiac cycle is initiated by the QRS complex of the ECG, which represents ventricular depolarization. As the ventricles depolarize, myocyte contraction leads to a rapid increase in intraventricular pressure. The abrupt rise in pressure causes the AV valves to close as the intraventricular pressure exceeds atrial pressure. Contraction of the papillary muscles with their attached chordae tendineae prevents the AV valve leaflets from bulging back or prolapsing into the atria and becoming incompetent (i.e., "leaky"). Closure of the AV valves results in the **First heart sound (S_1).** A heart sound is generated when sudden closure of a heart valve and the accompanying oscillation of the blood cause vibrations (i.e., sound waves) that can be heard with a stethoscope overlying the heart. The first heart sound is normally split (~0.04 sec) because mitral valve closure precedes tricuspid closure; however, because this very short time interval normally cannot be perceived through a stethoscope, only a single sound is heard.

During the time between the closure of the AV valves and the opening of the semilunar valves, ventricular pressure rises rapidly without a change in ventricular volume (i.e., no ejection of blood into the aorta or pulmonary artery occurs). Ventricular contraction, therefore, is said to be "isovolumic" or "isovolumetric" during this phase. However, individual myocyte contraction is not necessarily isometric. Some individual fibers contract isotonically (i.e., concentric, shortening contraction), whereas others contract isometrically (i.e., with no change in length) or eccentrically (i.e., lengthening contraction). Ventricular chamber geometry changes considerably as the heart becomes more spheroid in shape, although the volume does not change. Early in this phase, the rate of pressure development becomes maximal. The maximal rate of pressure development, abbreviated "dP/dt max," is the maximal slope of the ventricular pressure tracing plotted against time during isovolumetric contraction.

Atrial pressures transiently increase owing to continued venous return and possibly to bulging of AV valves back into the atrial chambers. The **"c-wave"** noted in the jugular pulse is thought to occur owing to increased right atrial pressure that results from bulging of tricuspid valve leaflets back into right atrium.

PHASE 3. RAPID EJECTION: AORTIC AND PULMONIC VALVES OPEN; AV VALVES REMAIN CLOSED

When the intraventricular pressures exceed the pressures within the aorta and pulmonary artery, the aortic and pulmonic valves open and blood is ejected out of the ventricles. Ejection occurs because the total energy of the blood within the ventricle exceeds the total energy of blood within the aorta. The total energy of the blood is the sum of the pressure energy and the kinetic energy; the latter is related to the square of the velocity of the blood flow (see Energetics of Flowing Blood on CD). In other words, ejection occurs because an energy gradient is present (mostly owing to pressure energy) that propels blood into the aorta and pulmonary artery. During this phase, ventricular pressure normally exceeds outflow tract pressure by only a few millimeters of mercury (mm Hg). Although blood flow across the valves is high, the relatively large valve opening (i.e., providing low resistance) requires only a few mm Hg of a pressure gradient to propel flow across the valve. Maximal outflow velocity is reached early in the ejection phase, and maximal (systolic) aortic and pulmonary artery pressures are achieved.

While blood is being ejected and ventricular volumes decrease, the atria continue to fill with blood from their respective venous inflow tracts. Although atrial volumes are increasing, atrial pressures initially decrease (**x′-descent**) as the base of the atria is pulled downward, expanding the atrial chambers.

No heart sounds are ordinarily heard during ejection. *The opening of healthy valves is silent.* The presence of a sound during ejection (i.e., ejection murmurs) indicates valve

disease or intracardiac shunts (see Valve Disease on CD).

PHASE 4. REDUCED EJECTION: AORTIC AND PULMONIC VALVES OPEN; AV VALVES REMAIN CLOSED

Approximately 150–200 milliseconds after the QRS, ventricular repolarization (T wave) occurs. This causes ventricular active tension to decrease (i.e., muscle relaxation occurs) and the rate of ejection (ventricular emptying) to fall. Ventricular pressure falls slightly below outflow tract pressure; however, outward flow still occurs owing to kinetic (or inertial) energy of the blood that helps to propel the blood into the aorta and pulmonary artery. Atrial pressures gradually rise during this phase owing to continued venous return into the atrial chambers.

PHASE 5. ISOVOLUMETRIC RELAXATION: ALL VALVES CLOSED

As the ventricles continue to relax and intraventricular pressures fall, a point is reached at which the total energy of blood within the ventricles is less than the energy of blood in the outflow tracts. When this occurs, a pressure gradient reversal causes the aortic and pulmonic valves to abruptly close (aortic before pulmonic), causing a **Second Heart Sound (S_2)** that is physiologically and audibly split. Normally, little or no blood backflows into the ventricles as these valves close. Valve closure is associated with a characteristic notch (**incisura**) in the aortic and pulmonary artery pressure tracings. Unlike in the ventricles, where pressure rapidly falls, the decline in aortic and pulmonary artery pressures is not abrupt because of potential energy stored in their elastic walls and because systemic and pulmonic vascular resistances impede the flow of blood into distributing arteries of the systemic and pulmonary circulations.

Ventricular volumes remain constant (isovolumetric) during this phase because all valves are closed. The residual volume of blood that remains in a ventricle is called the **end-systolic volume (ESV).** For the left ventricle, this is approximately 50 mL of blood. The difference between the end-diastolic volume and the end-systolic volume represents the stroke volume (SV) of the ventricle and is about 70 mL. In a normal ventricle, about 60% or more of the end-diastolic volume is ejected. The volume of blood ejected (stroke volume) divided by the end-diastolic volume is called the **ejection fraction** of the ventricle, which normally is greater than 0.55 (or 55%). Although ventricular volume does not change during isovolumetric relaxation, atrial volumes and pressures continue to increase owing to venous return.

PHASE 6. RAPID FILLING: AV VALVES OPEN; AORTIC AND PULMONIC VALVES CLOSED

When the ventricular pressures fall below atrial pressures, the AV valves open and ventricular filling begins. The ventricles briefly continue to relax, which causes intraventricular pressures to continue to fall by several mm Hg despite on-going ventricular filling. Filling is very rapid because the atria are maximally filled just prior to AV valve opening. Once the valves open, the elevated atrial pressures coupled with the low resistance of the opened AV valves results in rapid, passive filling of the ventricles. Rapid, active relaxation of the left ventricle early in this phase causes left ventricular pressure to fall more rapidly than left atrial pressure, thereby producing diastolic suction, which aids in the initial filling.

The opening of the AV valves causes a rapid fall in atrial pressures and proximal venous pressures. On the right side of the heart, the peak of the jugular pulse just before the valve opens is the **"v-wave."** This peak is followed by the **"y-descent"** of the jugular pulse.

If the AV valves are functioning normally, no prominent sounds will be heard during filling. When a **Third Heart Sound (S_3)** is audible during ventricular filling, it may represent tensing of chordae tendineae and the AV ring, which is the connective tissue support for the valve leaflets. This S_3 heart sound is normal in children, but it is considered pathologic in

adults because it is often associated with ventricular dilation.

PHASE 7. REDUCED FILLING: AV VALVES OPEN; AORTIC AND PULMONIC VALVES CLOSED

No clear demarcation exists between the phases of rapid and reduced ventricular filling. The reduced filling phase is the period during diastole when passive ventricular filling is nearing completion. As the ventricles continue to fill with blood and expand, they become less compliant (i.e., "stiffer"). This causes the intraventricular pressures to rise, as described later in this chapter. Increased intraventricular pressure reduces the pressure gradient across the AV valve (the pressure gradient is the difference between the atrial and ventricular pressure) so that the rate of filling declines, even though atrial pressures continue to increase slightly as venous blood continues to flow into the atria. Aortic pressure and pulmonary arterial pressure continue to fall during this period as blood flows into the systemic and pulmonary circulations.

It is important to note that Figure 4-2 depicts the cardiac cycle at a relatively low heart rate (75 beats/minute). At low heart rates, the length of time allotted to diastole is relatively long, which lengthens the time of the reduced filling phase. High heart rates reduce the overall cycle length and are associated with reductions in the duration of both systole and diastole, although diastole shortens much more than systole. Without compensatory mechanisms, this cycle reduction would lead to less ventricular filling (i.e., reduced end-diastolic volume). Compensatory mechanisms are important for maintaining adequate ventricular filling during exercise (see Chapter 9).

Summary of Intracardiac Pressures

It is important to know normal values of intracardiac pressures, as well as the pressures within the veins and arteries entering and leaving the heart, because abnormal pressures can be used to diagnose certain types of cardiac disease and dysfunction. Figure 4-3 summarizes normal, typical pressures in an adult heart. Note that the pressures on the right side of the heart are considerably lower than those on the left side of the heart, and that the pulmonary circulation has low pressures compared to the systemic arterial system. The ranges in pressures in the right and left atria indicate the extent by which atrial pressure changes during the cardiac cycle.

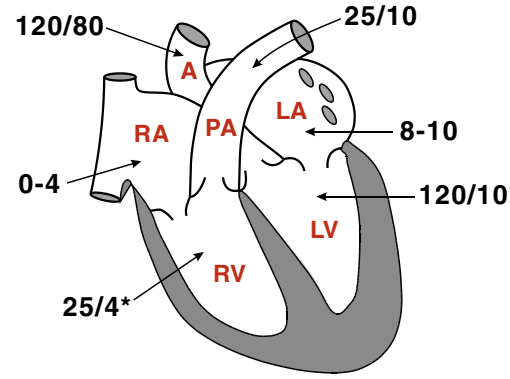


FIGURE 4-3 Summary of normal pressures within the cardiac chambers and great vessels. The higher values for pressures (expressed in mm Hg) in the right ventricle (*RV*), left ventricle (*LV*), pulmonary artery (*PA*), and aorta (*A*) represent the peak pressures during ejection (systolic pressure), whereas the lower pressure values represent the end of diastole (ventricles) or the lowest pressure (diastolic pressure) found in the pulmonary artery and aorta.

Ventricular Pressure-Volume Relationship

Although measurements of pressures and volumes over time can provide important insights into ventricular function, pressure-volume loops provide another powerful tool for analyzing the cardiac cycle, particularly ventricular function.

Pressure-volume loops (Fig. 4-4, bottom panel) are generated by plotting left ventricular pressure against left ventricular volume at many time points during a complete cardiac cycle (Fig. 4-4, top panel). In Figure 4-4, the letters represent the periods of ventricular filling (a), isovolumetric contraction (b), ventricular ejection (c), and isovolumetric relaxation (d). The EDV is the maximal volume achieved

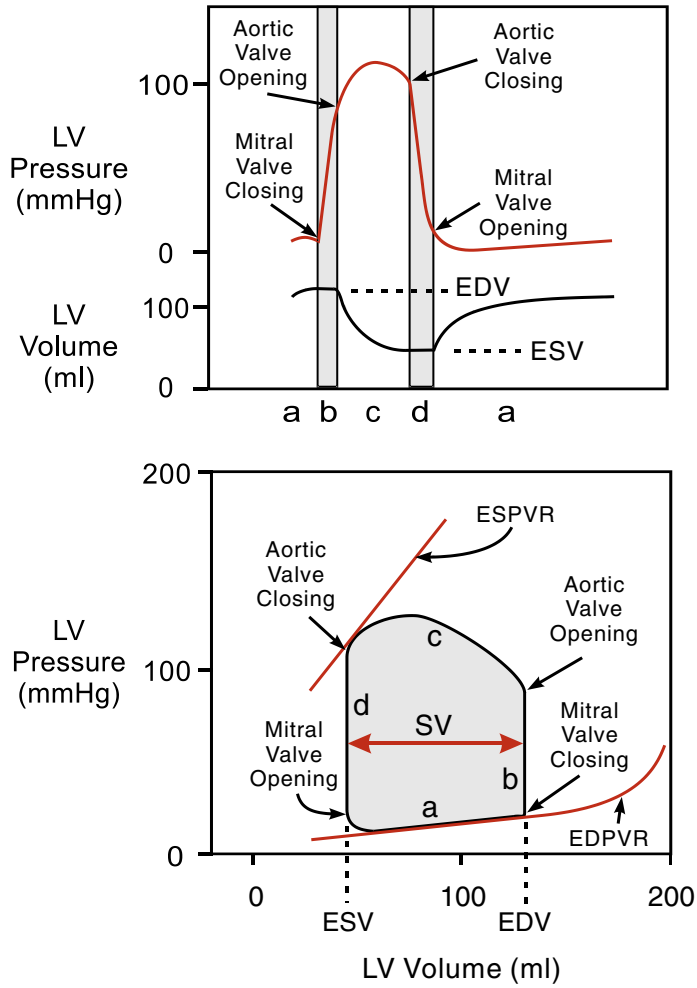


FIGURE 4-4 Ventricular pressure-volume loops. The left ventricular pressure-volume loop (bottom panel) is generated by plotting ventricular pressure against ventricular volume at many different corresponding points during a single cardiac cycle (upper panel). *a,* ventricular filling; *b,* isovolumetric contraction; *c,* ventricular ejection; *d,* isovolumetric relaxation; *EDV* and *ESV,* left ventricular end-diastolic and end-systolic volumes, respectively; *EDPVR,* end-diastolic pressure-volume relationship; *ESPVR,* end-systolic pressure-volume relationship; *SV,* stroke volume (EDV – ESV).

at the end of filling, and ESV is the minimal volume (i.e., residual volume) of the ventricle found at the end of ejection. The width of the loop, therefore, represents the difference between EDV and ESV, which is the SV. The area within the pressure-volume loop is the **ventricular stroke work** (see Ventricular Stroke Work on CD).

The filling phase moves along the **end-diastolic pressure-volume relationship** (EDPVR), or passive filling curve for the ventricle. The slope of the EDPVR at any point along the curve is the reciprocal of ventricular compliance, as described later in this chapter.

The maximal pressure that can be developed by the ventricle at any given left ventricular volume is described by the **end-systolic pressure-volume relationship** (ESPVR). The pressure-volume loop, therefore, cannot cross over the ESPVR, because the ESPVR defines the maximal pressure that can be generated at any given volume under a given inotropic state, as described later in this chapter.

Altered Pressure and Volume Changes during the Cardiac Cycle

The changes in pressures and volumes described in the cardiac cycle diagram and by the pressure-volume loop are for normal adult hearts at resting heart rates. The pressures and volumes can appear very differently in the presence of valve disease and heart failure. Changes in cardiac pressures and volumes in different types of valve disease are described in the accompanying CD-ROM. Heart failure and the way it alters cardiac pressures and volumes is discussed in Chapter 9.

REGULATION OF CARDIAC OUTPUT

The primary function of the heart is to impart energy to blood to generate and sustain an arterial blood pressure sufficient to adequately perfuse organs. The heart achieves this by contracting its muscular walls around a closed chamber to generate sufficient pressure to propel blood from the left ventricle, through the aortic valve, and into the aorta. Each time the left ventricle contracts, a volume of blood is ejected into the aorta. This stroke volume (SV), multiplied by the number of beats per minute (heart rate, HR), equals the cardiac output (CO) (Equation 4-1).

Eq. 4-1 $$CO = SV \cdot HR$$

Therefore, changes in either stroke volume or heart rate alter cardiac output.

The units for cardiac output are expressed as either mL/min or liters/min. The units for stroke volume are milliliters/beat (mL/beat), and the units for heart rate are beats/min. In a resting adult, cardiac output typically ranges from 5–6 L/min. Sometimes cardiac output is expressed as a **cardiac index,** which is the cardiac output divided by the estimated body surface area (BSA) in square meters. Several different formulas can be used to estimate BSA. One formula is BSA (m^2) equals the square root of the (height [cm] times weight [kg] divided by 3600); BSA = $(cm \cdot kg/3600)^{1/2}$ (Mosteller formula). Calculating the cardiac index normalizes cardiac output to individuals of different size. A normal range for cardiac index is 2.6 to 4.2 L/min/m^2.

Influence of Heart Rate on Cardiac Output

Although cardiac output is determined by both heart rate and stroke volume, changes in heart rate are generally more important quantitatively in producing changes in cardiac output. For example, heart rate may increase by 100% to 200% during exercise, whereas stroke volume may increase by less than 50%. These changes in heart rate are brought about primarily by changes in sympathetic and parasympathetic nerve activity at the sinoatrial node.

Changes in heart rate alone inversely affect stroke volume. For example, doubling heart rate from 70–140 beats/minute by pacemaker stimulation alone does not double cardiac output because stroke volume falls nearly proportionately. This occurs because the ventricular filling time decreases as the length of diastole shortens. However, when physiological mechanisms during exercise cause the heart rate to double, cardiac output more than doubles because stroke volume actually increases. This

PROBLEM 4-1

Calculate left ventricular stroke volume in milliliters/beat when the cardiac output is 8.8 liters/minute and the heart rate is 110 beats/min.

Stroke volume equals cardiac output divided by heart rate. Because stroke volume uses milliliters for units, cardiac output (8.8 liters/min) must be expressed in mL/min (8,800 mL/min). This value, divided by a heart rate of 110 beats/min, gives a stroke volume of 80 mL/beat.

increase in stroke volume, despite the elevation in heart rate, is brought about by several mechanisms acting on the heart and systemic circulation (see Chapter 9). When these mechanisms fail, stroke volume cannot be maintained at elevated heart rates. It is important to understand the mechanisms that regulate stroke volume because impaired stroke volume regulation can lead to a state of heart failure and limited exercise capacity (see Chapter 9).

Regulation of Stroke Volume

Ventricular stroke volume is the difference between the ventricular EDV and the ESV. In a typical heart, the EDV may be 120 mL of blood and the ESV 50 mL of blood. The difference in these two volumes, 70 mL, represents the stroke volume. Therefore, any factor that alters either the EDV or the ESV changes stroke volume.

Three primary mechanisms regulate EDV and ESV, and therefore stroke volume: preload, afterload, and inotropy (Fig. 4-5). A change in preload primarily alters EDV, whereas changes in afterload and inotropy primarily affect ESV. For example, increased preload increases stroke volume by increasing EDV, whereas increased afterload decreases stroke volume by increasing ESV. EDV and ESV are interdependent variables, so a change in one variable leads to a change in the other. The following section highlights the importance of preload, afterload, and inotropy in the regulation of EDV, ESV, and stroke volume.

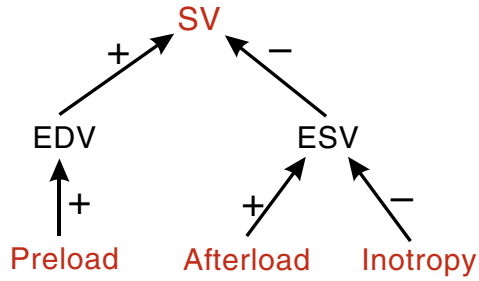


FIGURE 4-5 Factors determining stroke volume (*SV*). Because SV equals end-diastolic volume (*EDV*) minus end systolic volume (*ESV*), factors that increase EDV (preload) or decrease ESV (afterload and inotropy) will increase SV. (+), increase; (−), decrease.

Effects of Preload on Stroke Volume

Preload *is the initial stretching of the cardiac myocytes prior to contraction; therefore, it is related to the sarcomere length at the end of diastole*. Sarcomere length cannot be determined in the intact heart so indirect indices of preload, such as ventricular end-diastolic volume or pressure, must be used. These measures of preload are not ideal because they may not reflect sarcomere length. For example, with an acute increase in ventricular volume, an increase in sarcomere length occurs. However, in a chronically dilated ventricle, as occurs in some types of heart failure, the sarcomere length might be normal because of the addition of new sarcomeres in series. End-diastolic pressure is a poor index of preload because compliance of the ventricle determines the actual stretching of sarcomeres and hence ventricular volume, and this may change to accommodate chronic conditions (see next section). Nevertheless, *acute changes* in end-diastolic pressure and volume are useful indices for examining the effects of acute preload changes on stroke volume. Note that the concepts on the influence of preload on cardiac function described in the following sections can be applied to both the atria and the ventricles.

Effects of Ventricular Compliance on Preload

As the left ventricle (or other cardiac chamber) fills with blood, the pressure generated at a given volume is determined by the **compliance** of the ventricle, in which compliance is defined as *the ratio of a change in volume divided by a change in pressure.* Normally, compliance curves are plotted with the volume as a function of pressure, and the compliance is the slope of the line at any given pressure (i.e., the slope of the tangent at a particular point on the line). (See Compliance on CD.) For the ventricle, however, it is common to plot pressure versus volume (Fig. 4-6). Plotted in this manner, the slope of the tangent at a given

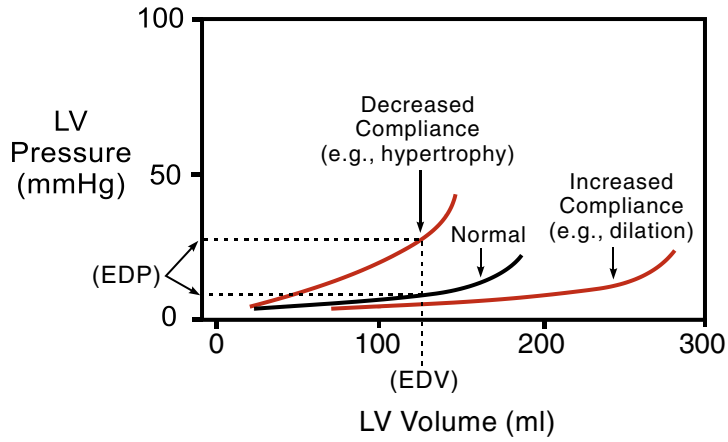


FIGURE 4-6 Ventricular compliance (or filling) curves. The slope of the tangent of the passive pressure-volume curve at a given volume represents the reciprocal of the ventricular compliance. The slope of the normal compliance curve is increased by a decrease in ventricular compliance (e.g., ventricular hypertrophy), whereas the slope of the compliance curve is reduced by an increase in ventricular compliance (e.g., ventricular dilation). Decreased compliance increases the end-diastolic pressure (*EDP*) at a given end-diastolic volume (*EDV*), whereas increased compliance decreases EDP at a given EDV. *LV,* left ventricle.

point on the line is the reciprocal of the compliance, which is sometimes referred to as ventricular elastance or "stiffness."

The relationship between pressure and volume is nonlinear in the ventricle (as in most biological tissues); therefore, compliance decreases with increasing pressure or volume. When pressure and volume are plotted as in Figure 4-6, we find that the slope of the filling curve (the end-diastolic pressure-volume relationship described in Figure 4-4) increases dramatically at higher volumes; i.e., the ventricle becomes less compliant or "stiffer" at higher volumes.

Ventricular compliance is determined by the physical properties of the tissues making up the ventricular wall and the state of ventricular relaxation. For example, in ventricular hypertrophy the increased muscle thickness decreases the ventricular compliance; therefore, ventricular end-diastolic pressure is higher for any given end-diastolic volume. This is shown in Figure 4-6, in which the filling curve of the hypertrophied ventricle shifts upwards and to the left. From a different perspective, for a given end-diastolic pressure, a less compliant ventricle will have a smaller end-diastolic volume (i.e., filling will be decreased). If ventricular relaxation is impaired, as occurs in some forms of diastolic ventricular failure (see Chapter 9), the effective ventricular compliance will be reduced. This will impair ventricular filling and increase end-diastolic pressure. If the ventricle becomes chronically dilated, as occurs in other forms of heart failure, the filling curve shifts downward and to the right. This enables a dilated heart to have a greater end-diastolic volume without causing a large increase in end-diastolic pressure.

The length of a sarcomere prior to contraction, which represents its preload, depends on the interplay between ventricular end-diastolic volume, end-diastolic pressure, and compliance. Although end-diastolic pressure and end-diastolic volume are sometimes used as indices of preload, care must be taken when interpreting the significance of these values in terms of how they relate to the preload of individual sarcomeres. For example, an elevated end-diastolic pressure may be associated with sarcomere lengths that are increased, decreased, or unchanged, depending on the ventricular volume and compliance at that volume.

Factors Determining Ventricular Preload

In the normal heart, right ventricular preload is determined by the volume of blood that fills

the ventricle at the end of passive filling and atrial contraction (i.e., the end-diastolic volume). Figure 4-7 summarize several factors that alter ventricular filling and therefore preload.

An increase in venous blood pressure increases ventricular preload. Venous blood volume and compliance determine venous pressure (see Chapter 5). Venous compliance relates to the state of smooth muscle contraction within venous blood vessels and is decreased, for example, by sympathetic activation, which contracts the venous smooth muscle. The reduced compliance leads to an increase in venous pressure. Venous blood volume, particularly in the thoracic (central) compartment, is influenced by the total blood volume (regulated by the kidneys) and the rate of venous return into the thoracic compartment. The rate of venous return is influenced by gravity, the mechanical pumping activity of skeletal muscles, and respiratory activity.

Several other important factors determine ventricular preload. (1) Ventricular compliance determines the end-diastolic volume for any given intraventricular filling pressure, as previously described. (2) Heart rate, through its influence on filling time, has an inverse effect on preload. (3) Atrial contraction (at resting heart rates) normally has only a small influence on ventricular preload because most of ventricular filling occurs during the passive filling phases. At high heart rates, however, increased atrial contractility (owing to sympathetic activation) significantly enhances (up to about 40%) the contribution of atrial contraction to ventricular filling, thereby helping to maintain preload. (4) Elevated inflow resistance decreases ventricular preload. For example, in tricuspid valve stenosis, the inflow resistance is increased and ventricular preload is reduced. (5) An increase in outflow resistance, as caused by pulmonic valve stenosis or pulmonary hypertension, impairs the ability of the right ventricle to empty, leading to an increase in preload. (6) In ventricular systolic failure, when ventricular inotropy is diminished, the ventricular preload increases because of the inability of the ventricle to eject normal volumes of blood. This causes blood to back up

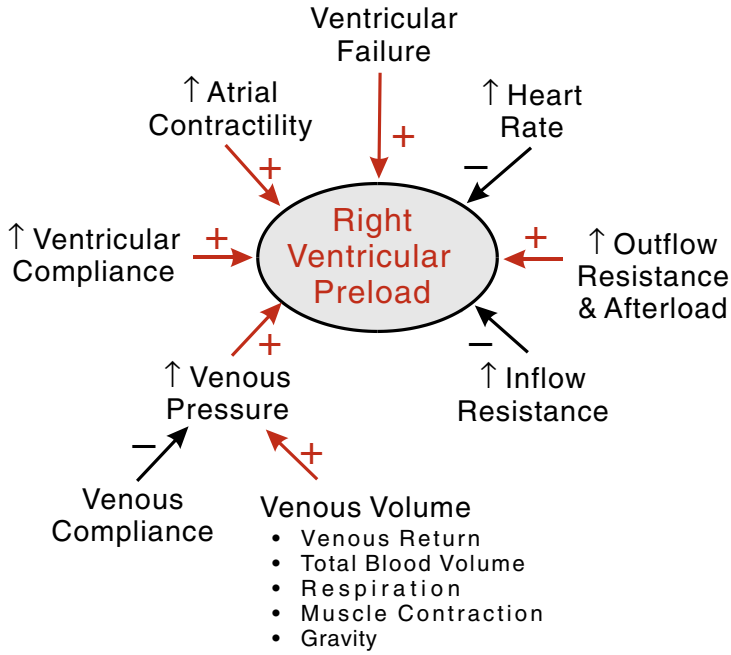
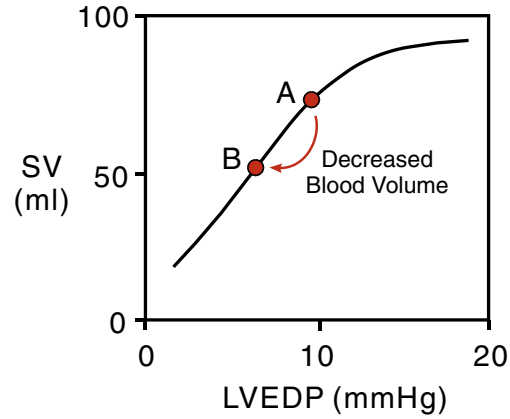


FIGURE 4-7 Factors determining right ventricular preload. (+) indicates that an increase in a variable increases right ventricular end-diastolic volume, and therefore preload; (–) indicates that the variable decreases preload.

CASE 4-1

A hospitalized patient is given a diuretic drug (which increases renal sodium and water excretion) to reduce blood volume. Using Frank-Starling curves, describe how the acute decrease in blood volume will affect ventricular stroke volume. Assume no significant changes in heart rate, inotropy, or aortic pressure.

A decrease in blood volume reduces venous return and ventricular preload (e.g., ventricular end-diastolic volume and pressure), which decreases force generation by the myocytes. This causes the stroke volume to fall from point *A* to *B* along a given Starling curve, as shown in Figure 4-26.



Effects of reducing blood volume on stroke volume. Reducing blood volume with a diuretic decreases ventricular filling so that the preload (left ventricular end-diastolic pressure, *LVEDP*) decreases. This causes stroke volume (*SV*) to fall from point *A* to point *B* along the Frank-Starling curve.

in the ventricle and proximal venous circulation.

Left ventricular preload is determined by the same factors as for right ventricular preload, except that the venous pressure is pulmonary venous pressure instead of central venous pressure, the inflow resistance is the mitral valve, and the outflow resistance is the aortic valve and aortic pressure. Respiratory activity also influences left ventricular preload, as described later in this chapter.

Effects of Venous Return on Stroke Volume (Frank-Starling Mechanism)

Altered preload is an important mechanism by which the ventricle changes its force of contraction. When venous return to the heart is increased, ventricular filling increases, as does preload. This stretching of the myocytes causes an increase in force generation, which enables the heart to eject the additional venous return and thereby increase stroke volume (Fig. 4-8). This is called the **Frank-Starling mechanism** in honor of the scientific contributions of Otto Frank (late 19th century) and Ernest Starling (early 20th century). Another term for this mechanism is "Starling's law of the heart." In summary, *the Frank-Starling mechanism states that increasing venous return and ventricular preload leads to an increase in stroke volume.*

There is no single Frank-Starling curve (sometimes called ventricular function curves) for the ventricle. Instead, there is a family of curves (Fig. 4-9), with each curve defined by the afterload imposed on the heart and the inotropic state of the heart. (These concepts are described later in this chapter.) Increasing afterload and decreasing inotropy shifts the curve down and to the right, whereas decreas-

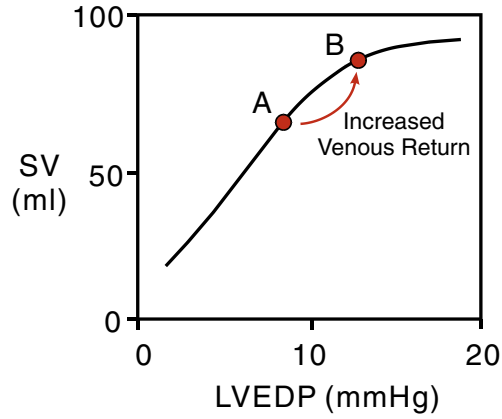


FIGURE 4-8 Frank-Starling mechanism. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (*LVEDP*) by increasing ventricular volume; this increases ventricular preload, resulting in an increase in stroke volume (*SV*) from point *A* to *B*. The "normal" operating point (*A*) is at a LVEDP of about 8 mm Hg and a SV of about 70 mL/beat.

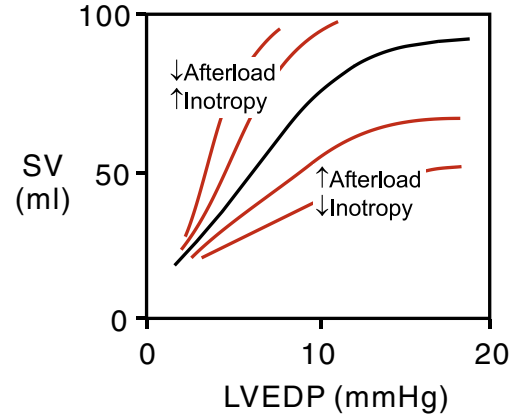


FIGURE 4-9 A family of Frank-Starling curves generated at different afterloads and inotropic states. Increased afterload or decreased inotropy shifts the Frank-Starling curve downward, whereas the opposite changes in afterload and inotropy shift the curve upward. Shifting the curves increases or decreases the stroke volume (*SV*) at any given left ventricular end-diastolic pressure (*LVEDP*).

ing afterload and increasing inotropy shifts the curve up and to the left. To summarize, *changes in venous return cause a ventricle to function along a Frank-Starling curve that is defined by the existing conditions of afterload and inotropy.*

The Frank-Starling mechanism plays an important role in balancing the output of the two ventricles. For example, when venous return increases to the right side of the heart during physical activity, the Frank-Starling mechanism enables the right ventricular

PROBLEM 4-2

If the left ventricular output is 60 mL/beat and the right ventricular stroke volume is only 0.1% greater, by how much would the pulmonary blood volume increase over 1 hour if the heart rate is 75 beats/min? Describe how the Frank-Starling mechanism normally prevents this large shift of blood from systemic to pulmonary circulation.

Because the right ventricular stroke volume is 0.1% greater than the left ventricular stroke volume of 60 mL/beat, the right ventricular stroke volume can be calculated by multiplying 60 times 1.001, which gives a stroke volume of 60.06 mL/beat. The difference in stroke volume between the two ventricles therefore is 0.06 mL/beat. To obtain the difference in total stroke volume over 1 hour when the rate is 75 beats/min, multiply the rate (75 beats/min) × 60 min/hr × stroke volume difference (0.06 mL/beat). This calculation yields a value of 270 mL.

This calculation demonstrates how a small difference in the output of the two ventricles (right being greater than left) can lead to a significant increase in pulmonary blood volume over time. Normally, this increase in pulmonary blood volume would increase pulmonary vascular pressures and the filling pressure for the left ventricle. This would increase the left ventricular stroke volume output by the Frank-Starling mechanism, which would maintain a balance in output over time between the two sides of the heart.

stroke volume to increase, thereby matching its output to the increased venous return. The increased right ventricular output increases the venous return to the left side of the heart, and the Frank-Starling mechanism operates to increase the output of the left ventricle. This mechanism ensures that the outputs of the two ventricles are matched over time; otherwise blood volume would shift between the pulmonary and systemic circulations.

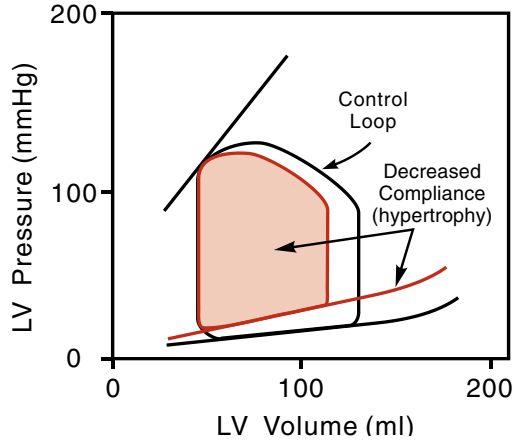
This analysis using Frank-Starling curves shows how changes in venous return and ventricular preload lead to changes in stroke volume. These curves, however, do not show how changes in venous return affect end-diastolic and end-systolic volumes. These changes in ventricular volumes are best illustrated by using pressure-volume diagrams.

When venous return is increased, increased filling of the ventricle occurs along its passive filling curve. This leads to an increase in end-diastolic volume (Fig. 4-10). If the ventricle now contracts at this increased preload, and the aortic pressure is held constant, the ventricle will empty to the same end-systolic volume, and therefore stroke volume will be increased. This is shown as an increase in the width of the pressure-volume loop. In reality, the increase in stroke volume that results from the increase in venous return will lead to an

CASE 4-2

Echocardiography reveals that the left ventricle of a chronically hypertensive patient is significantly hypertrophied. Using left ventricular pressure-volume loops, describe how end-diastolic pressure and volume and stroke volume will be altered by the hypertrophy. Assume no change in heart rate, inotropy, or aortic pressure.

A hypertrophied ventricle is less compliant. This causes the end-diastolic pressure-volume curve to shift up and to the left, as shown in Figure 4-27. This shift will reduce the end-diastolic volume and increase the end-diastolic pressure at the end of ventricular filling. The end-systolic volume will be normal unless there is a significant change in inotropy or aortic diastolic pressure. The width of the pressure-volume loop is narrower; therefore, the stroke volume is reduced.



Effects of left ventricular hypertrophy on the pressure-volume loop. Hypertrophy causes a reduction in ventricular compliance, which increases the slope of the end-diastolic pressure-volume relationship. This leads to an increase in end-diastolic pressure and a decrease in ventricular filling (end-diastolic volume). Reduced filling leads to a decrease in stroke volume (Frank-Starling mechanism), which is shown as a decrease in the width of the pressure-volume loop. End-systolic volume does not change unless inotropy or afterload changes. *LV,* left ventricle.

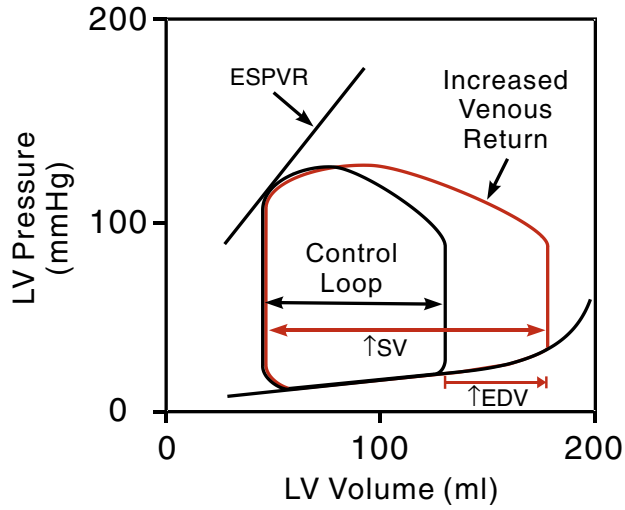


FIGURE 4-10 Effects of increasing venous return on left ventricular (*LV*) pressure-volume loops. This diagram shows the acute response to an increase in venous return. It assumes no cardiac or systemic compensation and that aortic pressure remains unchanged. Increased venous return increases end-diastolic volume (*EDV*), but it normally does not change end-systolic volume; therefore, stroke volume (*SV*) is increased. *ESPVR,* end-systolic pressure-volume relationship.

increase in aortic blood pressure because of the increase in cardiac output. For reasons described later in this chapter, this will lead to a small increase in end-systolic volume; the net effect, however, will still be an increase in the width of the pressure-volume loop (i.e., increased stroke volume). The normal ventricle, therefore, is capable of increasing its stroke volume to match an increase in venous return. The increase in the area within the pressure-volume loop, which represents the ventricular stroke work, will also be increased.

Effects of Preload Length on Tension Development (Length-Tension Relationship)

The mechanical or biophysical basis for the Frank-Starling mechanism can be described by the length-tension relationship for cardiac myocytes. The **length-tension relationship** examines how changes in the initial length of a muscle (i.e., preload) affect the ability of the muscle to develop force (tension). To illustrate this relationship, a piece of cardiac muscle (e.g., papillary muscle) is isolated and placed within an in vitro bath containing an oxygenated, physiologic salt solution. One end of the muscle is attached to a force transducer to measure tension, and the other end is attached to an immovable support rod (Fig. 4-11, left panel). The end that is attached to the force transducer is movable so that the initial length (preload) of the muscle can be fixed at a desired length. The muscle is then electrically stimulated to contract; however, the length is not permitted to change and therefore the contraction is isometric.

If the muscle is stimulated to contract at a relatively short initial length (low preload), a characteristic increase in tension (termed "active" tension) will occur, lasting about 200 m/sec (Fig. 4-11, right panel, curve *a*). By stretching the muscle to a longer initial length, the passive tension will be increased prior to stimulation. The amount of passive tension depends on the elastic modulus ("stiffness") of the tissue. The elastic modulus of a tissue is related to the ability of a tissue to resist deformation; therefore, the higher the elastic modulus, the "stiffer" the tissue. When the muscle is stimulated at the increased preload, there will be a larger increase in active tension (curve *b*) than had occurred at the lower preload. If the preload is again increased, there will be a further increase in active tension (curve *c*). Therefore, *increases in preload lead to an increase in active tension.* Not only is the

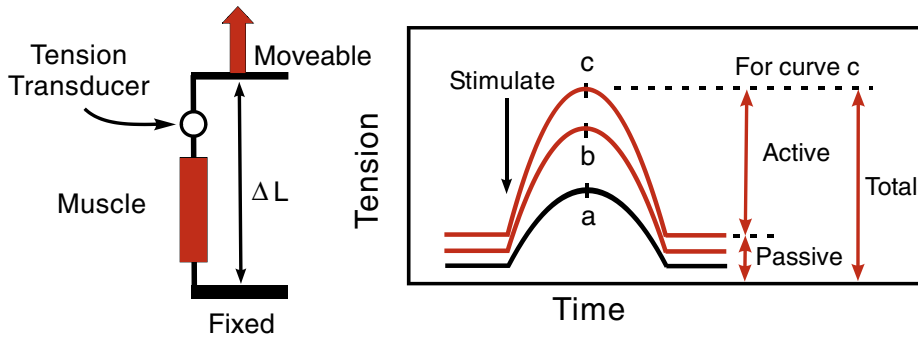


FIGURE 4-11 Effects of increased preload on tension development by an isolated strip of cardiac muscle. The left panel shows how muscle length and tension are measured in vitro. The bottom of the muscle strip is fixed to an immovable rod, whereas the top of the muscle is connected to a tension transducer and a movable bar that can be used to adjust initial muscle length (ΔL). The right panel shows how increased preload (initial length) increases both passive and active (developed) tension. The greater the preload, the greater the active tension generated by the muscle.

magnitude of active tension increased, but also the rate of active tension development (i.e., the maximal slope with respect to time of the tension curve during contraction). The duration of contraction and the time-to-peak tension, however, are not changed.

If the results shown in Figure 4-11 are plotted as tension versus initial length (preload), a length-tension diagram is generated (Fig. 4-12). In the top panel, the passive tension curve is the tension that is generated as the muscle is stretched prior to contraction. Points *a*, *b*, and *c* on the passive curve correspond to the passive tensions and initial preload lengths for curves *a*, *b*, and *c* in Figure 4-11 prior to contraction. The total tension curve represents the maximal tension that occurs during contraction at different initial preloads. The total tension curve is the sum of the passive tension and the additional tension generated during contraction (active tension). The active tension, therefore, is the difference between the total and passive tension curves; it is shown in the bottom panel of Figure 4-12. The active tension diagram demonstrates that as preload increases, there is an increase in active tension up to a maximal limit. The maximal active tension in cardiac muscle corresponds to a sarcomere length of about 2.2 microns. Cardiac muscle, unlike skeletal muscle, does not display a descending limb on the active tension curve because the greater stiffness of cardiac muscle normally prevents the sarcomeres from being stretched beyond 2.2 microns.

This discussion described how changes in preload affect the force generated by cardiac muscle fibers during isometric contractions (i.e., with no change in length). Cardiac muscle fibers, however, normally shorten when they contract (i.e., undergo isotonic contractions). If a strip of cardiac muscle in vitro is set at a given preload length and stimulated to contract, it will shorten and then return to its resting preload length (Fig. 4-13). If the initial preload is increased and the muscle stimulated again, it will ordinarily shorten to the same minimal length, albeit at a higher velocity of shortening. This explains why, in Figure 4-10, the increase in end-diastolic volume resulted in an increase in stroke volume with no change in end-systolic volume.

The length-tension relationship, although usually used to describe the contraction of isolated muscles, can be applied to the whole heart. By substituting ventricular volume for length and ventricular pressure for tension, the length-tension relationship becomes a pressure-volume relationship for the ventricle. This can be done because a quantitative relationship exists between tension and pressure and between length and volume that is determined by the geometry of the ventricle. Figure 4-14 shows that as ventricular preload

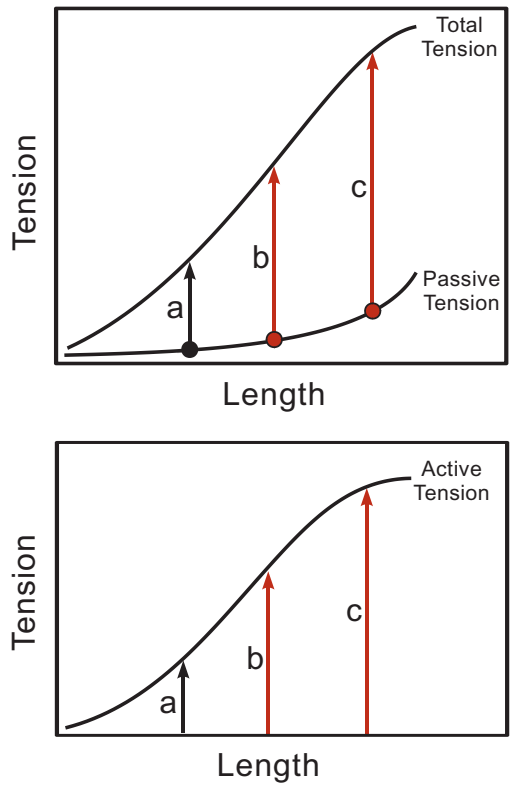


FIGURE 4-12 Length-tension relationship for cardiac muscle undergoing isometric contraction. The top panel shows that increasing the preload length from points *a* to *c* increases the passive tension. Furthermore, increasing the preload increases the total tension during contraction as shown by arrows *a, b,* and *c,* which correspond to active tension changes depicted by curves a, b, and c in Figure 4-11. The length of the arrow is the active tension, which is the difference between the total and passive tensions. The bottom panel shows that the active tension increases to a maximum value as preload increases.

volume is increased (i.e., end-diastolic volume increased), an increase in isovolumetric ventricular pressure development occurs during ventricular contraction, analogous to what is observed with a single papillary muscle (see Fig. 4-12). This can be observed experimentally in the ventricle by occluding the aorta during ventricular contraction and measuring the peak systolic pressure generated by the ventricle under this isovolumetric condition. If the ventricle were permitted to eject blood, the increased pressure development resulting from increased preload would augment stroke volume, as depicted in Figure 4-10.

What mechanisms are responsible for the increase in force generation with increased preload in the heart? In the past, it was thought that changes in active tension caused by altered preload could be explained by a change in the number of actin and myosin cross bridges formed (see Chapter 3). Although this can be a factor if sarcomere length is increased beyond 2.2 μ (the length of maximal force generation), the intact heart under physiologic conditions operates at sarcomere lengths in the range of 1.8–2.2 μ (i.e., on the ascending limb of the length-tension relationship for the sarcomere). For various structural and mechanical reasons, the sarcomere length in cardiac myocytes does not normally exceed 2.2 μ. These observations have led to the concept of **length-dependent activation.** Experimental evidence supports three possible explanations. First, studies have shown that increased sarcomere length sensitizes the regulatory protein troponin C to calcium without necessarily increasing intracellular release of calcium. This increases calcium binding by troponin C, leading to an increase in force generation as described in Chapter 3. A second explanation is that fiber stretching alters calcium homeostasis within the cell so that increased calcium is available to bind to troponin C. A third explanation is that as a myocyte (and sarcomere) lengthens, the diameter must decrease because the volume has to remain constant. It has been proposed that this would bring the actin and myosin molecules closer to each other (decreased lateral spacing), which would facilitate their interactions.

It has traditionally been taught that the Frank-Starling mechanism does not result in a change in inotropy (intrinsic contractility) despite a change in force generation. However, we can no longer rigidly differentiate between the mechanisms responsible for preload and inotropic effects on force generation because of what we now understand about length-dependent activation of the myofilaments.

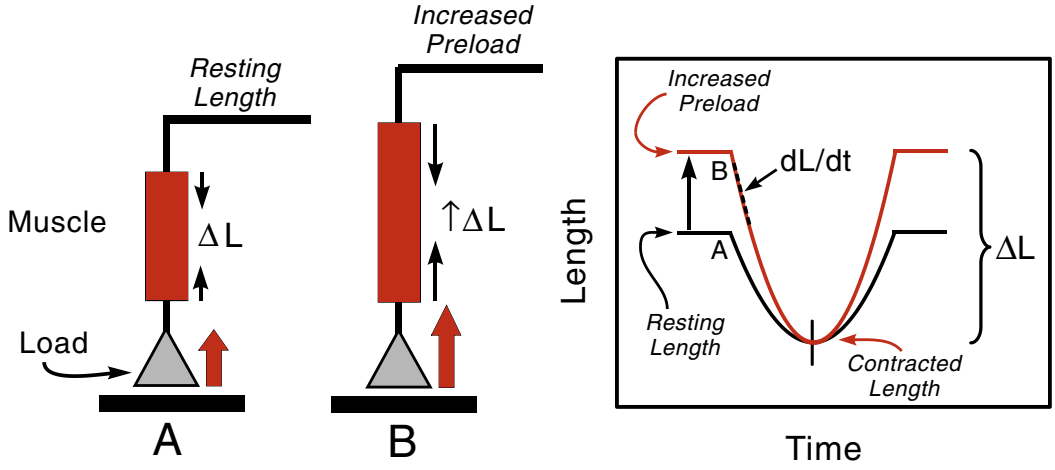


FIGURE 4-13 Effects of increased initial muscle length (increased preload) on muscle shortening (isotonic contractions). The left panel shows a muscle lifting a load (afterload) at two different preload lengths (*A* and *B*). The right panel shows how increasing the preload leads to increased shortening (Δ*L*) and increased velocity of shortening (*dL/dt;* change in length with respect to time). The muscle shortens to the same minimal length when preload is increased.

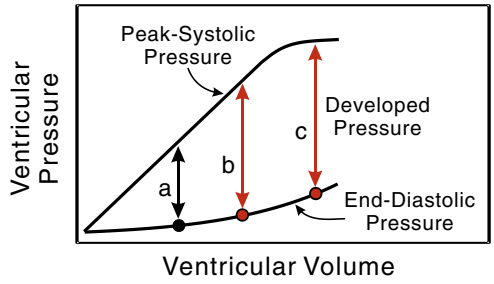


FIGURE 4-14 Effects of increasing ventricular volume (preload) on ventricular pressure development. Increasing ventricular volume from *a* to *c* and then stimulating the ventricle to contract isovolumetrically increases the developed pressure and the peak-systolic pressure.

Effects of Afterload on Stroke Volume

Afterload *is the "load" against which the heart must contract to eject blood.* A major component of the afterload for the left ventricle is the aortic pressure, or the pressure the ventricle must overcome to eject blood. The greater the aortic pressure, the greater the afterload on the left ventricle. For the right ventricle, the pulmonary artery pressure represents the major afterload component.

Ventricular afterload, however, involves factors other than the pressure that the ventricle must develop to eject blood. One way to estimate the afterload on the individual cardiac fibers within the ventricle is to examine ventricular wall stress (σ), which is proportional to the product of the intraventricular pressure (P) and ventricular radius (r), divided by the wall thickness (h) (Equation 4-2). This relationship for wall stress assumes that the ventricle is a sphere. The determination of actual wall stress is complex and must consider not only ventricular geometry, but also muscle fiber orientation. Nonetheless, Equation 4-2 helps to illustrate the factors that contribute to wall stress and therefore afterload on the muscle fibers.

Eq. 4-2

$$\sigma \propto \frac{P \cdot r}{h}$$

Wall stress can be thought of as the average tension that individual muscle fibers within the ventricular wall must generate to shorten against the developed intraventricular pressure. At a given intraventricular pressure, wall stress is increased by an increase in radius (ventricular dilation). Therefore, afterload is increased whenever intraventricular pressures are increased during systole and by ventricular dilation. On the other hand, a thickened, hypertrophied ventricle will have reduced wall stress and afterload on individual fibers. Ventricular wall hypertrophy can be thought

of as an adaptive mechanism by which the ventricle is able to offset the increase in wall stress that accompanies increased aortic pressure, aortic valve stenosis, or ventricular dilation.

Effects of Afterload on Frank-Starling Curves

An increase in afterload shifts the Frank-Starling curve down and to the right (Fig. 4-15). Therefore, at a given preload (LVEDP in Figure 4-15), an increase in afterload decreases stroke volume. Conversely, decreasing afterload shifts the curves up and to the left, thereby increasing the stroke volume at any given preload. For reasons discussed later, changes in afterload result in a subsequent change in preload so that as the Frank-Starling curve shifts, the operating point for the curve shifts diagonally, as shown in Figure 4-15. In the normal heart, changes in afterload do not have pronounced effects on stroke volume; however, the failing ventricle is very sensitive to changes in afterload.

Effects of Afterload on the Velocity of Fiber Shortening (Force-Velocity Relationship)

The decrease in stroke volume that accompanies an increase in afterload is caused by impaired emptying of the ventricle. The basis for this is found in the **force-velocity relationship** of cardiac myocytes. The force-velocity relationship shows how afterload affects the velocity of shortening when muscle fibers contract isotonically. To illustrate this, a papillary muscle is placed in an in vitro bath and a load is attached to one end (Fig. 4-16, left panel). When the muscle contracts, the fiber first generates tension isometrically (right panel, *a* to *b*) until the developed tension exceeds the load imposed on the muscle. When this point is reached, the muscle fiber begins to shorten and the tension remains constant and equal to the load that is being lifted (*b* to *c*). The maximal velocity of shortening occurs shortly after the muscle begins to shorten. The muscle continues to shorten until the muscle begins to relax. When active tension falls below the load (point *c*), the muscle resumes its resting length (i.e., preload) (point *c*). Active tension continues to fall isometrically (*c* to *d*) until only the passive tension remains (point *d*).

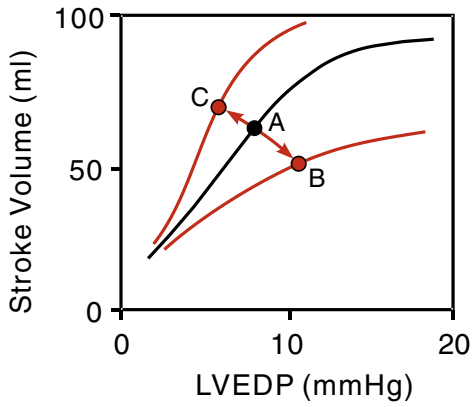


FIGURE 4-15 Effects of changes in afterload on Frank-Starling curves. An increase in afterload shifts the operating point of the Frank-Starling curve from *A* to *B*, whereas a decrease in afterload shifts the operating point from *A* to *C*. Therefore, increased afterload decreases stroke volume and increases end-diastolic pressure (preload). The converse also is true.

If this experiment with the papillary muscle were repeated with increasing loads, a decrease would occur in both the maximal velocity of fiber shortening (maximal slope of line) and the degree of shortening, as shown in Figure 4-17. Plotting the maximal velocity of shortening against the load that the muscle fiber must shorten against (i.e., the afterload) generates an inverse relationship between velocity of shortening and afterload (Fig. 4-18). In other words, *the greater the afterload, the slower the velocity of shortening.*

To further illustrate the force-velocity relationship, consider the following example. If a man holds a 2-pound dumbbell at his side while standing, and then contracts his biceps muscle at maximal effort, the weight will be lifted at a relatively high velocity as the biceps muscle shortens. If the weight is increased to 20 pounds, and the weight once again is lifted at maximal effort, the velocity will be much slower. Higher weights further reduce the velocity until the weight can no longer be lifted and the contraction of the biceps muscle becomes isometric. The x-intercept in the force velocity diagram (see Fig. 4-18) is the point at

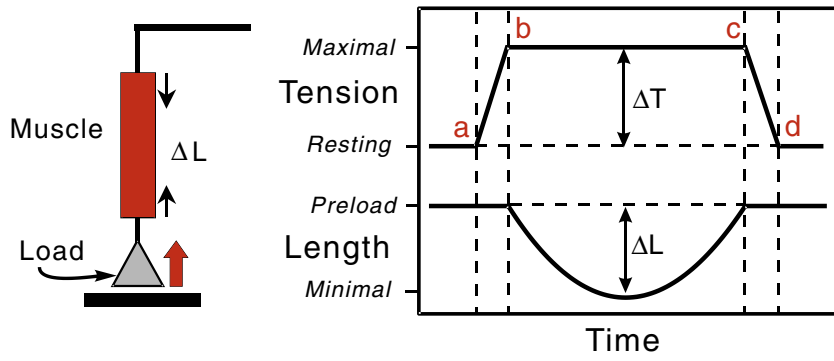


FIGURE 4-16 Cardiac muscle isotonic contractions. The left panel shows how muscle length and tension are measured in vitro. The lower end of the muscle is attached to a weight (load) that is lifted up from an immovable platform as the muscle develops tension and shortens (Δ*L*). A bar attached to the top of the muscle can be moved to adjust initial muscle length (preload). The right panel shows changes in tension and length during contraction. The periods from *a* to *b* and from *c* to *d* represent periods of isometric contraction and relaxation, respectively. Muscle shortening (ΔL) occurs between *b* and *c,* which occurs when the developed tension (ΔT) exceeds the load.

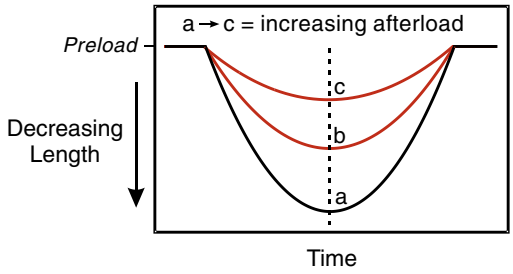


FIGURE 4-17 Effects of afterload on myocyte shortening. Increased afterload (curves *a* to *c*) decreases the degree of muscle shortening and velocity of shortening at a given preload.

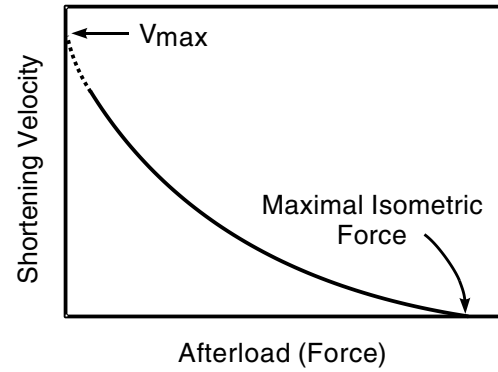


FIGURE 4-18 Force-velocity relationship. Increased afterload (which requires increased force generation) decreases velocity of shortening by the muscle fiber. The x-intercept represents the maximal isometric force; the y-intercept represents the maximal velocity of shortening (V_{max}) extrapolated to zero load.

which the afterload is so great that the muscle fiber cannot shorten. The x-intercept therefore represents the maximal isometric force. The y-intercept represents an extrapolated value for the maximal velocity (V_{max}) that would be achieved if there was no afterload. The value is extrapolated because it cannot be measured experimentally (a muscle will not contract in the absence of any load).

It is important to note that a cardiac muscle fiber does not operate on a single force-velocity curve (Fig. 4-19). If preload is increased, a cardiac muscle fiber will have a greater velocity of shortening at a given afterload. This occurs because the length-tension relationship requires that as the preload is increased, there is an increase in active tension development. Once the fiber begins to shorten, an increased preload with an increase in tension-generating capability causes a greater shortening velocity. In other words, increasing the preload enables the muscle to contract faster against a given afterload; this shifts the force-velocity relationship to the right. Note that increasing the preload increases the maximal isometric force (x-intercept) as well as the shortening velocity at a given afterload. Changes in preload, however, do not alter V_{max}.

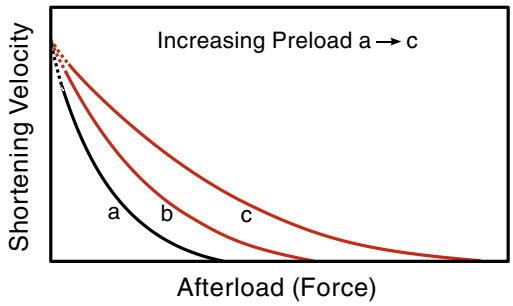


FIGURE 4-19 Effects of increasing preload (shift from curve *a* to *c*) on the force-velocity relationship. At a given afterload, increasing the preload increases the velocity of shortening. Furthermore, increasing the preload shifts the x-intercept to the right, representing an increase in isometric force generation.

Therefore, *an increase in preload on a cardiac myocyte helps to offset the reduction in velocity that occurs when afterload is increased.*

Effects of Afterload on Pressure-Volume Loops

Changes in afterload produce secondary changes in preload, as shown in Figure 4-15. Therefore, afterload and preload are interdependent variables. This interdependence can best be described using pressure-volume loops (Fig. 4-20). If afterload is increased by increasing aortic diastolic pressure, the ventricle has to generate increased pressure before the aortic valve can open. The ejection velocity after the valve opens will be reduced because increased afterload decreases the velocity of cardiac fibers shortening, as described by the force-velocity relationship. Because only a finite period of time exists for electrical and mechanical systole, less blood will be ejected (decreased stroke volume) so that ventricular end-systolic volume increases as shown in the pressure-volume loop. The increased end-systolic volume inside the ventricle will be added to the venous return, thereby increasing end-diastolic volume. After several beats, a steady state is achieved in which the increase in end-systolic volume is greater than the increase in end-diastolic volume so that the difference between the two—the stroke volume—is decreased (i.e., the width of the pressure-volume loop is decreased). This increase in preload secondary to the increase in afterload activates the Frank-Starling mechanism to partially compensate for the reduction in stroke volume caused by the increase in afterload.

Effects of Inotropy on Stroke Volume

Effects of Inotropy on Length-Tension Relationship

Ventricular stroke volume is altered both by changes in preload and afterload, and by changes in ventricular **inotropy** (sometimes referred to as contractility). *Changes in inotropy are caused by intrinsic cellular mechanisms that regulate the interaction between actin and myosin independent of changes in sarcomere length.* For example, if cardiac muscle is exposed to norepinephrine, it increases active tension development at any initial preload length as shown by the length-tension relationship (Fig. 4-21). This occurs because the norepinephrine binds to β_1-adrenoceptors, increasing calcium entry into the cell and calcium release by the sarcoplasmic reticulum during contraction (see Chapter 3).

Effects of Inotropy on Force-Velocity Relationship

Changes in inotropy also alter the force-velocity relationship. If the inotropic state of the

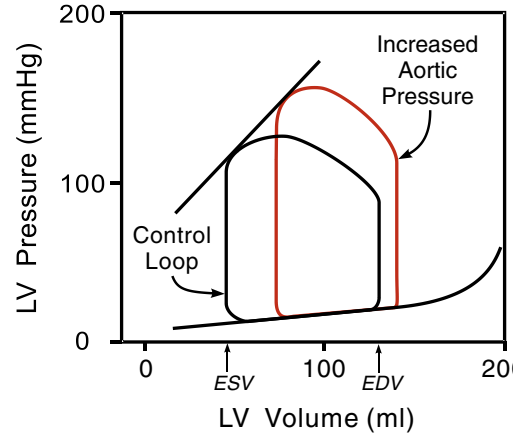


FIGURE 4-20 Effects of increased afterload (aortic pressure) on the steady-state left ventricular (*LV*) pressure-volume loop. Heart rate and inotropy are held constant in this illustration. Increased aortic pressure leads to an increase in end-systolic volume (*ESV*), followed by a secondary, but smaller increase in end-diastolic volume (*EDV*). The net effect is a narrower loop and therefore decreased stroke volume.

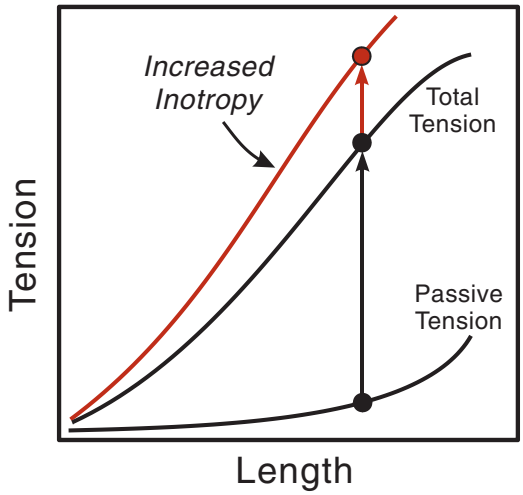


FIGURE 4-21 Effects of increased inotropy on the length-tension relationship for cardiac muscle. Increasing inotropy (for example, by stimulating the cardiac muscle with norepinephrine) shifts the total tension curve upward, which increases active tension development (vertical arrows) at any given preload length.

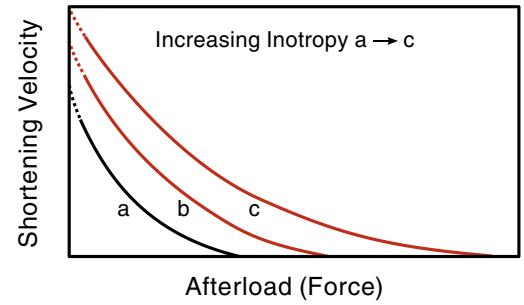


FIGURE 4-22 Effects of increasing inotropy (parallel shift from curve *a* to *c*) on the force-velocity relationship. Increased inotropy increases the velocity of shortening at any given afterload, and increases V_{max} (y-intercept). Furthermore, increased inotropy increases maximal isometric force (x-intercept).

myocyte is increased, the force-velocity curve has a parallel shift up and to the right, resulting in an increase in both V_{max} and maximal isometric force (Fig. 4-22). The increase in velocity at any given afterload results from the increased inotropy enhancing force generation by the actin and myosin filaments and increasing the rate of cross-bridge turnover. The increase in V_{max} represents an increased intrinsic capability of the muscle fiber to generate force independent of load.

Effects of Inotropy on Pressure-Volume Loops

The increased velocity of fiber shortening that occurs with increased inotropy causes an increased rate of ventricular pressure development (dP/dt). This increases ejection velocity and stroke volume and reduces end-systolic volume, as shown in Figure 4-23. When inotropy is increased, the end-systolic pressure-volume relationship is shifted to the left and becomes steeper, because the ventricle can generate increased pressure at any given volume. The end-systolic pressure-volume relationship sometimes is used experimentally to define the inotropic state of the ventricle. It is analogous to the upward shift that occurs in the total tension curve in the length-tension relationship (Fig. 4-21) when inotropy increases. Furthermore, the increased stroke volume leads to a reduction in ventricular end-diastolic volume because less end-systolic volume is available to be added to the incoming venous return.

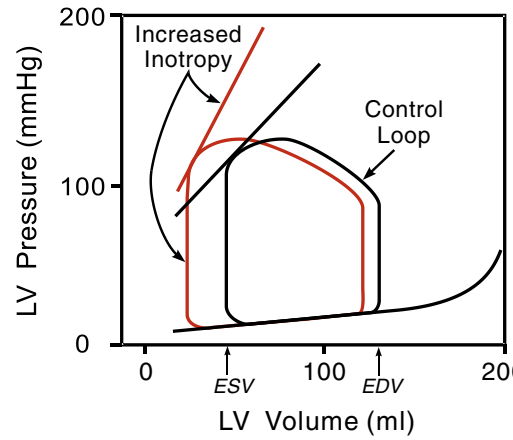


FIGURE 4-23 Effects of increasing inotropy on the steady state of the left ventricular pressure-volume loop. Heart rate and aortic pressure are held constant in this illustration. Increased inotropy shifts the end-systolic pressure-volume relationship (see Fig. 4-4) up and to the left, thereby decreasing end-systolic volume (*ESV*). A secondary, but smaller decrease in end-diastolic volume (*EDV*) follows. The net effect is an increase in stroke volume (EDV – ESV). *LV,* left ventricle.

Effects of Inotropy on Frank-Starling Curves

An increase in inotropy causes the Frank-Starling curve to shift up and to the left (Fig. 4-24). This leads to an increase in stroke volume along with a reduction in ventricular preload. Conversely, a decrease in inotropy (as occurs in systolic heart failure; see Chapter 9), shifts the relationship down and to the right, thereby decreasing stroke volume and increasing preload.

Changes in inotropy change the **ejection fraction,** which is defined as the stroke volume divided by the end-diastolic volume. A normal ejection fraction is greater than 0.55 (or 55%). Increasing inotropy increases ejection fraction, whereas decreasing inotropy decreases ejection fraction. Therefore, ejection fraction often is used as a clinical index for evaluating the inotropic state of the heart. In heart failure, for example, a decrease in inotropy leads to a fall in stroke volume as well as an increase in preload, thereby decreasing ejection fraction sometimes to a value less than 20%. Treating a patient in heart failure with an inotropic drug (e.g., β-adrenoceptor agonist or digoxin) shifts the depressed Frank-Starling curve up and to the left, thereby increasing stroke volume, decreasing preload, and increasing ejection fraction.

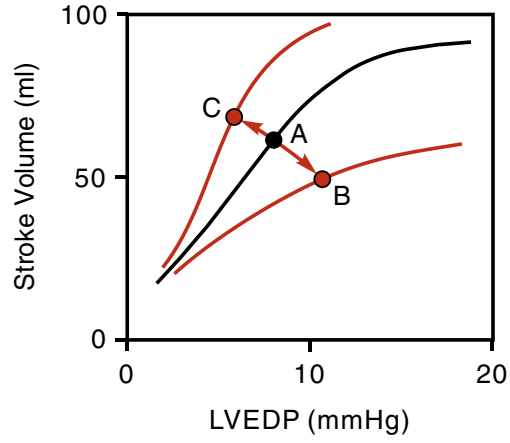


FIGURE 4-24 Effects of changes in inotropy on Frank-Starling curves. Decreased inotropy shifts the operating point from *A* to *B,* which decreases stroke volume and increases left ventricular end-diastolic pressure (*LVEDP*). Increased inotropy causes a shift from point *A* to *C,* which increases stroke volume and decreases LVEDP.

Changes in inotropic state are particularly important during exercise (see Chapter 9). Increases in inotropic state help to maintain stroke volume at high heart rates. Increased heart rate alone decreases stroke volume because of reduced time for diastolic filling (decreased end-diastolic volume). When inotropic state increases at the same time, this decreases end-systolic volume to help maintain stroke volume.

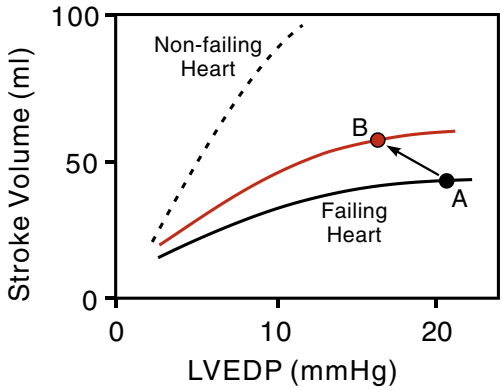
Factors Influencing Inotropic State

Several factors influence inotropy (Fig. 4-25); the most important of these is the activity of autonomic nerves. Sympathetic nerves, by releasing norepinephrine that binds to β_1-adrenoceptors on myocytes, are prominent in ventricular and atrial inotropic regulation (see Chapter 3). Parasympathetic nerves (vagal efferents), which release acetylcholine that binds to muscarinic (M_2) receptors on myocytes (see Chapter 3), have a significant negative inotropic effect in the atria but only a small effect in the ventricles. High levels of circulating epinephrine augment sympathetic adrenergic effects via β_1-adrenoceptor activation. In humans and some other mammalian hearts, an abrupt increase in afterload can cause a modest increase in inotropy (**Anrep effect**) by a mechanism that is not fully understood. In addition, an increase in heart rate can cause a small positive inotropic effect (also termed the **Bowditch effect,** treppe, or frequency-dependent activation). This latter phenomenon probably is due to an inability of the Na^+/K^+-ATPase to keep up with the sodium influx at higher frequency of action potentials at elevated heart rates, leading to an accumulation of intracellular calcium via the sodium-calcium exchanger (see Chapter 2). Systolic failure that results from cardiomyopathy, ischemia, valve disease, arrhythmias, and other conditions is characterized by a loss of intrinsic inotropy. In addition to these physiologic and pathologic mechanisms, a variety of inotropic drugs are used clinically to increase inotropy in acute and chronic heart failure. These drugs include digoxin (inhibits sar-

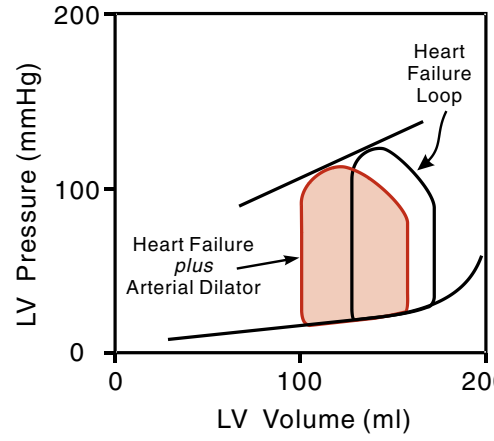
CASE 4-3

A 67-year-old male is diagnosed with left ventricular failure 4 months following an acute myocardial infarction. One of the drugs he is given for treatment acts as a systemic arterial vasodilator. Using Frank-Starling curves and left ventricular pressure-volume loops, explain how decreasing afterload will improve left ventricular ejection fraction.

A systemic vasodilator reduces afterload on the left ventricle. This causes the Starling curve to shift up and to the left from its depressed state (because of the loss of inotropy in failure) (left figure). This shift increases stroke volume and at the same time reduces preload (end-diastolic pressure) from point A to B in left figure. Systemic vasodilation reduces aortic diastolic pressure, which enables the ventricle to eject sooner, more rapidly, and to a smaller end-systolic volume (right figure). The reduced end-systolic volume leads to a compensatory decrease in end-diastolic volume; however, the reduction in end-systolic volume will be greater than the reduction in end-diastolic volume so that stroke volume is increased. By increasing stroke volume and reducing the end-diastolic volume, the ejection fraction is increased.



Effects of an arterial vasodilator on stroke volume and left ventricular end-diastolic pressure (LVEDP) in heart failure. In heart failure (specifically systolic failure – see Chapter 9), the Frank-Starling curve shifts downward because of depressed inotropy. Arterial vasodilation, which reduces afterload on the ventricle, moves the operating point from *A* to *B* by shifting the Frank-Starling curve upward. This leads to an increase in stroke volume and a decrease in LVEDP (preload).



Effects of an arterial vasodilator on left ventricular pressure-volume loops. Heart failure causes a downward shift (reduced slope) of the end-systolic pressure-volume relationship. This leads to an increase in end-systolic volume, a smaller compensatory increase in end-diastolic volume, and reduced stroke volume. Reducing arterial pressure decreases afterload on the ventricle, which leads to an increase in stroke volume. This decreases left ventricular end-systolic volume, and to a smaller extent, end-diastolic volume. The net effect is an increase in stroke volume. *LV,* left ventricle.

colemmal Na^+/K^+-ATPase), β-adrenoceptor agonists (e.g., dopamine, dobutamine, epinephrine, isoproterenol), and phosphodiesterase inhibitors (e.g., milrinone).

Mechanisms of Inotropy

Inotropy can be thought of as a **length-independent activation** of the contractile proteins. Any cellular mechanism that ultimately

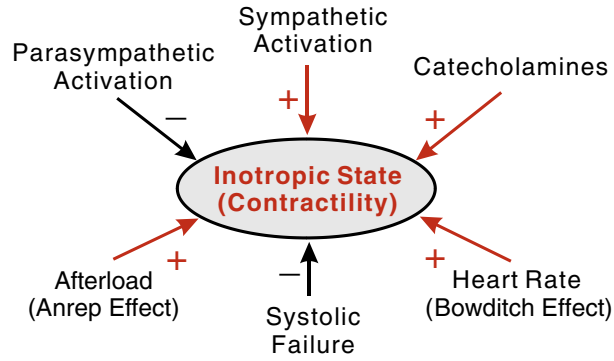


FIGURE 4-25 Factors regulating inotropy. (+), increased inotropy; (−), decreased inotropy.

alters myosin ATPase activity at a given sarcomere length alters force generation and therefore can be considered an inotropic mechanism. Most of the signal transduction pathways that regulate inotropy involve Ca^{++} (see Chapter 3). Briefly, inotropic state can be enhanced by (1) increasing Ca^{++} influx across the sarcolemma during the action potential (via L-type Ca^{++} channels); (2) increasing the release of Ca^{++} by the sarcoplasmic reticulum; or (3) sensitizing troponin C to Ca^{++}. For example, β_1-adrenoceptor activation acting through Gs-proteins increases cAMP, which activates protein kinase-A. This enzyme can phosphorylate different intracellular sites to influence Ca^{++} entry, Ca^{++} release, and Ca^{++} affinity. Cardiac glycosides such as digoxin inhibit the Na^+/K^+-ATPase, leading to an increase in intracellular Ca^{++} and an increase in inotropy.

MYOCARDIAL OXYGEN CONSUMPTION

Changes in stroke volume, whether caused by changes in preload, afterload, or inotropy, significantly alter the oxygen consumption of the heart. Changes in heart rate likewise affect myocardial oxygen consumption. The contracting heart consumes a considerable amount of oxygen because of its need to regenerate the large amount of ATP hydrolyzed during contraction and relaxation. Therefore, any change in myocardial function that affects either the generation of force by myocytes or their frequency of contraction will alter oxygen consumption. In addition, even in noncontracting cells, ATP utilized by ion pumps and other transport functions requires oxygen for the resynthesis of ATP.

How Myocardial Oxygen Consumption is Determined

Oxygen consumption is defined as the volume of oxygen consumed per min (e.g., mL O_2/min) and is sometimes expressed per 100 g of tissue weight (mL O_2/min per 100 g). The myocardial oxygen consumption ($M\dot{V}O_2$) can be calculated by knowing the coronary blood flow (CBF) and the arterial and venous oxygen contents (AO_2 and VO_2) according to the following equation that uses the **Fick Principle:**

Eq. 4-3 $$M\dot{V}O_2 = CBF \cdot (AO_2 - VO_2)$$

Myocardial oxygen consumption, therefore, is equal to the coronary blood flow multiplied by the amount of oxygen extracted from the blood (the arterial-venous oxygen difference). The content of oxygen in blood is usually expressed as mL O_2/100 mL blood (or, vol % O_2). The oxygen content of arterial blood is normally about 20 mL O_2/100 mL blood. To calculate the myocardial oxygen consumption in the correct units, mL O_2/100 mL blood is converted to mL O_2/mL blood; with this conversion, the arterial oxygen content is 0.2 mL O_2/mL blood. For example, if CBF is 80 mL/min per 100 g, the AO_2 is 0.2

mL O_2/mL blood and VO_2 is 0.1 mL O_2/mL blood, $M\dot{V}O_2$ = 8 mL O_2/min per 100 g. This value of myocardial oxygen consumption is typical for what is found in a heart contracting at resting heart rates against normal aortic pressures. During heavy exercise, myocardial oxygen consumption can increase to 70 mL O_2/min per 100 g, or more. If contractions are arrested (e.g., by depolarization of the heart with a high concentration of potassium chloride), the myocardial oxygen consumption decreases to about 2 mL O_2/min per 100g. This value represents the energy costs of cellular functions not associated with contraction. Therefore, myocardial oxygen consumption varies considerably depending on the state of mechanical activity.

Although myocardial oxygen consumption can be calculated as described above, generally it is not feasible to measure coronary blood flow and venous oxygen content except in experimental studies. Coronary blood flow can be measured by placing flow probes on coronary arteries or a thermodilution catheter within the coronary sinus. Arterial oxygen content can be taken from a peripheral artery, but the venous oxygen content has to be obtained from the coronary sinus by inserting a catheter into the right atrium and then into the coronary sinus.

Indirect indices of myocardial oxygen consumption have been developed to estimate myocardial oxygen consumption when it is not feasible to measure it. Although no index has proven to be satisfactory over a wide range of physiologic conditions, one simple index sometimes used in clinical studies is the **pressure-rate product** (also called the double-product). This index can be measured noninvasively by multiplying heart rate and systolic arterial pressure (mean arterial pressure sometimes is used instead of systolic arterial pressure). The pressure-rate product assumes that the pressure generated by the ventricle is not significantly different than the aortic pressure (i.e., there is no aortic valve stenosis). Experiments have shown that a reasonable correlation exists between changes in the pressure-rate product and myocardial oxygen consumption. For example, if arterial pressure, heart rate, or both become elevated, oxygen consumption will increase.

Factors Influencing Myocardial Oxygen Consumption

Part of the difficulty in finding a suitable index of oxygen consumption is that several factors determine myocyte oxygen consumption, including frequency of contraction, inotropic state, afterload, and preload (Table 4-1). For example, doubling heart rate approximately doubles oxygen consumption, because myocytes are generating twice the number of ten-

PROBLEM 4-3

In an experimental study, administration of an inotropic drug is found to increase coronary blood flow (CBF) from 50 to 150 mL/min and increase the arterial-venous oxygen difference ($AO_2 - VO_2$) from 10 to 14 mL O_2/100 mL blood. Calculate the percent increase in myocardial oxygen consumption ($M\dot{V}O_2$) caused by infusion of this drug.

Myocardial oxygen consumption can be calculated from Equation 4-3, such that

$$M\dot{V}O_2 = CBF \cdot (AO_2 - VO_2)$$

The control oxygen consumption is 50 mL/min times the A-V oxygen difference of 0.1 mL O_2/mL blood, which equals 5 mL O_2/min. Note that the arterial-venous oxygen difference must be converted from mL O_2/100 mL blood to mL O_2/mL blood. The experimental oxygen consumption is 150 mL/min times 0.14 mL O_2/mL blood, which equals 21 mL O_2/min. This is a 320% increase in oxygen consumption ([(21 -5)/5] x 100).

TABLE 4-1 FACTORS INCREASING MYOCARDIAL OXYGEN CONSUMPTION

↑ Heart Rate
↑ Inotropy
↑ Afterload
↑ Preload*

*Changes in preload affect oxygen consumption much less than do changes in the other factors.

sion cycles per minute. Increasing inotropy increases oxygen consumption because both the rate of tension development and the magnitude of tension are increased, and they both are associated with increased ATP hydrolysis and oxygen consumption. An increase in afterload likewise increases oxygen consumption because it increases the tension that must be developed by myocytes. Increasing stroke volume by increasing preload (end-diastolic volume) also increases oxygen consumption.

Quantitatively, increased preload has less impact on oxygen consumption than does an increase in afterload (e.g., aortic pressure). To understand why, we need to examine the relationship between wall stress, pressure, and radius of the ventricle. As discussed earlier (see Equation 4-2), ventricular wall stress (σ) is proportional to the intraventricular pressure (P) multiplied by the ventricular internal radius (r) and divided by the wall thickness (h).

$$\sigma \propto \frac{P \cdot r}{h}$$

Wall stress is related to the tension an individual myocyte must develop during contraction to generate a given ventricular pressure. At a given radius and wall thickness, a myocyte must generate increased contractile force (i.e., wall stress) to develop a higher pressure. The contractile force must be increased even further to generate the same elevated pressure if the ventricular radius is increased. For example, if the ventricle is required to generate 50% more pressure than normal to eject blood because of elevated aortic pressure, the wall stress that individual myocytes must generate will be increased by approximately 50%. This will increase the oxygen consumption of these myocytes by about 50% because changes in oxygen consumption are closely related to changes in wall stress. As a second example, if the radius of the ventricle is increased by 50%, the wall stress needed by the myocytes to eject blood at a normal pressure will be increased by about 50%. On the other hand, if the ventricular end-diastolic volume is increased by 50% and the pressure and wall thickness remain unchanged, the wall stress will be increased by only about 14%. The reason for this is that a large change in ventricular volume (V) requires only a small change in radius (r). If we assume that the shape of the ventricle is a sphere, then

$$V = \frac{4}{3}\,\pi \cdot r^3$$

By rearranging this relationship, we find that

$$r \propto \sqrt[3]{V}$$

Substituting this into the wall stress equation results in

Eq. 4-4

$$\sigma \propto \frac{P \cdot \sqrt[3]{V}}{h}$$

Although no single acceptable model for the shape of the ventricle exists because its shape changes during contraction, a sphere serves as a convenient model for illustrating why changes in volume have a relatively small affect on wall stress and oxygen consumption. Using this model, Equation 4-4 shows that increasing the end-diastolic volume by 50% (by a factor of 1.5) represents only a 14% (cube root of 1.5) increase in wall stress at a given ventricular pressure, whereas a 50% increase in pressure increases wall stress by 50%. Therefore, increasing pressure by a given percentage increases wall stress about four times more than the same change in volume.

Relating the wall stress equation to oxygen consumption helps to explain why increases in pressure generation have a much greater influence on oxygen consumption than a similar percentage increase in ventricular preload. It is important, however, not to use the wall

stress equation to estimate oxygen demands by the whole heart. The reason for this is that wall stress estimates the tension required by individual myocytes to generate pressure as they contract. This wall stress, in large part, determines the oxygen consumption of individual myocytes, but oxygen consumption of the whole heart is the sum of the oxygen consumed by all of the myocytes. A hypertrophied ventricle with a thicker wall, which has reduced wall stress, may not have a reduction in overall oxygen consumption as suggested by Equation 4-4. In fact, because of its greater muscle mass, oxygen consumption may be significantly increased in a hypertrophied heart, particularly if its efficiency is impaired by disease. A less efficient heart performs less work per unit oxygen consumed (i.e., it generates less pressure and stroke volume).

The concepts described above have implications for treating patients with coronary artery disease (CAD). For example, drugs that decrease afterload, heart rate, and inotropy are particularly effective in reducing myocardial oxygen consumption and relieving symptoms of chest pain (i.e., angina), which results from inadequate oxygen delivery relative to the oxygen demands of the myocardium. CAD patients are counseled to avoid activities such as lifting heavy weights that lead to large increases in arterial blood pressure. In contrast, CAD patients are often encouraged to participate in exercise programs such as walking that utilize preload changes to augment cardiac output by the Frank-Starling mechanism. It is important to minimize stressful situations in these patients because stress causes sympathetic activation of the heart and vasculature that increases heart rate, inotropy, and afterload, all of which lead to significant increases in oxygen demand by the heart.

SUMMARY OF IMPORTANT CONCEPTS

- The cardiac cycle is divided into two general phases: diastole and systole. Diastole refers to the period of time that the ventricles are undergoing relaxation and filling with blood from the atria. Ventricular filling is primarily passive, although atrial contraction has a variable effect on the final extent of ventricular filling (end-diastolic volume). Systole, or ventricular contraction, is initiated by electrical depolarization of the ventricles, which is represented by the QRS complex of the electrocardiogram. Ventricular ejection begins when ventricular pressure exceeds the pressure within the outflow tract (aorta or pulmonary artery) and continues until ventricular relaxation causes the ventricular pressures to fall sufficiently below the aortic and pulmonary artery pressures to cause the aortic and pulmonic valves to close. The volume of blood remaining in the ventricle at the end of ejection is the end-systolic volume.
- The first heart sound (S_1) originates from closure of the atrioventricular valves (tricuspid and mitral) as the ventricles begin to contract. The second heart sound (S_2) results from the closure of the pulmonic and aortic valves at the end of ventricular systole. The third and fourth heart sounds (S_3 and S_4), when audible, occur during early diastole and atrial contraction, respectively.
- Ventricular stroke volume is the difference between the end-diastolic and end-systolic volumes. Ventricular ejection fraction is calculated as the stroke volume divided by the end-diastolic volume. Ejection fraction is frequently used in a clinical setting to assess the inotropic state of the left ventricle.
- Cardiac output is the product of stroke volume and heart rate. Normally, cardiac output is influenced more by changes in heart rate than by changes in stroke volume; however, impaired regulation of stroke volume can have a significant adverse affect on cardiac output, as occurs during heart failure.
- Ventricular preload is related to the extent of ventricular filling (end-diastolic volume) and the sarcomere length. Preload can be increased by several factors: increased blood volume, augmented venous return, decreased venous compliance (venous constriction), atrial contraction force, and decreased heart rate (increases filling time); indirectly, preload can be increased by a

loss of ventricular inotropy or an increase in afterload.

- Increased preload increases the force of contraction. The length-tension diagram, in which an increase in preload increases active tension, shows this. Additionally, increased preload increases the velocity of fiber shortening, as shown by a shift in the force-velocity relationship to the right. By itself, an increase in preload increases stroke volume (Frank-Starling mechanism) without changing the end-systolic volume.
- Ventricular afterload can be estimated by ventricular wall stress, which is the product of ventricular pressure and ventricular radius divided by the ventricular wall thickness. Therefore, left ventricular afterload (wall stress) is increased by elevated ventricular pressures during systole (e.g., as occurs in hypertension) or when the ventricle is dilated (increased radius). Increased wall thickness, as occurs in hypertrophy, reduces the wall stress experienced by individual myocytes.
- Increased afterload decreases the velocity of fiber shortening during contraction, as shown by the force-velocity relationship. In the whole heart, this reduces stroke volume and increases end-systolic volume at a given preload and causes the Frank-Starling curve to shift downward. In addition, increased afterload increases end-diastolic volume secondarily to the increase in end-systolic volume.
- Inotropy is the property of a cardiac myocyte that enables it to alter its tension development independent of changes in preload length. Autonomic nerves and circulating catecholamines are important mechanisms for regulating inotropy, although increases in afterload and heart rate can augment inotropy. Loss of inotropy results in heart failure.
- Increased inotropy enhances active tension development by individual muscle fibers and increases ventricular pressure development, ejection velocity, and stroke volume at a given preload and afterload. Increased inotropy normally leads to a reduction in preload secondary to the decrease in end-systolic volume.
- Myocardial oxygen consumption can be calculated using the Fick Principle, in which oxygen consumption equals the product of the coronary blood flow and the arteriovenous oxygen difference. Myocardial oxygen consumption is strongly influenced by changes in arterial pressure, heart rate, and inotropy; it is less influenced by changes in stroke volume.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. During the phase of rapid ventricular filling,
   a. S_4 may sometimes be heard.
   b. The aortic valve is open.
   c. The mitral valve is open.
   d. Ventricular pressure is higher than aortic pressure.

2. Right ventricular preload is increased by which of the following?
   a. Decreased atrial contractility
   b. Decreased blood volume
   c. Decreased heart rate
   d. Decreased ventricular compliance

3. As the preload on a ventricular myocyte is increased,
   a. Active tension development increases.
   b. Inotropy decreases.
   c. Sarcomere length decreases.
   d. Velocity of shortening decreases.

4. Left ventricular end-diastolic pressure is increased by
   a. Decreased afterload.
   b. Decreased venous return.
   c. Increased inotropy.
   d. Ventricular hypertrophy.

5. Ventricular stroke volume is reduced by
   a. Decreased inotropy.
   b. Increased venous return.
   c. Reduced afterload.
   d. Reduced heart rate.

6. Left ventricular end-systolic volume is
   a. Decreased when aortic pressure is suddenly increased.
   b. Greater than end-diastolic volume.
   c. Increased when inotropy is impaired.
   d. Reduced at increased preloads.

7. Myocardial inotropic state is enhanced by
   a. β_1-adrenoceptor mediated increases in cAMP.
   b. Decreasing heart rate.
   c. Inhibiting slow inward calcium movement.
   d. Vagal activation.

8. Increasing the inotropic state of the myocardium will
   a. Increase end-systolic volume.
   b. Increase the width of the pressure-volume loop.
   c. Increase ventricular end-diastolic volume.
   d. Shift the force-velocity relationship to the left.

9. Increased afterload on the ventricle
   a. Decreases end-systolic volume.
   b. Decreases the velocity of shortening.
   c. Increases stroke volume.
   d. Increases V_{max} in the force-velocity relationship.

10. If each of the following is increased by 50%, which one would cause the *smallest* change in myocardial oxygen consumption?
    a. Heart rate
    b. Ventricular end-diastolic volume
    c. Mean arterial pressure
    d. Ventricular radius

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chapter

5

Vascular Function

CD CONTENTS

Critical Stenosis
Valsalva Maneuver

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Name the different types of vessels constituting the vascular network of the body and describe the general function of each.**
2. **Describe the factors that determine arterial pulse pressure.**
3. **Describe how changes in cardiac output, systemic vascular resistance, and central venous pressure affect mean arterial pressure.**
4. **Describe in quantitative terms how changes in vessel radius, vessel length, blood viscosity, and perfusion pressure affect blood flow.**
5. **Calculate total resistance from series or parallel resistance networks.**
6. **Explain why the pressure drop across small arteries and arterioles is much greater than the pressure drop across other vessel types.**
7. **Define vascular tone and list factors that alter vascular tone.**
8. **Explain how each of the following affects central venous pressure: blood volume, venous compliance, gravity, respiration, and muscle contraction.**
9. **Define mean circulatory filling pressure and explain what determines its value.**
10. **Using cardiac and systemic function curves, explain how changes in blood volume, venous compliance, vascular resistance, and cardiac performance influence the equilibrium between right atrial pressure and cardiac output.**

INTRODUCTION

The vascular system serves two basic functions: distribution and exchange. Distribution includes transporting blood to and away from organs. The anatomical arrangement of the vasculature and physiologic control mechanisms that dilate or constrict blood vessels determine this transport. Changes in vessel diameters regulate blood pressure and determine the amount of blood flow to specific organs and regions within organs. This chapter focuses on vascular anatomy and the general principles involved in the regulation of blood pressure and blood flow. Chapters 6 and 7 describe these physiologic control mechanisms in more detail. The exchange function is described in Chapter 8.

ANATOMY AND FUNCTION

Vascular Network

The left ventricle ejects blood into the aorta, which then distributes the blood flow throughout the body using a network of arterial vessels. These vessels are illustrated in Figure 5-1. Table 5-1 summarizes the relative sizes and functions of different blood vessels.

The **aorta,** besides being the main vessel to distribute blood from the heart to the arterial system, dampens the pulsatile pressure that results from the intermittent ejection of blood from the left ventricle. The dampening is a function of the aortic compliance, which is discussed in more detail later in this chapter. **Large arteries** branching off the aorta (e.g., carotid, mesenteric, and renal arteries) dis-

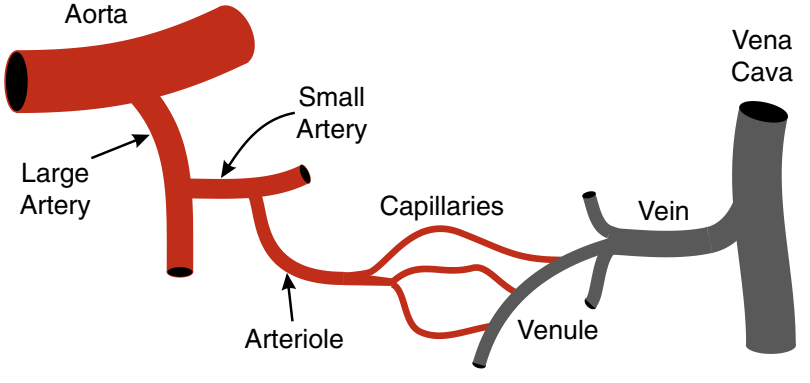

FIGURE 5-1 Major types of blood vessels found within the circulation.

TABLE 5-1 SIZE AND FUNCTION OF DIFFERENT TYPES OF BLOOD VESSELS IN THE SYSTEMIC CIRCULATION

VESSEL TYPE	DIAMETER (MM)	FUNCTION
Aorta	25	Pulse dampening and distribution
Large arteries	1.0–4.0	Distribution
Small arteries	0.2–1.0	Distribution and resistance
Arterioles	0.01–0.20	Resistance (pressure/flow regulation)
Capillaries	0.006–0.010	Exchange
Venules	0.01–0.20	Exchange, collection, and capacitance
Veins	0.2–5.0	Capacitance function (blood volume)
Vena cava	35	Collection

tribute the blood flow to specific organs or regions of the body. These large arteries, although capable of constricting and dilating, serve no significant role in the regulation of pressure and blood flow under normal physiologic conditions. Once the distributing artery reaches the organ to which it supplies blood, it branches into **smaller arteries** that distribute blood flow within the organ. These smaller arteries continue branching into smaller and smaller vessels. Once they reach diameters of less 200 μm, they are termed **arterioles.** No clear demarcation between small arteries and arterioles exists; therefore, no consensus has been reached regarding the point at which a small artery becomes an arteriole. Many investigators speak of different branching orders of arterial vessels within a tissue or organ. Most would agree that arterioles have only a few layers of vascular smooth muscle and are, in general, less than 200 μm in diameter.

Together, the small arteries and arterioles represent the primary **resistance vessels** that regulate arterial blood pressure and blood flow within organs. Resistance vessels are highly innervated by autonomic nerves (particularly sympathetic adrenergic), and they constrict or dilate in response to changes in nerve activity. The resistance vessels are richly endowed with receptors that bind circulating hormones (e.g., catecholamines, angiotensin II), which can alter vessel diameter (see Chapters 3 and 6). They also respond to various substances (e.g., adenosine, potassium ion, and nitric oxide) produced by the tissue surrounding the vessel or by the vascular endothelium.

As arterioles become smaller in diameter (<10 μm), they lose their smooth muscle. Vessels that have no smooth muscle and are composed of only endothelial cells and a basement membrane are termed **capillaries.** Although they are the smallest vessels within the circulation, they have the greatest cross-sectional area because they are so numerous. Because the total blood flow of capillaries is the same as the flow within the aorta leaving the heart, and because the capillary cross-sectional area is about 1000 times greater than the aorta, the mean velocity of blood flowing within capillaries (0.05 cm/sec) is about one thousand-fold less than the velocity in the aorta (50 cm/sec). The reason for this is that flow (F) is the product of mean velocity (V) times cross-sectional area (A) ($F = V \cdot A$). When this expression is rearranged, we find that the mean velocity is inversely proportional to cross-sectional area ($V = F/A$).

Capillaries have the greatest surface area for exchange. Endothelium, oxygen, carbon dioxide, water, electrolytes, proteins, metabolic substrates and by-products, and circulating hormones are exchanged across the capillary between the plasma and the tissue interstitium surrounding it (see Chapter 8). Capillaries, therefore, are the primary exchange vessels within the body.

When capillaries join together, they form post-capillary venules, which serve as exchange vessels for fluid and macromolecules because of their high permeability. As post-capillary venules converge and form larger venules, smooth muscle reappears. These vessels, like the resistance vessels, are capable of dilating and constricting. Changes in venular diameter regulate capillary pressure and venous blood volume.

Venules converge to form larger veins. Together, venules and veins are the primary capacitance vessels of the body, i.e., the site where most of the blood volume is found and regional blood volume is regulated. Constriction of veins decreases venous blood volume and increases venous pressure, which can alter cardiac output by affecting right atrial and ventricular preload. The final venous vessels are the inferior and superior vena cavae, which carry the blood back to the right atrium of the heart.

Distribution of Pressures and Volumes

Blood pressure is highest in the aorta and progressively decreases as the blood flows further away from the heart (Fig. 5-2). The mean aortic pressure is about 95 mm Hg in a normal adult. The mean blood pressure does not fall much as the blood flows down the aorta and through large distributing arteries. The reason

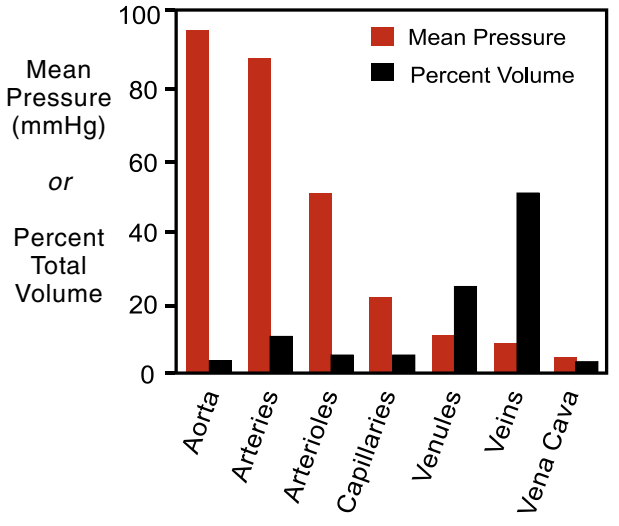

FIGURE 5-2 Distribution of pressures and volumes in the systemic circulation. The greatest pressure drop occurs across small arteries and arterioles; most of the blood volume is found within the veins and venules.

for this is that the aorta and large arteries have relatively little resistance to flow, and therefore little loss of pressure energy occurs along their lengths. It is not until the blood reaches the small arteries and arterioles (the primary resistance vessels) that there is a large fall in mean arterial blood pressure. Approximately 50% to 70% of the pressure drop within the vasculature occurs within the resistance vessels. The reason for this is that small arteries and arterioles, as a group, have the highest resistance to flow and therefore produce the greatest pressure drop along their length. By the time blood reaches the capillaries the mean blood pressure may be 25–30 mm Hg, depending on the organ. It is important that the capillary pressure is relatively low; otherwise, large amounts of fluid would leak through the capillaries (and post-capillary venules), causing tissue edema (see Chapter 8). The pressure falls further as blood travels through veins back to the heart. Pressure within the thoracic vena cava near the right atrium is very close to zero, although it fluctuates by a few millimeters of mercury (mm Hg) during the cardiac cycle and because of respiratory activity.

The greatest volume (60% to 80%) of blood within the circulation resides within the venous vasculature. This is why veins are referred to as capacitance vessels. The relative volume of blood between the arterial and venous sides of the circulation can vary considerably depending on total blood volume, intravascular pressures, and vascular compliance. The latter varies depending on the state of venous contraction, which is primarily regulated by sympathetic nerves innervating the veins.

ARTERIAL BLOOD PRESSURE

Ejection of blood into the aorta by the left ventricle results in a characteristic aortic pressure pulse (Fig. 5-3). The peak pressure of the aortic pulse is termed the **systolic pressure,** and the lowest pressure in the aorta, which is

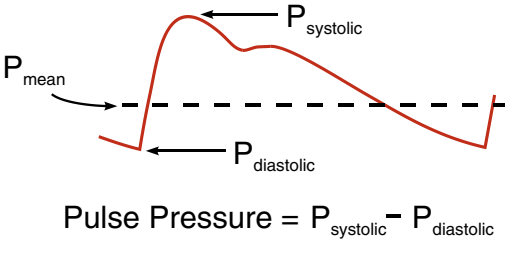

FIGURE 5-3 Pressure pulse within the aorta. The pulse pressure is the difference between the maximal pressure (systolic) and the minimal pressure (diastolic). The mean pressure is approximately equal to the diastolic pressure plus one-third the pulse pressure.

found just before the ventricle ejects blood into the aorta (see Fig. 4-2), is termed the **diastolic pressure.** The difference between the systolic and diastolic pressures is the aortic **pulse pressure.** If, for example, the systolic pressure is 130 mm Hg and the diastolic pressure is 85 mm Hg, then the pulse pressure is 45 mm Hg. Therefore, any factor that affects either systolic or diastolic pressures affects pulse pressure.

As blood flows down the aorta and into distributing arteries, characteristic changes take place in the shape of the pressure wave contour. As the pressure pulse moves away from the heart, the systolic pressure rises, and the diastolic pressure falls. Although it is not clear why the pressure pulse changes shape, it probably is related to a number of factors including (1) decreased compliance of distal arteries and (2) reflective waves, particularly from arterial branch points, which summate with the pulse wave traveling down the aorta and arteries. In addition, mean arterial pressure declines as the pressure pulse travels down distributing arteries owing to the resistance of the arteries; however, the reduction in mean pressure is small (just a few mm Hg) because the distributing arteries have a relatively low resistance. Therefore, the values measured for arterial pressure differ depending on the site of measurement. When the arterial pressure is measured using a sphygmomanometer (i.e., blood pressure cuff) on the upper arm, the pressure measurement represents the pressure within the brachial artery. The measured pressures, however, are not identical with the systolic and diastolic pressures found in the aorta or the pressures measured in other distributing arteries.

Aortic Pulse Pressure

The compliance of the aorta and the ventricular stroke volume determines pulse pressure. **Compliance** is defined by the relationship between volume and pressure, in which compliance equals the slope of that relationship, or the change in volume (ΔV) divided by the change in pressure (ΔP) at a given pressure (see Compliance from Chapter 4 on CD). The compliance of a blood vessel is determined in large part by the relative proportion of elastin fibers versus smooth muscle and collagen in the vessel wall (see Fig. 3-7). Elastin fibers offer the least resistance to stretch, whereas collagen offers the greatest resistance. A vessel such as the aorta that has a greater proportion of elastin fibers versus smooth muscle and collagen has a relatively low resistance to stretch and therefore has the greatest compliance.

The relatively high compliance of the aorta dampens the pulsatile output of the left ventricle, thereby reducing the pulse pressure. If the aorta were a rigid tube, the pulse pressure would be very high. However, as blood is ejected into the aorta, the walls of the aorta expand to accommodate the increase in blood volume contained within the aorta because the aorta is compliant. As the aorta expands, the increase in pressure is determined by change in aortic volume divided by the compliance of the aorta at that particular range of volumes. The more compliant the aorta, the smaller the pressure change (i.e., pulse pressure) at any given change in aortic volume (Fig. 5-4).

A change in compliance affects only pulse pressure and not the mean pressure, which remains unchanged as long as cardiac output and systemic vascular resistance do not change. In contrast, a change in stroke volume changes mean aortic pressure in addition to pulse pressure if the cardiac output changes. For example, if stroke volume and cardiac output are increased by an increase in inotropy, both pulse pressure and mean arterial pressure increase. If, however, cardiac output is not changed when stroke volume changes (e.g., if a decrease in heart rate accompanies the increase in stroke volume), then only the pulse pressure changes—the mean aortic pressure does not change.

No single value for aortic compliance exists because the relationship between volume and pressure is not linear. At higher volumes and pressures, the slope of the relationship decreases and compliance decreases. Therefore, at very high mean arterial pressures, the reduced compliance results in an increase in pulse pressure at a given stroke volume. Age and arteriosclerotic disease also decrease aortic compliance, which increases aortic pulse

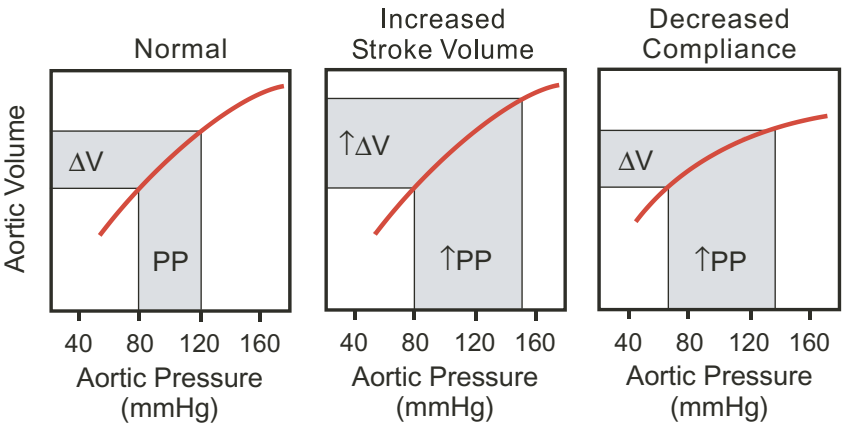

FIGURE 5-4 Effects of stroke volume and aortic compliance on aortic pulse pressure. At a given aortic compliance, increasing the stroke volume (*ΔV*) into the aorta increases the pulse pressure (*PP*). At a given stroke volume, decreasing the aortic compliance (decreased slope of ΔV/ΔP) increases the pulse pressure.

pressure (see Fig. 5-4). It is common for elderly people to have aortic pulse pressures of 60 mm Hg or more, whereas younger adults have aortic pulse pressures of about 40-45 mm Hg at resting heart rates.

In summary, aortic pulse pressure is determined by ventricular stroke volume and aortic compliance (Fig. 5-5). Any factor that changes stroke volume (e.g., ventricular preload, afterload and inotropy; heart rate) or aortic compliance (e.g., age, arteriosclerosis, hypertension) alters aortic pulse pressure. Beat-to-beat changes in pulse pressure occur owing to changes in stroke volume. In contrast, chronic, long-term increases in pulse pressure are due to decreased aortic compliance.

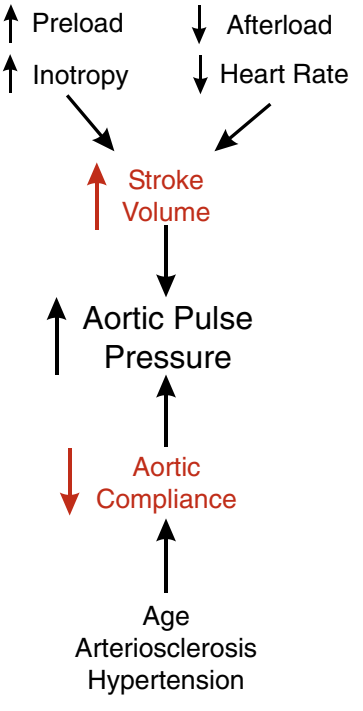

FIGURE 5-5 Factors affecting aortic pulse pressure. Pulse pressure is increased by those factors that increase stroke volume or decrease aortic compliance.

Mean Arterial Pressure

Because of the shape of the aortic pressure pulse, the value for the **mean pressure** (geometric mean) is less than the arithmetic average of the systolic and diastolic pressures as shown in Figure 5-3. At normal resting heart rates, mean aortic (or arterial) pressure (MAP) can be *estimated* from the diastolic (P_{dias}) and systolic (P_{sys}) pressures by Equation 5-1:

Eq. 5-1 $$MAP \cong P_{dias} + \tfrac{1}{3}(P_{sys} - P_{dias})$$

For example, if systolic pressure is 120 mm Hg and diastolic pressure is 80 mm Hg, the mean arterial pressure will be approximately 93 mm Hg. At high heart rates, however, mean arterial pressure is more closely approximated by the arithmetic average of systolic and diastolic pressure because the shape of

the arterial pressure pulse changes (it becomes narrower) as the period of diastole shortens more than does systole. Therefore, to determine mean arterial pressure accurately, analog electronic circuitry or digital techniques are used. In clinical practice (e.g., during routine blood pressure measurement using a sphygmomanometer), only systolic and diastolic arterial pressures are measured. Mean arterial pressure, however, is needed whenever hemodynamic information is required to assess systemic vascular function.

No single value exists for normal mean arterial pressure. In infant children, the mean arterial pressure may be only 70 mm Hg, whereas in older adults, mean arterial pressure may be 100 mm Hg. With increasing age, the systolic pressure generally rises more than diastolic pressure; therefore, the pulse pressure increases with age. Small differences exist between men and women, with women having slightly lower pressures at equivalent ages. In adults, arterial pressure is considered normal when the systolic pressure is less than 120 mm Hg (but > 90 mm Hg) and the diastolic pressure is less than 80 mm Hg (but > 60 mm Hg), which represents a normal mean pressure of less than 95 mm Hg. Abnormally low and elevated arterial pressures are discussed in Chapter 9.

What factors determine mean arterial pressure? As blood is pumped into the resistance network of the systemic circulation, pressure is generated within the arterial vasculature. The mean arterial pressure (MAP) is determined by the cardiac output (CO), systemic vascular resistance (SVR), and central venous pressure (CVP) as shown in Equation 5-2, which is based on the relationship between flow, pressure, and resistance as described in the next section.

Eq. 5-2 $MAP = (CO \bullet SVR) + CVP$

Therefore, changes in cardiac output, systemic vascular resistance or central venous pressure affect mean arterial pressure. If cardiac output and systemic vascular resistance change reciprocally and proportionately, MAP will not change. For example, if cardiac output is reduced by one-half and systemic vascular resistance is doubled, mean arterial pressure will remain unchanged.

Figure 5-6, which is based upon Equation 5-2, shows that as cardiac output is increased, a linear increase occurs in arterial pressure (assuming that resistance and venous pressure remain constant). An increase in resistance (increased slope of the line) results in a greater arterial pressure for any given cardiac output. Conversely, a decrease in resistance results in a lower arterial pressure for any given cardiac output.

Cardiac output, systemic vascular resistance, and venous pressure are constantly changing, and they are interdependent (i.e., changing one variable can change each of the other variables). For example, increasing systemic vascular resistance increases the afterload on the heart, which decreases cardiac output and central venous pressure, as described in more detail later in this chapter. Furthermore, extrinsic control mechanisms acting on the heart and circulation can affect these variables. If, for example, cardiac output suddenly falls by 20% (as can occur when standing), mean arterial pressure will not decrease by 20% because the body compensates by increasing systemic vascular resistance through baroreceptor mechanisms to maintain constant pressure (see Chapter 6).

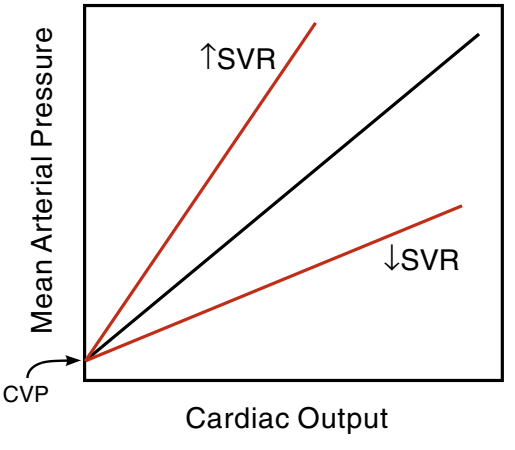

FIGURE 5-6 The relationship between cardiac output (CO), systemic vascular resistance (*SVR*), mean arterial pressure (MAP), and central venous pressure (*CVP*). Increasing SVR increases MAP at any given cardiac output, whereas decreasing SVR decreases MAP at a given cardiac output. This figure is based on Equation 5-2, in which MAP = (CO x SVR) + CVP.

Hemodynamics (Pressure, Flow, and Resistance)

The term **hemodynamics** describes the physical factors governing blood flow within the circulatory system. Blood flow through an organ is determined by the pressure gradient (ΔP) driving the flow divided by the resistance (R) to flow (Equation 5-3). The pressure gradient (or perfusion pressure) driving flow through an organ is the arterial minus the venous pressure. For an individual blood vessel, the pressure gradient is the pressure difference between two defined points along the vessel. Equation 5-3 is a hydrodynamic form of Ohm's Law, where current (I) equals the voltage difference (ΔV) divided by resistance (R).

Eq. 5-3 $$F = \frac{\Delta P}{R}$$

By rearranging Equation 5-3, we see that the driving pressure across an organ or along the length of a vessel is determined by the product of the flow and resistance (Equation 5-4).

Eq. 5-4 $$\Delta P = F \cdot R$$

Equation 5-4 serves as the basis for Equation 5-2 in which cardiac output is substituted for flow, systemic vascular resistance is substituted for resistance, and mean arterial pressure minus central venous pressure is substituted for the pressure gradient. These components are then rearranged to solve for mean arterial pressure.

Blood flow through organs (as well as through the entire systemic circulation) is determined largely by changes in resistance because arterial and venous pressures are normally maintained within a narrow range by various feedback mechanisms. Therefore, it is important to understand what determines resistance in individual vessels and within vascular networks.

Effects of Vessel Length, Radius, and Blood Viscosity on Resistance to Blood Flow

Three factors determine the resistance (R) to blood flow within a single vessel: vessel length (L), blood viscosity (η) and diameter (or radius, r) of the vessel. These are described by Equation 5-5 as follows:

Eq. 5-5 $$R \propto \frac{\eta \cdot L}{r^4}$$

Resistance is directly proportional to vessel length. Therefore, a vessel that is twice as long as another vessel with the same radius will have twice the resistance to flow. In the body, individual vessel lengths do not change appreciably; therefore, changes in vessel length have only a minimal effect on resistance.

Resistance to flow is directly related to the viscosity of the blood. For example, if viscosity increases two-fold, the resistance to flow increases two-fold. At normal body temperatures, the viscosity of plasma is about 1.8 times the viscosity of water. The viscosity of whole blood is about three to four times the viscosity of water owing to the presence of red cells and proteins. Blood viscosity normally does not change much; however, it can be significantly altered by changes in hematocrit and temperature and by low flow states. Hematocrit is the volume of red blood cells expressed as a percentage of a given volume of whole blood. If hematocrit increases from a normal value of 40% to an elevated value of 60% (this is termed polycythemia), the blood viscosity approximately doubles. Decreasing blood temperature increases viscosity by about 2% per degree Centigrade. The flow rate of blood also affects viscosity. At very low flow states in the microcirculation—as occurs during circulatory shock—the blood viscosity can increase several-fold. This occurs because at low flow states, cell-to-cell and protein-to-cell adhesive interactions increase, which can cause erythrocytes to adhere to one another and increase the blood viscosity.

Vessel radius is the most important factor determining resistance to flow. Because radius and resistance are inversely related, an increase in radius reduces resistance. Furthermore, *a change in radius alters resistance inversely to the fourth power of the radius.* For example, a two-fold increase in radius decreases resistance sixteen-fold! Therefore, vessel resistance is exquisitely sensitive to changes in radius. Because changes in radius

PROBLEM 5-1

An isolated, cannulated arteriole is perfused with an oxygenated physiologic salt solution at a constant flow, and the pressure gradient across the two ends of the arteriole is initially 2 mm Hg. If the application of a drug constricts the vessel diameter by 50%, what will be the new pressure gradient across the arteriole?

Under constant flow conditions, $\Delta P \propto \Delta R$ (from Equation 5-4). Furthermore, $R \propto 1/r^4$ (from Equation 5-5). Therefore, $\Delta P \propto 1/r^4$. Using this relationship, we find that decreasing diameter (or radius, which is proportional to diameter) by 50% (to 1/2 its original radius) increases ΔP by a factor of 16 (reciprocal of 1/2 to the fourth power). Therefore, the new pressure gradient along the length of vessel will be 32 mm Hg (2 mm Hg x 16).

and diameter are directly proportional, diameter can be substituted for radius in Equation 5-5.

If the expression for resistance (Equation 5-5) is combined with the equation describing the relationship between flow, pressure, and resistance ($F=\Delta P/R$; Equation 5-3), the following relationship is obtained:

Eq. 5-6
$$F \propto = \frac{\Delta P \cdot r^4}{\eta \cdot L}$$

This relationship (**Poiseuille's equation**) was first described by the French physician Poiseuille (1846). The full equation contains π in the numerator, and the number 8 in the denominator (a constant of integration). Equation 5-6 describes how flow is related to perfusion pressure, radius, length, and viscosity. In the body, however, flow does not conform precisely to this relationship because the equation assumes the following: (1) the vessels are long, straight, rigid tubes; (2) the blood behaves as a Newtonian fluid in which viscosity is constant and independent of flow; and (3) the blood is flowing under steady laminar flow conditions. Despite these assumptions, which clearly are not achieved in vivo, the relationship is important because it describes the dominant influence of vessel radius on resistance and flow, and therefore provides a conceptual framework to understand how physiologic and pathologic changes in blood vessels and blood viscosity affect pressure and flow.

The relationship between flow and radius (Equation 5-6) for a single vessel is shown graphically in Figure 5-7. In this analysis, laminar flow conditions are assumed, and driving pressure, viscosity, and vessel length are held constant. As vessel radius decreases from a relative value of 1.0, a dramatic fall in flow occurs because flow is directly related to radius to the fourth power. For example, when radius is one-half normal (0.5 relative radius), flow is decreased sixteen-fold. Therefore, the new flow is only about 6% of the original flow. This figure dramatically illustrates how very small changes in vessel radius can have profound effects on flow (and on perfusion pressure if this were the dependent variable and flow were held constant).

Series and Parallel Arrangement of the Vasculature

It is crucial that Poiseuille's equation should be applied only to single vessels. If, for example, a single arteriole within the kidney were constricted by 50%, although the resistance of that single vessel would increase sixteen-fold, the vascular resistance for the *entire* renal circulation would not increase sixteen-fold. The change in overall renal resistance would be immeasurable. This is because the single arteriole is one of many resistance vessels within a complex network of vessels, and therefore it constitutes only a small fraction of the resistance for the whole organ. To help understand this complex arrangement of vessel architecture, it is necessary to examine the vascular components in terms of series and parallel elements.

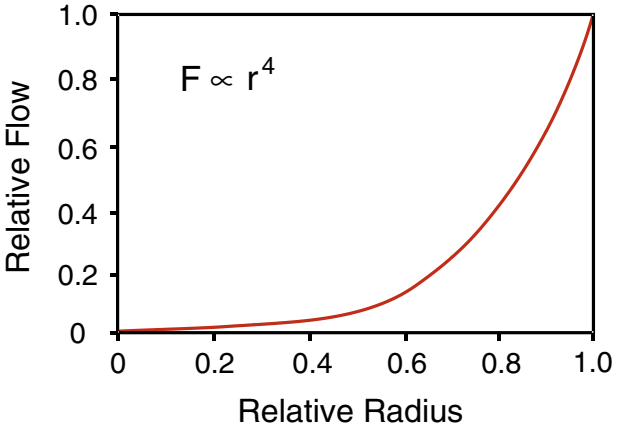

FIGURE 5-7 The effects of changes of vessel radius on flow through a single vessel. This quantitative relationship is derived from Poiseuille's equation (Equation 5-6). Decreasing vessel radius (*r*) dramatically increases resistance and decreases flow (*F*) at constant perfusion pressure because flow is proportional to radius to the fourth power.

The parallel arrangement of organs and their circulations (see Fig. 1-2) is important because *parallel vessels decrease total vascular resistance.* When there is a parallel arrangement of resistances, the reciprocal of the total resistance is equal to the sum of the reciprocals of the individual resistances. For example, the total resistance (R_T) of three parallel resistances (R_1, R_2, R_3) would be:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$$

or, solving for R_T,

Eq. 5-7
$$R_T = \frac{1}{\frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}}$$

Two important principles emerge from Equation 5-7. First, *the total resistance of a network of parallel resistances is less than the resistance of the single lowest resistance;* therefore, parallel vessels greatly reduce resistance. For example, assume that $R_1 = 5$, $R_2 = 10$, and $R_3 = 20$. When the equation is solved, $R_T = 2.86$, a value that is less than the lowest individual resistance. The resistance calculation for parallel networks explains why capillaries constitute a relatively small fraction of the total vascular resistance of an organ or microvascular network. Although capillaries have the highest resistance of individual vessels because of their small diameter, they also form a large network of parallel vessels. This reduces their resistance as a group of vessels. The second principle is that *when many parallel vessels exist, changing the resistance of a small number of these vessels will have little effect on total resistance.*

Within an organ, the vascular arrangement is a combination of series and parallel elements. In Figure 5-8, the artery, arterioles, capillaries, venules, and vein are in series with each other. All of the blood that flows through the artery likewise flows through each of the other vascular segments. Within each of the series segments, many parallel components may exist (e.g., several parallel capillaries may arise from a single arteriole). Each vascular segment will have a resistance value that is determined by vessel length, radius, and number of parallel vessels.

For an in-series resistance network, the total resistance (R_T) equals the sum of the individual segmental resistances. The total resistance for the model depicted in Figure 5-8 is:

Eq. 5-8
$$R_T = R_A + R_a + R_c + R_v + R_V$$
(A = artery; a = arterioles;
c = capillary; v = venules; V = vein)

The resistance of each segment relative to the total resistance of all the segments determines how changing the resistance of one seg-

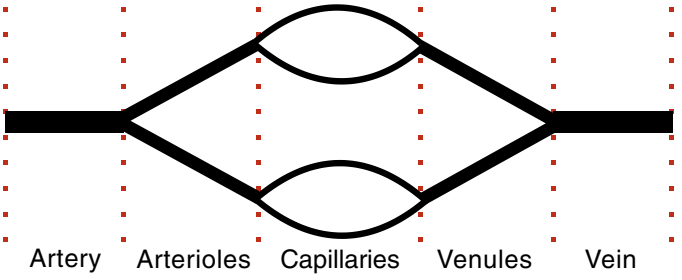

FIGURE 5-8 Model of the circulation within an organ showing the series arrangement of multiple segments of parallel vessels.

ment affects total resistance. To illustrate this principle, assign a relative resistance value to each of the five resistance segments in this model. The relative resistances are similar to what is observed in a typical vascular bed.

Assume $R_A = 1$, $R_a = 70$, $R_c = 20$, $R_v = 8$, $R_V = 1$;
Therefore, $R_T = 1 + 70 + 20 + 8 + 1 = 100$

If R_A were to increase four-fold (to a value of 4), R_T would increase to 104, a 4% increase. In contrast, if R_a were to increase four-fold (to a value of 280), the R_T would increase to 310, a 210% increase. In this model, R_A represents a large artery distributing blood flow to an organ, and R_a represents the small arteries and arterioles, which are the primary site of vascular resistance. Therefore, this empirical example demonstrates that *changes in large artery resistance have little effect on total resistance,* whereas *changes in small artery and arteriolar resistances greatly affect total resistance.* This is why small arteries and arterioles are the principal vessels regulating organ blood flow and systemic vascular resistance.

The above analysis explains why the radius of a large, distributing artery must be decreased by more than 60% or 70% to have a significant effect on organ blood flow. This is referred to as a "critical" stenosis (see Critical Stenosis on CD). The concept of a critical stenosis can be confusing because Poiseuille's equation indicates that resistance to flow is inversely related to radius to the fourth power.

PROBLEM 5-2

A parent arteriole branches into two smaller arterioles. In relative terms, the resistance of the parent arteriole is 1, and the resistance of each daughter vessel is 4. What is the combined resistance of the parent vessel and its branches?

In this problem, the two smaller daughter arterioles (R_D) are parallel with each other and in series with the parent arteriole (R_P). Therefore, the total resistance (R_T) can be found by the following equation:

$$R_T = R_P + \frac{1}{\frac{1}{R_D} + \frac{1}{R_D}}$$

Substituting the relative resistances given in this problem, we obtain:

$$R_T = 1 + \frac{1}{\frac{1}{4} + \frac{1}{4}} = 3$$

Therefore, a 50% reduction in radius should increase resistance sixteen-fold (a 1,500% increase). Indeed, within that single vessel segment, resistance will increase sixteen-fold; however, total resistance will increase only by about 15% if the large artery resistance is normally 1% of the total resistance.

REGULATION OF SYSTEMIC VASCULAR RESISTANCE

Systemic vascular resistance, which is sometimes called total peripheral resistance (TPR), is the resistance to blood flow offered by all of the systemic vasculature, excluding the pulmonary vasculature. Mechanisms that cause generalized vasoconstriction will increase systemic vascular resistance, and mechanisms that cause vasodilation will decrease systemic vascular resistance. The increase in systemic vascular resistance in response to sympathetic stimulation, for example, depends on the degree of sympathetic activation, the responsiveness of the vasculature, the number of vascular beds involved, and the relative series and parallel arrangement of these vascular beds to each other. Systemic vascular resistance primarily is determined by changes in vascular diameters, although changes in blood viscosity also affect systemic vascular resistance.

Calculation of Systemic Vascular Resistance

Systemic vascular resistance (SVR) can be calculated if cardiac output (CO), mean arterial pressure (MAP), and central venous pressure (CVP) are known. This calculation is done by rearranging Equation 5-2 as follows:

Eq. 5-9
$$SVR = \frac{(MAP - CVP)}{CO}$$

Although systemic vascular resistance can be calculated from mean arterial pressure and cardiac output, its value is not determined by either of these variables (although its value changes depending upon the pressure – see below). Systemic vascular resistance is determined by vascular diameters, length, anatomical arrangement of vessels, and blood viscosity. Because vessels are compliant, increasing intravascular pressure expands the vessels, thereby causing a small reduction in resistance. Nonetheless, the decrease in systemic vascular resistance that occurs when pressure

CASE 5-1

A patient was found to have S-T segment depression in his electrocardiogram during an exercise stress test, suggesting the presence of coronary artery disease. A follow-up coronary angiogram revealed that the diameter of the left main coronary artery (see Chapter 7, Figure 7-6) was reduced by 50%. If this vessel normally contributes to 1% of the total coronary vascular resistance under resting flow conditions, how much will this reduction in diameter increase total coronary vascular resistance? Express your answer as a percentage increase.

The total coronary resistance (R_T) equals the sum of the series resistance elements. Therefore, the left main coronary artery resistance (R_L) would be in series with the remainder of the resistance elements (R_X), so that $R_T = R_L + R_X$. Normally, $R_L = 0.01(R_T)$ and $R_X = 0.99(R_T)$ because R_L is 1% of R_T, and therefore $R_T = 0.01(R_T) + 0.99(R_T) = 1(R_T)$. Decreasing the vessel diameter by 50% increases R_L by a factor of 16 because $R \propto 1/r^4$. Therefore, the resistance of the stenotic vessel will be 16 times its normal resistance, so that $R_L = 16(0.01)R_T$, or $R_L = 0.16(R_T)$. We can now say that $R_T = 0.16(R_T) + 0.99(R_T)$. Therefore, $R_T = 1.15(R_T)$, which means that total coronary resistance increases by only 15% [(1.15/1) x 100] when the resistance of the left main coronary artery increases 1,500% (16-fold increase).

increases is not owing to the pressure directly but rather is caused by passive increases in vessel diameter. Mathematically, systemic vascular resistance is the dependent (calculated) variable in Equation 5-9; however, physiologically, systemic vascular resistance and cardiac output are the independent variables normally, and mean arterial pressure is the dependent variable; that is, mean arterial pressure changes in response to changes in cardiac output and systemic vascular resistance.

When calculating systemic vascular resistance, it is customary to use the units of mm Hg/mL • min^{-1} (peripheral resistance units, PRU) or the units of dynes • sec/cm^5 (in which pressure is expressed in dynes/cm^2 instead of mm Hg; 1 mm Hg = 1,330 dynes/cm^2) and flow is expressed in cm^3/sec). When calculating resistance in PRU, pressure has the units of mm Hg and cardiac output is expressed in mL/min.

Vascular Tone

Under normal physiologic conditions, changes in the diameter of precapillary resistance vessels (small arteries and arterioles) represent the most important mechanism for regulating systemic vascular resistance. Resistance vessels are normally in a partially constricted state that is referred to as the **vascular tone** of the vessel. This tone is generated by smooth muscle contraction within the wall of the blood vessel. From this partially constricted state, a vessel can constrict further and thereby increase resistance, or it can dilate by smooth muscle relaxation and thereby decrease resistance. Venous vessels likewise possess a level of vascular tone.

Extrinsic and intrinsic mechanisms determine the degree of smooth muscle activation (Fig. 5-9). Extrinsic mechanisms, such as sympathetic nerves and circulating hormones, originate outside of the organ or tissue. Intrinsic mechanisms originate from within the blood vessel or the tissue surrounding the vessel. Examples of intrinsic mechanisms include endothelial-derived factors, smooth muscle myogenic tone, locally produced hormones, and tissue metabolites. Some of these extrinsic and intrinsic factors promote vasoconstriction (e.g., sympathetic nerves and angiotensin II, endothelin-1), whereas others

PROBLEM 5-3

Infusion of a drug is found to increase cardiac output by 30% and decrease mean arterial pressure by 10%. By what percentage does this drug change systemic vascular resistance? Is this drug a vasodilator or vasoconstrictor? Assume that central venous pressure is 0 mm Hg and does not change.

From Equation 5-9, we know that

$$SVR = \frac{(MAP - CVP)}{CO}$$

Because central venous pressure (CVP) is zero, this equation simplifies to:

$$SVR = \frac{MAP}{CO}$$

In this problem, CO is increased by 30% and MAP is decreased by 10%:

$$SVR = \frac{0.9\ MAP}{1.3\ CO} = 0.69$$

Therefore, SVR is decreased by 31% (0.69 SVR is the equivalent of a 31% decrease), and the drug is a vasodilator. Note: In solving this problem, MAP and CO cannot be multiplied by their percentage change.

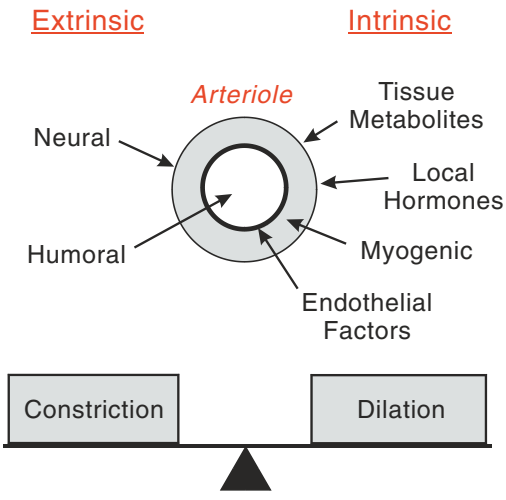

FIGURE 5-9 Vascular tone. The state of vessel tone is determined by the balance between constrictor and dilator influences.

promote smooth muscle relaxation and vascular dilation (e.g., endothelial-derived nitric oxide and tissue metabolites such as adenosine and hydrogen ion). Therefore, at any given time, vasoconstrictor and vasodilator influences are competing to determine the vascular tone. The extrinsic and intrinsic mechanisms regulating vascular tone are described in more detail in Chapters 2, 6, and 7.

In general, the vasoconstrictor mechanisms are important for maintaining systemic vascular resistance and arterial pressure, whereas vasodilator mechanisms regulate blood flow within organs. For example, if the body needs to maintain arterial blood pressure when a person stands up, vasoconstrictor mechanisms (primarily sympathetic adrenergic) are activated to constrict resistance vessels and increase systemic vascular resistance. If an organ requires more blood flow and oxygen delivery (e.g., exercising muscle), vasodilator mechanisms will predominate and override vasoconstrictor influences. Therefore, the competition between vasoconstrictor and vasodilator influences can be thought of as competition between maintenance of arterial blood pressure and organ perfusion.

VENOUS BLOOD PRESSURE

Venous pressure is a general term that represents the average blood pressure within the venous compartment. A more specific term, **central venous pressure,** describes the blood pressure in the thoracic vena cava near the right atrium. This pressure is important because it determines the filling pressure of the right ventricle, and thereby determines ventricular stroke volume through the Frank-Starling mechanism as discussed in Chapter 4.

Venous Blood Volume and Compliance

Several factors influence central venous pressure: cardiac output, respiratory activity, contraction of skeletal muscles (particularly leg and abdominal muscles), sympathetic vasoconstrictor tone, and gravitational forces. All of these factors ultimately change central venous pressure (ΔP_V) by changing either venous blood volume (ΔV_V) or venous compliance (C_V) as described by Equation 5-10.

Eq. 5-10
$$\Delta P_V \propto \frac{\Delta V_V}{C_V}$$

Equation 5-10 is a rearrangement of the equation used to define compliance, in which compliance (in this case venous compliance) equals a change in venous volume divided by the change in venous pressure that occurs with the change in volume (see Compliance in Chapter 4 on the CD). Therefore, an increase in venous volume increases venous pressure by an amount determined by the compliance of the veins. Furthermore, a decrease in venous compliance, as occurs during sympathetic activation of veins, increases venous pressure.

The relationship described by Equation 5-10 can be depicted graphically as shown in Figure 5-10, in which venous blood volume is plotted against venous blood pressure. The different curves represent different states of venous tone, and the slope of a tangent line at any point on the curve represents the compliance. Looking at a single curve, it is evident

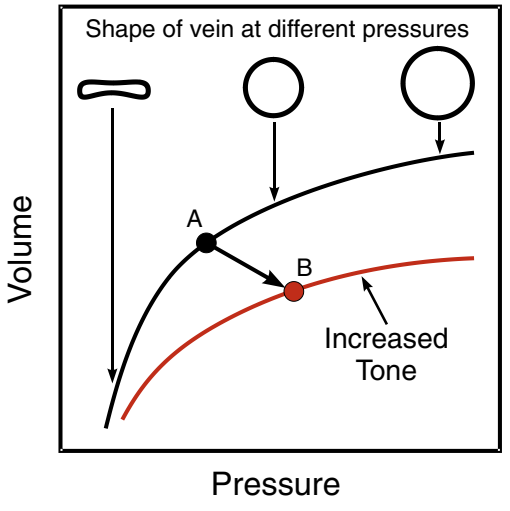

FIGURE 5-10 Compliance curves for a vein. Venous compliance (the slope of line tangent to a point on the curve) is very high at low pressures because veins collapse. As pressure increases, the vein assumes a more circular cross-section and its walls become stretched; this reduces compliance (decreases slope). Point *A* is the control pressure and volume. Point *B* is the pressure and volume resulting from increased tone (decreased compliance) brought about, for example, by sympathetic stimulation of the vein.

that an increase in venous volume will increase venous pressure. The amount by which the pressure increases for a given change in volume depends on the slope of the relationship between the volume and pressure (i.e., the compliance). As with arterial vessels (see Fig. 5-4), the relationship between venous volume and pressure is not linear (see Fig. 5-10). The slope of the compliance curve ($\Delta V/\Delta P$) is greater at low pressures and volumes than at higher pressures and volumes. The reason for this is that at very low pressures, a large vein collapses. As the pressure increases, the collapsed vein assumes a more cylindrical shape with a circular cross-section. Until a cylindrical shape is attained, the walls of the vein are not stretched appreciably. Therefore, small changes in pressure can result in a large change in volume by changes in vessel geometry rather than by stretching the vessel wall. At higher pressures, when the vein is cylindrical in shape, increased pressure can increase the volume only by stretching the vessel wall, which is resisted by the structure and composition of the wall (particularly by collagen, smooth muscle, and elastin components). Therefore, at higher volumes and pressures, the change in volume for a given change in pressure (i.e., compliance) is less.

The smooth muscle within veins is ordinarily under some degree of tonic contraction. Like arteries and arterioles, a major factor determining venous smooth muscle contraction is sympathetic adrenergic stimulation, which occurs under basal conditions. Changes in sympathetic activity can increase or decrease the contraction of venous smooth muscle, thereby altering venous tone. When this occurs, a change in the volume-pressure relationship (or compliance curve) occurs, as depicted in Figure 5-10. For example, increased sympathetic activation will shift the compliance curve down and to the right, decreasing its slope (compliance) at any given volume (from point *A* to *B* in Fig. 5-10). This rightward diagonal shift in the venous compliance curve results in a decrease in venous volume and an increase in venous pressure. Drugs that reduce venous tone (e.g., nitrodilators) will decrease venous pressure while increasing venous volume by shifting the compliance curve to the left.

The previous discussion emphasized that venous pressure can be altered by changes in venous blood volume or in venous compliance. These changes can be brought about by the factors or conditions summarized in Table 5-2. Central venous pressure is increased by:

1. A decrease in cardiac output. This can result from decreased heart rate (e.g., bradycardia associated with atrioventricular [AV] nodal block) or stroke volume (e.g., in ventricular failure), which results in blood backing up into the venous circulation (increased venous volume) as less blood is pumped into the arterial circulation. The resultant increase in thoracic blood volume increases central venous pressure.
2. An increase in total blood volume. This occurs in renal failure or with activation of the renin-angiotensin-aldosterone system

TABLE 5-2 FACTORS INCREASING CENTRAL VENOUS PRESSURE (CVP), EITHER BY DECREASING VENOUS COMPLIANCE OR BY INCREASING VENOUS BLOOD VOLUME

	CVP INCREASED BY CHANGE IN:
Decreased cardiac output	Volume
Increased blood volume	Volume
Venous constriction	Compliance
Changing from standing to supine body posture	Volume
Arterial dilation	Volume
Forced expiration (e.g., Valsalva)	Compliance
Muscle contraction (abdominal and limb)	Volume & Compliance

(see Chapter 6) and leads to an increase in venous pressure.

3. Venous constriction (reduced venous compliance). Whether elicited by sympathetic activation or by circulating vasoconstrictor substances (e.g., catecholamines, angiotensin II), venous constriction reduces venous compliance, thereby increasing central venous pressure.
4. A shift in blood volume into the thoracic venous compartment. This shift occurs when a person changes from standing to a supine or sitting position and results from the effects of gravity.
5. Arterial dilation. This occurs during withdrawal of sympathetic tone or when arterial vasodilator drugs increase blood flow from the arterial into the venous compartments, thereby increasing venous volume and central venous pressure.
6. A forceful expiration, particularly against a high resistance (as occurs with a Valsalva maneuver). This expiration causes external compression of the thoracic vena cava as intrapleural pressure rises.
7. Muscle contraction. Rhythmic muscular contraction, particularly of the limbs and abdomen, compresses the veins (which decreases their functional compliance) and forces blood into the thoracic compartment.

Mechanical Factors Affecting Central Venous Pressure and Venous Return

Several of the factors affecting central venous pressure can be classified as mechanical (or physical) factors. These include gravitational effects, respiratory activity, and skeletal muscle contraction. Gravity passively alters central venous pressure and volume, and respiratory activity and muscle contraction actively promote or impede the return of blood into the central venous compartment, thereby altering central venous pressure and volume.

Gravity

Gravity exerts significant effects on venous return. When a person changes from supine to a standing posture, gravity acts on the vascular volume, causing blood to accumulate in the lower extremities. Because venous compliance is much higher than arterial compliance, most of the blood volume accumulates in veins, leading to venous distension and an elevation in venous pressure in the dependent limbs. The shift in blood volume causes central venous volume and pressure to fall. This reduces right ventricular filling pressure (preload) and stroke volume by the Frank-Starling mechanism. Left ventricular stroke volume subsequently falls because of reduced pul-

monary venous return to the left ventricle; the reduced stroke volume causes cardiac output and arterial blood pressure to decrease. If systemic arterial pressure falls by more than 20 mm Hg upon standing, this is termed **orthostatic** or **postural hypotension.** When this occurs, cerebral perfusion may fall and a person may become "light headed" and experience a transient loss of consciousness (syncope). Normally, baroreceptor reflexes (see Chapter 6) are activated to restore arterial pressure by causing peripheral vasoconstriction and cardiac stimulation (increased heart rate and inotropy).

The effects of changes in posture on hydrostatic pressures are illustrated Figure 5-11. In this model, mean aortic pressure (MAP) and central venous pressure (CVP) are shown as reservoirs. The vertical height between these two reservoirs represents the systemic perfusion pressure. Cardiac output constantly refills the aortic reservoir as it empties into the systemic circulation. In a horizontal configuration (Figure 11, Diagram A), mean capillary hydrostatic pressure (P_C) is some value between MAP and CVP, typically about 25 mm Hg. If the horizontal tube (i.e., the vasculature) is orientated vertically (Diagram B), P_C increases because of hydrostatic forces. If the vasculature is rigid (Diagram B), there is no volume shift between the arterial and venous reservoirs, and MAP and CVP remain unchanged (as does cardiac output). However, if the vasculature is highly compliant (as it actually is), the increased hydrostatic forces increase **transmural pressure** (intravascular minus extravascular pressure; i.e., the distending pressure) across the vessel walls and expand the vessels, particularly the highly compliant veins (Diagram C). The blood for this venous expan-

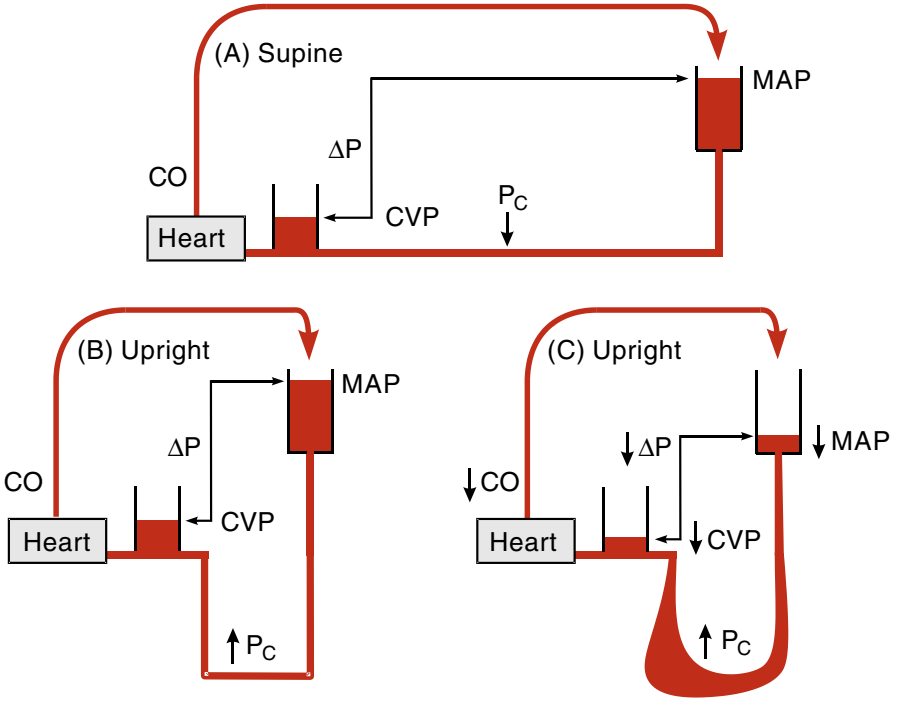

FIGURE 5-11 Effects of gravity on central venous pressure (*CVP*), cardiac output (*CO*), and mean arterial pressure (*MAP*). Diagram *A,* supine position. Diagram *B:* an upright position with rigid vessel results in elevated capillary pressure (P_C) owing to hydrostatic forces, but no change in CVP, CO, MAP, or systemic perfusion pressure (ΔP). Diagram *C:* upright position with compliant vessels; elevated P_C from hydrostatic pressure owing to gravity distends blood vessels (particularly veins) and increases vascular volume (especially in lower limbs), leading to a fall in CVP, MAP, ΔP, and CO.

sion comes from the venous and arterial reservoirs, thereby decreasing CVP and MAP. The decrease in CVP decreases cardiac preload and decrease cardiac output by the Frank-Starling mechanism. The decreased cardiac output results in a fall in MAP (decreased reservoir height). The net effect is reductions in both MAP and CVP, although quantitatively, the fall in MAP is 10 to 20 times greater than the fall in CVP for reasons explained later in this chapter.

Upright posture not only shifts venous blood volume from the thoracic compartment to the dependent limbs, but it also results in a large elevation in capillary pressure in the dependent limbs. When a person is lying down, there is no appreciable hydrostatic pressure difference between the level of the heart and feet. The mean aortic pressure may be 95 mm Hg, the mean capillary pressure in the feet may be about 20 mm Hg, and the central venous pressure near the right atrium may be near 0 mm Hg. When the person stands upright, if no baroreceptor or myogenic reflexes operate, the mean aortic and central venous pressures will fall quite significantly. A hydrostatic column equal to the vertical distance from the heart to the feet will increase capillary pressure in the feet. If the distance from the heart to the feet is 120 cm, the hydrostatic pressure exerted on the capillaries in the feet will be 120 cmH_20, which is the equivalent of 88 mm Hg (mercury is 13.6 times denser than water). Theoretically, this hydrostatic pressure added to the normal capillary pressure will increase the capillary pressure in the feet to 108 mm Hg! Without the activation of important compensatory mechanisms, this would rapidly lead to significant edema in the feet and dependent limbs (see Chapter 8) and loss of intravascular blood volume.

The changes depicted in Figure 5-11, Diagram C, are rapidly compensated in a normal individual by myogenic vasoconstrictor mechanisms, sympathetic-mediated vasoconstriction, venous valve functioning, muscle pump activity, and the abdominothoracic pump. When these mechanisms are operating, capillary and venous pressures in the feet will be elevated by only 10–20 mm Hg, mean aortic pressure will be maintained, and central venous pressure will be only slightly reduced. Because of these compensatory mechanisms, a person who is standing has a higher systemic vascular resistance (primarily owing to sympathetic activation of resistance vessels), decreased venous compliance (owing to sympathetic activation of veins), decreased stroke volume and cardiac output (owing to decreased ventricular preload), and increased heart rate (baroreceptor-mediated tachycardia). The net effect of these changes is maintenance of normal mean aortic pressure.

Respiratory Activity (Abdominothoracic or Respiratory Pump)

Venous return to the right atrium from the abdominal vena cava is determined by the pressure difference between the abdominal vena cava and the right atrial pressure, as well as by the resistance to flow, which is primarily determined by the diameter of the thoracic vena cava. Therefore, increasing right atrial pressure impedes venous return, whereas lowering right atrial pressure facilitates venous return. These changes in venous return significantly influence stroke volume through the Frank-Starling mechanism.

Pressures in the right atrium and thoracic vena cava depend on intrapleural pressure. This pressure is measured in the space between the thoracic wall and the lungs and is generally negative (subatmospheric). During inspiration, the chest wall expands and the diaphragm descends (red arrows on chest wall and diaphragm in Figure 5-12). This causes the intrapleural pressure (P_{pl}) to become more negative, causing expansion of the lungs, atrial and ventricular chambers, and vena cava (smaller red arrows). This expansion decreases the pressures within the vessels and cardiac chambers. As right atrial pressure falls during inspiration, the pressure gradient for venous return to the heart is increased. During expiration the opposite occurs, although the net effect of respiration is that the increased rate and depth of ventilation facilitates venous return and ventricular stroke volume.

Although it may appear paradoxical, the fall in right atrial pressure during inspiration is associated with an *increase* in right atrial and

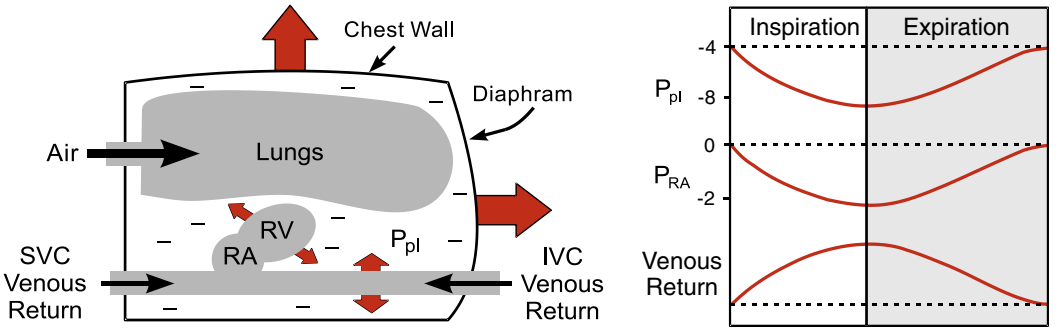

FIGURE 5-12 Effects of respiration on venous return. Left panel: During inspiration, intrapleural pressure (P_{pl}) decreases as the chest wall expands and the diaphragm descends (large red arrows). This increases the transmural pressure across the superior and inferior vena cava (*SVC* and *IVC*), right atrium (*RA*), and right ventricle (*RV*), which causes them to expand. This facilitates venous return and leads to an increase in atrial and ventricular preloads. Right panel: During inspiration, P_{pl} and right atrial pressure (P_{RA}) become more negative, which increases venous return. During expiration, P_{pl} and P_{RA} become less negative and venous return falls. Numeric values for P_{pl} and P_{RA} are expressed as mm Hg.

ventricular preloads and right ventricular stroke volume. This occurs because the fall in intrapleural pressure causes the transmural pressure to increase across the chamber walls, thereby increasing the chamber volume, which increases sarcomere length and myocyte preload. For example, if intrapleural pressure is normally –4 mm Hg at end-expiration and right atrial pressure is 0 mm Hg, the transmural pressure (the pressure that distends the atrial chamber) is 4 mm Hg. During inspiration, if intrapleural pressure decreases to –8 mm Hg and atrial pressure decreases to –2 mm Hg, the transmural pressure across the atrial chamber increases from 4 mm Hg to 6 mm Hg, thereby expanding the chamber. At the same time, because blood pressure within the atrium is diminished, this leads to an increase in venous return to the right atrium from the abdominal vena cava. Similar increases in right ventricular transmural pressure and preload occur during inspiration. The increase in sarcomere length during inspiration augments right ventricular stroke volume by the Frank-Starling mechanism. In addition, changes in intrapleural pressure during inspiration influence the left atrium and ventricle; however, the expanding lungs and pulmonary vasculature act as a capacitance reservoir (pulmonary blood volume increases) so that the left ventricular filling is not enhanced during inspiration. During expiration, however, blood is forced from the pulmonary vasculature into the left atrium and ventricle, thereby increasing left ventricular filling and stroke volume. Expiration, in contrast, decreases right atrial and ventricular filling. *The net effect of respiration is that increasing the rate and depth of respiration increases venous return and cardiac output.*

If a person exhales forcefully against a closed glottis (**Valsalva maneuver**), the large increase in intrapleural pressure impedes venous return to the right atrium (see Valsalva Maneuver on CD). This occurs because the large increase in intrapleural pressure can collapse the thoracic vena cava, which dramatically increases resistance to venous return. Because of the accompanying decrease in transmural pressure across the ventricular chamber walls, ventricular volume decreases despite the large increase in the pressure within the chamber. Decreased chamber volume (i.e., decreased preload) leads to a fall in ventricular stroke volume by the Frank-Starling mechanism. Similar changes can occur when a person strains while having a bowel movement, or when a person lifts a heavy weight while holding their breath.

Skeletal Muscle Pump

Veins, particularly in extremities, contain one-way valves that permit blood flow toward the heart and prevent retrograde flow. Deep veins

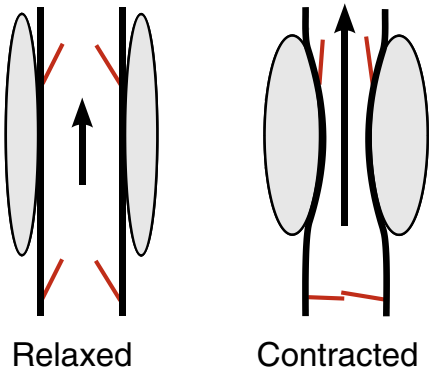

FIGURE 5-13 Rhythmic contraction of skeletal muscle compresses veins, particularly in the lower limbs, and propels blood toward the heart through a system of one-way valves.

in the lower limbs are surrounded by large groups of muscle that compress the veins when the muscles contract. This compression increases the pressure within the veins, which closes upstream valves and opens downstream valves, thereby functioning as a pumping mechanism (Fig. 5-13). This pumping mechanism plays a significant role in facilitating venous return during exercise. The muscle pump also helps to counteract gravitational forces when a person stands up by facilitating venous return and lowering venous and capillary pressures in the feet and lower limbs. When the venous valves become incompetent, as occurs when veins become enlarged (varicose veins), muscle pumping becomes ineffective. Besides the loss of muscle pumping in aiding venous return, blood volume and pressure increase in the veins of the dependent limbs, which increases capillary pressure and may cause edema (see Chapter 8).

VENOUS RETURN AND CARDIAC OUTPUT

The Balance between Venous Return and Cardiac Output

Venous return is the flow of blood back to the heart. Previous sections described how the venous return to the right atrium from the abdominal vena cava is determined by the pressure gradient between the abdominal vena cava and the right atrium, divided by the resistance of the vena cava. However, that analysis looks at only a short segment of the venous system and does not show what factors determine venous return from the capillaries. Venous return is determined by the difference between the mean capillary and right atrial pressures divided by the resistance of all the post-capillary vessels. If we consider venous return as being all the systemic flow returning to the heart, venous return is determined by the difference between the mean aortic and right atrial pressures divided by the systemic vascular resistance. Under steady-state conditions, this venous return equals cardiac output when averaged over time because the cardiovascular system is essentially a closed system. (The cardiovascular system, strictly speaking, is not a closed system because fluid is lost through the kidneys and by evaporation through the skin, and fluid enters the circulation through the gastrointestinal tract. Nevertheless, a balance is maintained between fluid entering and leaving the circulation during steady-state conditions. Therefore, think of cardiac output and venous return as being equal.)

Systemic Vascular Function Curves

Blood flow through the entire systemic circulation, whether viewed as the flow leaving the heart (cardiac output) or returning to the heart (venous return), depends on both cardiac and systemic vascular function. As described in more detail below, cardiac output under normal physiologic conditions depends on systemic vascular function. Cardiac output is limited to a large extent by the prevailing state of systemic vascular function. Therefore, it is important to understand how changes in systemic vascular function affect cardiac output and venous return (or total systemic blood flow because cardiac output and venous return are equal under steady-state conditions).

The best way to show how systemic vascular function affects systemic blood flow is by use of systemic vascular and cardiac function curves. Credit for the conceptual understanding of the relationship between cardiac output

and systemic vascular function goes to Arthur Guyton and colleagues, who conducted extensive experiments in the 1950s and 1960s. To develop the concept of systemic vascular function curves, we must understand the relationship between cardiac output, mean aortic, and right atrial pressures. Figure 5-14 shows that at a cardiac output of 5 L/min, the right atrial pressure is near zero and mean aortic pressure is about 95 mm Hg. If cardiac output is reduced experimentally, right atrial pressure increases and mean aortic pressure decreases. The fall in aortic pressure reflects the relationship between mean aortic pressure, cardiac output, and systemic vascular resistance (see Equation 5-2). As cardiac output is reduced to zero, right atrial pressure continues to rise and mean aortic pressure continues to fall, until both pressures are equivalent, which occurs when systemic blood flow ceases. The pressure at zero systemic flow, which is called the **mean circulatory filling pressure,** is about 7 mm Hg. This value is found experimentally when baroreceptor reflexes are blocked; otherwise the value for mean circulatory filling pressure is higher because of vascular smooth muscle contraction and decreased vascular compliance owing to sympathetic activation.

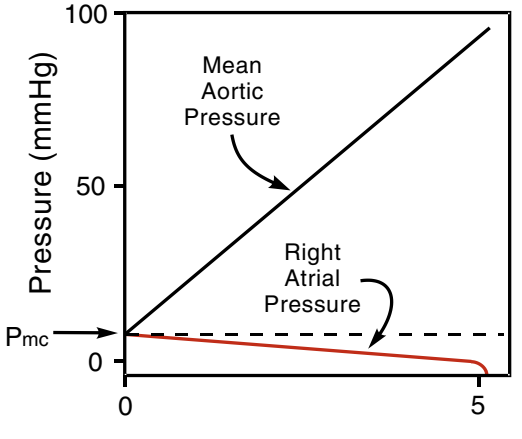

FIGURE 5-14 Effects of cardiac output on mean aortic and right atrial pressures. Decreasing cardiac output to zero results in a rise in right atrial pressure and a fall in aortic pressure. Both pressures equilibrate at the mean circulatory filling pressure (*Pmc*).

The reason right atrial pressure increases in response to a decrease in cardiac output is that less blood per unit time is translocated by the heart from the venous to the arterial vascular compartment. This leads to a reduction in arterial blood volume and an increase in venous blood volume, which increases right atrial pressure. When the heart is completely stopped and there is no flow in the systemic circulation, the intravascular pressure found throughout the entire vasculature is a function of total blood volume and vascular compliance.

The magnitude of the relative changes in aortic and right atrial pressures from a normal cardiac output to zero cardiac output is determined by the ratio of venous to arterial compliances. If venous compliance (C_V) equals the change in venous volume (ΔV_V) divided by the change in venous pressure (ΔP_V), and arterial compliance (C_A) equals the change in arterial volume (ΔV_A) divided by the change in arterial pressure (ΔP_A), the ratio of venous to arterial compliance (C_V/C_A) can be expressed by the following equation:

Eq. 5-11

$$\frac{C_V}{C_A} = \frac{\Delta V_V/\Delta P_V}{\Delta V_A/\Delta P_A}$$

When the heart is stopped, the decrease in arterial blood volume (ΔV_A) equals the increase in venous blood volume (ΔV_V). Because ΔV_A equals ΔV_V, Equation 5-11 can be simplified to the following relationship:

Eq. 5-12

$$\frac{C_V}{C_A} \propto \frac{\Delta P_A}{\Delta P_V}$$

Equation 5-12 shows that the ratio of venous to arterial compliance is proportional to the ratio of the changes in arterial to venous pressures when the heart is stopped. This ratio is usually in the range of 10–20. If, for example, the ratio of venous to arterial compliance is 15, there is a 1 mm Hg increase in right atrial pressure for every 15 mm Hg decrease in mean aortic pressure.

If the right atrial pressure curve from Figure 5-14 is plotted as cardiac output versus right atrial pressure (i.e., reversing the axis),

the relationship shown in Figure 5-15 (black curve in both panels) is observed. This curve is called the **systemic vascular function curve.** This relationship can be thought of as either the effects of cardiac output on right atrial pressure (cardiac output being the independent variable) or the effect of right atrial pressure on venous return (right atrial pressure being the independent variable). When viewed from the latter perspective, systemic vascular function curves are sometimes called venous return curves.

The value of the x-intercept in Figure 5-15 is the mean circulatory filling pressure, or the pressure throughout the vascular system when there is no blood flow. This value depends on the vascular compliance and blood volume (Fig. 5-15, Panel A). Increased blood volume or decreased venous compliance causes a parallel shift of the vascular function curve to the right, which increases mean circulatory filling pressure. Decreased blood volume or increased venous compliance causes a parallel shift to the left and a decrease in the mean circulatory filling pressure.

Decreased systemic vascular resistance increases the slope without appreciably changing mean circulatory filling pressure (Fig. 5-15, Panel B). Increased systemic vascular resistance decreases the slope while keeping the same mean circulatory filling pressure. Therefore, at a given cardiac output, a decrease in systemic vascular resistance increases right atrial pressure, whereas an increase in systemic vascular resistance decreases right atrial pressure. These changes can be difficult to conceptualize, but the following explanation might help to clarify. When the small resistance vessels dilate, systemic vascular resistance decreases. If the cardiac output remains constant, arterial pressure *and* arterial blood volume must decrease. Arterial blood volume shifts over to the venous side of the circulation, and the increase in venous volume increases the right atrial pressure. Changes in systemic vascular resistance have little effect on mean circulatory filling pressure because the rather small changes in arterial diameter required to produce large changes in resistance have little affect on overall vascular compliance, which is overwhelmingly determined by venous compliance.

Cardiac Function Curves

According to the Frank-Starling relationship, an increase in right atrial pressure increases cardiac output. This relationship can be depicted using the same axis as used in systemic function curves in which cardiac output (dependent variable) is plotted against right atrial

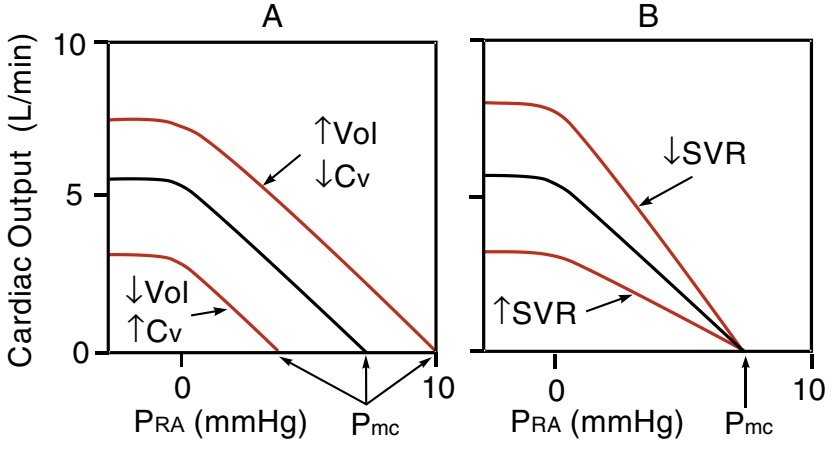

FIGURE 5-15 Systemic function curves. Panel *A* shows the effects of changes in cardiac output on right atrial pressure (P_{RA}) and mean circulatory filling pressures (*Pmc*) at different blood volumes (*Vol*) and venous compliances (*Cv*). Panel *B* shows how changes in systemic vascular resistance (*SVR*) affect the systemic function curves.

pressure (independent variable) (Fig. 5-16). These curves are similar to the Frank-Starling curves shown in Figure 4-9. There is no single cardiac function curve, but rather a family of curves that depends on the inotropic state and afterload (see Chapter 4). Changes in heart rate also shift the cardiac function curve because cardiac output, not stroke volume as in Figure 4-9, is the dependent variable. With a "normal" function curve, the cardiac output is about 5 L/min at a right atrial pressure of about 0 mm Hg. If cardiac performance is enhanced by increasing heart rate or inotropy or by decreasing afterload, it shifts the cardiac function curve up and to the left. At the same right atrial pressure of 0 mm Hg, the cardiac output will increase. Conversely, a depressed cardiac function curve, as occurs with decreased heart rate or inotropy or with increased afterload, will decrease the cardiac output at any given right atrial pressure. However, *the magnitude by which cardiac output changes when cardiac performance is altered is determined in large part by the state of systemic vascular function.* Therefore, it is necessary to examine both cardiac and system vascular function at the same time.

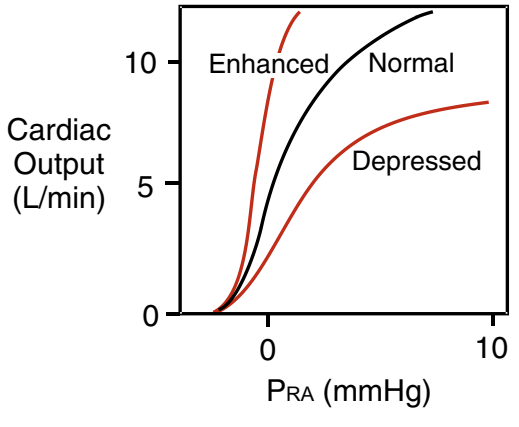

FIGURE 5-16 Cardiac function curves. Cardiac output is plotted as a function of right atrial pressure (P_{RA}); normal (solid black), enhanced (red) and depressed (red) curves are shown. Cardiac performance, measured as cardiac output, is enhanced (curves shift up and to the left) by an increase in heart rate and inotropy and a decrease in afterload.

Interactions between Cardiac and Systemic Vascular Function Curves

By themselves, systemic vascular function and cardiac function curves provide an incomplete picture of overall cardiovascular dynamics; however, when coupled together, these curves can offer a new understanding as to the way cardiac and vascular function are coupled.

When the cardiac function and vascular function curves are superimposed (Fig. 5-17), a unique intercept between a given cardiac and a given vascular function curve (point *A*) exists. This intercept is the equilibrium point that defines the relationship between cardiac and vascular function. The heart functions at this equilibrium until one or both curves shift. For example, if the sympathetic nerves to the heart are stimulated to increase heart rate and inotropy, only a small increase in cardiac output will occur, accompanied by a small decrease in right atrial pressure (point *B*). If at the same time the venous compliance is decreased by sympathetic activation of venous vasculature, cardiac output will be greatly augmented (point *C*). If the decrease in venous compliance is accompanied by a decrease in systemic vascular resistance, cardiac output would be further enhanced (point *D*). These changes in venous compliance and systemic vascular resistance, which occur during exercise, permit the cardiac output to increase. This example shows that for cardiac output to increase significantly during cardiac stimulation, there must be some alteration in vascular function so that venous return is augmented and right atrial pressure (ventricular filling) is maintained. Therefore, *in the normal heart, cardiac output is limited by factors that determine vascular function.*

In pathologic conditions such as heart failure, cardiac function limits venous return. In heart failure, ventricular inotropy is lost; total blood volume is increased; and afterload is increased (see Chapter 9). The former two lead to an increase in atrial and ventricular pressures and volumes (increased preload), which enables the Frank-Starling mechanism to partially compensate for the loss of inotropy. These changes during heart failure can be

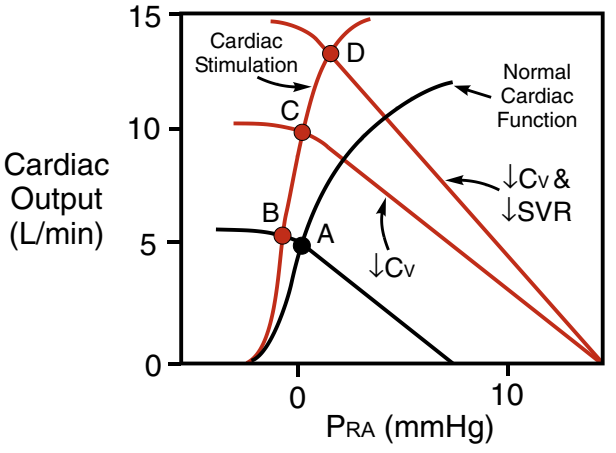

FIGURE 5-17 Combined cardiac and systemic function curves: effects of exercise. Cardiac output is plotted against right atrial pressure (P_{RA}) to show the effects of altering both cardiac and systemic function. Point *A* represents the normal operating point described by the intercept between the normal cardiac and systemic function curves. Cardiac stimulation alone changes the intercept from point *A* to *B*. Cardiac stimulation coupled with decreased venous compliance (C_V) (or increased venous volume) shifts the operating intercept to point *C*. If systemic vascular resistance (*SVR*) also decreases, which is similar to what occurs during exercise, the new intercept becomes point *D*.

depicted using cardiac and systemic function curves as shown in Figure 5-18. In this figure, point *A* represents the operating point in a normal heart, and point *B* indicates where a heart might operate when it is in failure in the absence of systemic compensation—cardiac output would be greatly reduced and right atrial pressure would be elevated. Compensatory increases in blood volume and systemic vascular resistance, along with reduced venous compliance, shift the systemic function to the right and decrease the slope. The new, combined intercept (point *C*) represents a partial compensation in the cardiac output at the expense of a large increase in right atrial pressure. The increased atrial pressure helps to support ventricular preload and stroke volume through the Frank-Starling mechanism.

In summary, total blood flow through the systemic circulation (cardiac output or venous

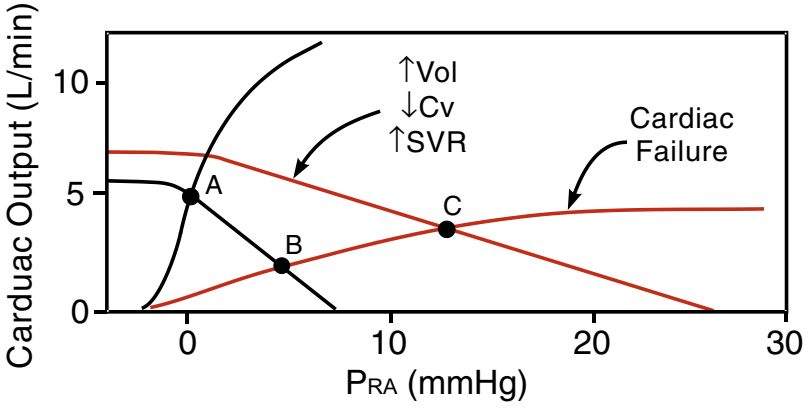

FIGURE 5-18 Combined cardiac and systemic function curves: effects of chronic heart failure. The normal operating intercept (point *A*) is shifted to point *B* when cardiac function alone is depressed by loss of inotropy. Compensatory increases in total blood volume (*Vol*) and systemic vascular resistance (*SVR*), along with reduced venous compliance (C_V), shifts the systemic function to the right and decreases the slope. The new combined intercept (point *C*) represents partial compensation in cardiac output at the expense of a large increase in right atrial pressure (P_{RA}).

return) depends on both cardiac and systemic vascular function. Cardiac stimulation in a normal heart has only a modest effect on cardiac output; however, if systemic function is additionally altered by decreasing venous compliance and systemic vascular resistance, the cardiac output is able to increase. Without changes in systemic function, cardiac output is limited by the return of blood to the heart and ventricular filling.

SUMMARY OF IMPORTANT CONCEPTS

- Regulation of arterial pressure and organ blood flow is primarily the function of the small arteries and arterioles. Capillaries are the principal site for exchange because they have the greatest surface area. Furthermore, capillaries have the lowest velocity of flow because they have the greatest cross-sectional area. Most of the blood volume is found in the venous circulation, which serves a capacitance function (it acts as a blood reservoir) within the body.
- Aortic pulse pressure is primarily determined by ventricular stroke volume and aortic compliance.
- Mean arterial pressure is determined by the product of cardiac output and systemic vascular resistance, plus central venous pressure.
- Vascular resistance is inversely related to the vessel radius to the fourth power, and it is directly related to vessel length and blood viscosity. Vessel radius is the most important factor for regulating resistance.
- The parallel arrangement of vascular beds in the body reduces overall resistance. Furthermore, because of this arrangement, a resistance change in one vascular bed has minimal influence on pressure and flow in other vascular beds.
- The resistance of a single vessel or group of vessels is the perfusion pressure divided by the blood flow.
- Changes in large artery resistance have little effect on total resistance of a vascular bed, whereas changes in small artery and arteriolar resistances greatly affect total resistance. The reason for this is that the resistance of a large artery is normally only a small percentage of the total resistance of a vascular bed.
- Arterial and venous vessels are normally in a partially constricted state (i.e., they possess vascular tone), which is determined by the net effect of vasoconstrictor and vasodilator influences acting upon the vessel.
- Central venous pressure is important because it determines the preload on the heart. Central venous pressure is altered by changes in venous blood volume and venous compliance. Gravity, respiratory activity, and the pumping action of rhythmically contracting skeletal muscle have important influences on central venous pressure.
- Cardiac output is strongly influenced by changes in systemic vascular function as described by cardiac and systemic vascular function curves. In the normal heart, cardiac output is limited by factors that determine vascular function.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. Concerning different types of blood vessels in a vascular network,
   a. Arterioles have the highest individual resistance, and therefore, as a group of vessels, have the greatest pressure drop.
   b. Capillaries as a group of vessels constitute the greatest resistance to flow within an organ.
   c. Capillaries and venules are the primary site for fluid exchange.
   d. Large arteries are the most important vessels for blood flow and pressure regulation.

2. Arterial pulse pressure
   a. Decreases at high heart rates if stroke volume decreases.

b. Decreases when cardiac inotropy is increased.
c. Increases when aortic compliance is increased with age.
d. Is the perfusion pressure for the systemic circulation.

3. A patient who has coronary artery disease is treated with a drug that reduces heart rate by 10% without changing stroke volume. Furthermore, the drug is found to decrease mean arterial pressure by 10%. Assume that central venous pressure remains at 0 mmHg. This drug
   a. Decreases systemic vascular resistance by 10%.
   b. Does not alter cardiac output.
   c. Does not alter systemic vascular resistance.
   d. Reduces pressure by dilating the systemic vasculature.

4. Which of the following will increase blood flow to the greatest extent in a single isolated blood vessel?
   a. Decreasing the blood temperature by 10°C
   b. Increasing perfusion pressure by 100%
   c. Increasing blood viscosity by 100%
   d. Increasing the vessel diameter by 50%

5. If cardiac output is 4500 mL/min, mean arterial pressure is 94 mm Hg, and right atrial pressure is 4 mm Hg, systemic vascular resistance (in peripheral resistance units, PRU; mm Hg/ml • min^{-1}) is:
   a. 0.02
   b. 20
   c. 50
   d. 4.05×10^5

6. If the renal artery supplying blood flow to the kidney has its internal diameter reduced by 50%, the blood flow to the kidney will decrease by what amount? Assume that renal artery resistance is 1% of total renal resistance and that there is no autoregulation.
   a. 50%
   b. Less than 20%
   c. 8-fold
   d. 16-fold

8. Central venous pressure is increased by
   a. Forcefully exhaling against a closed glottis.
   b. Increasing cardiac output.
   c. Increasing venous compliance.
   d. Standing.

8. Venous return to the right atrium is
   a. Decreased as cardiac output increases.
   b. Decreased by sympathetic activation of veins.
   c. Increased during a forced expiration against a closed glottis.
   d. Increased during inspiration.

9. Mean circulatory filling pressure is increased by
   a. Decreased venous compliance.
   b. Increased systemic vascular resistance.
   c. Decreased blood volume.
   d. Increased cardiac output.

10. In a normal heart, cardiac output and right atrial pressure are both increased by
    a. Decreased blood volume.
    b. Decreased systemic vascular resistance.
    c. Increased heart rate.
    d. Increased venous compliance.

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chapter

Neurohumoral Control of the Heart and Circulation

6

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Describe the roles of the following regions of the brain in the autonomic regulation of cardiac and vascular function: medullary "cardiovascular centers," hypothalamus, and cortex.**
2. **Describe the origin and distribution of sympathetic and parasympathetic nerves to the heart and circulation.**
3. **Know the location and function of alpha- and beta-adrenoceptors and muscarinic receptors in the heart and blood vessels.**
4. **Describe the effects of sympathetic and parasympathetic stimulation on the heart and circulation.**
5. **Describe the location and afferent connections from the carotid sinus, aortic arch, and cardiopulmonary baroreceptors to the medulla oblongata.**
6. **Describe how carotid sinus baroreceptors respond to changes in arterial pressure (mean pressure and pulse pressure), and explain how changes in baroreceptor activity affect sympathetic and parasympathetic outflow to the heart and circulation.**
7. **Describe (a) the location of peripheral and central chemoreceptors; (b) the way they respond to hypoxemia, hypercapnia, and acidosis; and (c) the effects of their stimulation on autonomic control of the heart and circulation.**
8. **List the factors that stimulate the release of catecholamines, renin, atrial natriuretic peptide, and vasopressin.**
9. **Describe how sympathetic nerves, circulating catecholamines, angiotensin II, aldosterone, atrial natriuretic peptide, and vasopressin interact to regulate arterial blood pressure.**

INTRODUCTION

Autonomic nerves and circulating hormones serve as important mechanisms for regulating cardiac and vascular function. These mechanisms are controlled by sensors that monitor blood pressure (baroreceptors), blood volume (volume receptors), blood chemistry (chemoreceptors), and plasma osmolarity (osmoreceptors). Peripheral sensors such as baroreceptors are found in arteries, veins, and cardiac chambers. They have afferent nerve fibers that travel to the central nervous system, where their activity is monitored and compared against a "set point" for arterial pressure. Deviations from the set point result in selective activation or deactivation of neurohumoral efferent control systems. Sensors located within the central nervous system (e.g., central chemoreceptors and osmoreceptors) also interact with regions within the brain that control neurohumoral status. The sensors work together with the neurohumoral mechanisms to ensure that arterial blood pressure is adequate for perfusing organs. Although the following sections describe several individual neurohumoral mechanisms, note that all of these mechanisms interact together to ensure cardiovascular homeostasis.

AUTONOMIC NEURAL CONTROL

Autonomic Innervation of the Heart and Vasculature

Autonomic regulation of cardiovascular function is controlled by the central nervous system. The medulla oblongata located within the brainstem, the hypothalamus, and the cortical regions work to regulate autonomic function (Figs. 6-1 and 6-2). Regions within the **medulla** contain the cell bodies for the parasympathetic (vagal) and sympathetic efferent nerves. The **hypothalamus** plays an integrative role by modulating medullary neuronal activity, for example, during exercise or when the body needs to adjust blood flow to the skin to regulate body temperature. Higher centers, including the **cortex,** connect with the hypothalamus and medulla. The higher centers can alter cardiovascular function during times of emotional stress (e.g., caused by fear and anxiety).

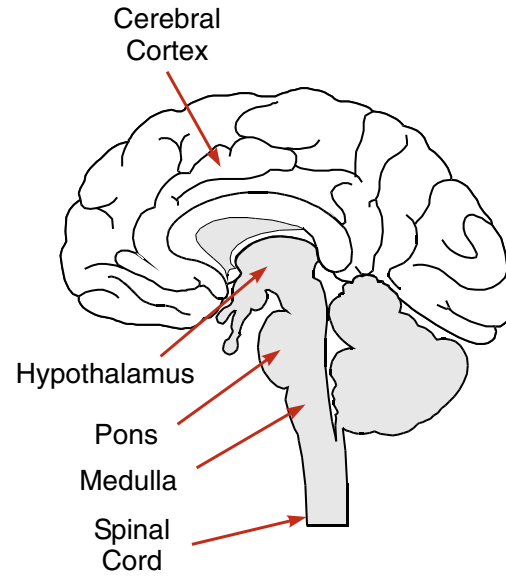

FIGURE 6-1 Regions of the central nervous system involved in cardiovascular regulation. The primary site of cardiovascular regulation resides in the medulla; the hypothalamus serves as an integrative region for coordinating cardiovascular responses. Higher centers such as the cortex influence cardiovascular function.

The central nervous system receives sensory (afferent) input from peripheral sensors and from sensors within the brain. Afferent fibers from peripheral baroreceptors and chemoreceptors, as well as respiratory stretch receptors, enter the medulla at the **nucleus tractus solitarius (NTS)** (see Fig. 6-2). Inhibitory interneurons from cells within the NTS project to other medullary regions containing cell bodies of sympathetic nerves. In addition, excitatory interneurons from the NTS project to medullary regions containing cells bodies of parasympathetic (vagal) nerves. The NTS also sends fibers to the hypothalamus. Sensors within the hypothalamus that monitor blood temperature (thermoreceptors) send fibers to medullary regions to modulate sympathetic outflow to the cutaneous circulation.

Parasympathetic Innervation

The parasympathetic vagal fibers innervating the heart originate from cell bodies located

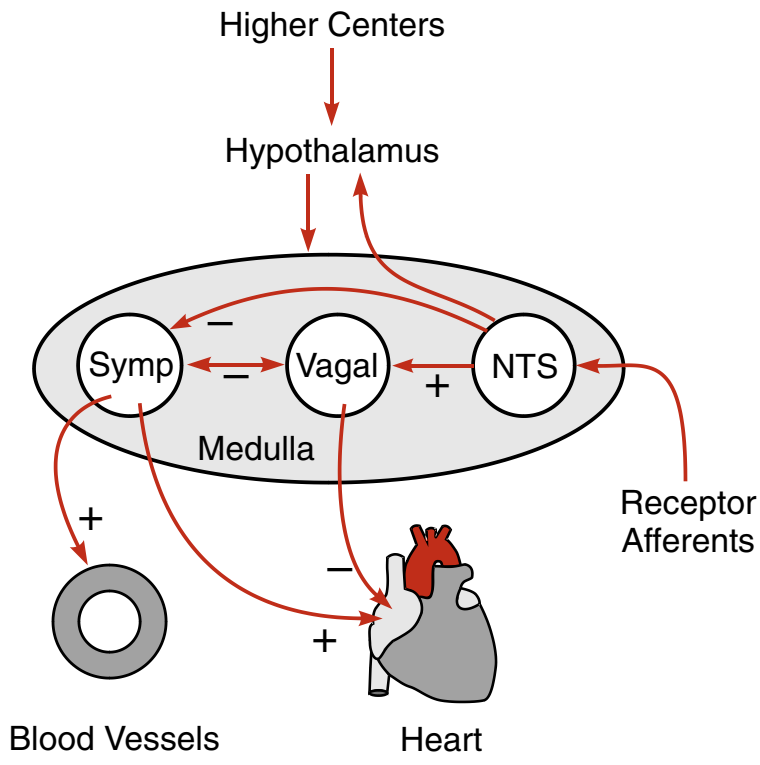

FIGURE 6-2 Schematic representation of autonomic sympathetic (*Symp*) and vagal interconnections within the central nervous system. Receptor afferent nerve fibers (e.g., from baroreceptors) enter the medulla at the nucleus tractus solitarius (*NTS*), which projects inhibitory interneurons to the sympathetic neurons and excitatory fibers to the vagal neurons. The medulla receives input from the hypothalamus and higher brain centers. Sympathetic activation (+) of blood vessels and the heart causes smooth muscle contraction (vasoconstriction), increased heart rate (positive chronotropy), increased conduction velocity within the heart (positive dromotropy), and increased contractility (positive inotropy). Vagal activation of the heart decreases (−) chronotropy, dromotropy, and inotropy.

within the medulla of the brainstem (see Figs. 6-1 and 6-2). These cell bodies are found in collections of neurons called the **dorsal vagal nucleus** and **nucleus ambiguous.** Electrical stimulation of these nuclei produces bradycardia; therefore, these regions of the medulla are sometimes referred to as the "cardioinhibitory center." Under normal resting conditions, these neurons are tonically active, thereby producing what is termed **"vagal tone"** on the heart, resulting in resting heart rates significantly below the intrinsic firing rate of the sinoatrial pacemaker. Afferent nerves, particularly from peripheral baroreceptors that enter the medulla through the NTS, modulate the activity of these vagal neurons. Excitatory interneurons from the NTS, which normally are excited by tonic baroreceptor activity, stimulate vagal activity. In addition, efferent fibers from the hypothalamus modulate the vagal neurons.

Efferent vagal fibers (also referred to as **preganglionic fibers**) exit the medulla as the tenth cranial nerve and travel to the heart within the left and right vagus nerves. Branches from these nerves innervate specific regions within the heart such as the sinoatrial and atrioventricular nodes, conduction pathways, myocytes, and the coronary vasculature. The preganglionic efferent fibers synapse within or near the target tissue and form small ganglia, from which short **postganglionic fibers** innervate specific tissue sites. Activation of these postganglionic fibers causes the release of the neurotransmitter acetylcholine. This neurotransmitter binds to

muscarinic receptors (M_2), which decreases chronotropy, dromotropy, and inotropy (more so in the atria than in the ventricles), and dilates the coronary vasculature (Table 6-1 and Figure 6-3).

The right vagus is usually the primary vagal branch that innervates the sinoatrial (SA) node, whereas the left vagus primarily innervates the atrioventricular (AV) node and the ventricular conduction system. This can be

TABLE 6-1 EFFECTS OF SYMPATHETIC AND PARASYMPATHETIC STIMULATION ON CARDIAC AND VASCULAR FUNCTION

	SYMPATHETIC	PARASYMPATHETIC
Heart		
Chronotropy (rate)	+ + +	– – –
Inotropy (contractility)	+ + +	– 1
Dromotropy (conduction velocity)	+ +	– – –
Vessels (Vasoconstriction)		
Resistance (arteries, arterioles)	+ + +	– 2
Capacitance (veins, venules)	+ + +	0

Relative magnitude of responses (+, increase; –, decrease; 0, no response) indicated by number of + or – signs.
[1] More pronounced in atria than ventricles.[2] Vasodilator effects only in specific organs such as genitalia.

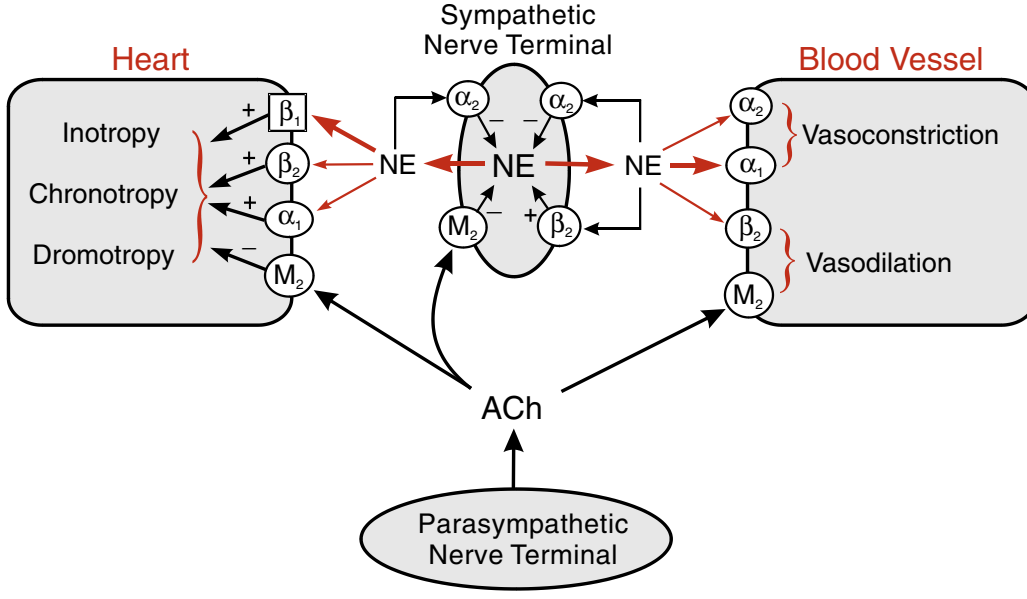

FIGURE 6-3 Adrenergic and muscarinic receptors in the heart and blood vessels. Norepinephrine (NE) released from sympathetic nerve terminals binds to postjunctional adrenoceptors in the heart (subtype affinity to NE: $\beta_1 >> \beta_2$ and α_1) to produce positive inotropy, chronotropy, and dromotropy. In blood vessels, NE binds to postjunctional adrenoceptors (subtype affinity to NE: $\alpha_1 >> \alpha_2$ and β_2). NE binding to postjunctional α-adrenoceptors causes vasoconstriction, whereas binding to β_2-adrenoceptors causes vasodilation. In both cardiac and vascular tissue, prejunctional α_2-adrenoceptors inhibit NE release, and prejunctional β_2-adrenoceptors enhance NE release. Parasympathetic (vagal) nerves in the heart release acetylcholine (ACh), which binds to prejunctional muscarinic receptors (M_2) to inhibit NE release. ACh also binds to postjunctional M_2 receptors to decrease inotropy, chronotropy, and dromotropy. In a few specific organs (e.g., genitalia), ACh released by parasympathetic nerves binds to vascular M_2 receptors to produce endothelial-dependent vasodilation.

demonstrated experimentally by electrically stimulating the right vagus nerve, which causes bradycardia (or SA nodal arrest) with little change in AV nodal conduction, as evidenced by a relatively small increase in the P-R interval of the electrocardiogram. Left vagal stimulation, in contrast, usually results in a pronounced AV nodal block (see Chapter 2), with relatively little decrease in heart rate. However, these responses to vagal stimulation can be markedly different between individuals because of crossover of the left and right vagal efferents.

Some efferent parasympathetic fibers innervate blood vessels in specific organs in which they directly or indirectly cause vasodilation. Direct vasodilation by parasympathetic activation in some tissues (e.g., genitalia erectile tissue) is achieved through the release of acetylcholine, which binds to muscarinic receptors on the vascular endothelium to cause vasodilation through the subsequent formation of nitric oxide (see Chapter 3). Parasympathetic stimulation causes indirect vasodilation in some organs (e.g., gastrointestinal circulation) by stimulating non-vascular tissue to produce vasodilator substances such as bradykinin, which then binds to vascular receptors to cause vasodilation. Note that *any existing parasympathetic nerves primarily serve to regulate blood flow within specific organs rather than to play a significant role in the regulation of systemic vascular resistance and arterial blood pressure.*

Sympathetic Innervation

The sympathetic adrenergic control of the heart and vasculature originates from neurons found within the medulla. These neurons are not organized into distinct nuclei, but instead make up a less defined but highly complex system of interconnected neurons. Electrical stimulation of certain regions within the medulla produce tachycardia and systemic vasoconstriction; therefore, terms such as "cardiostimulatory centers" and "pressor" and "vasoconstrictor centers" are sometimes used to describe these neuronal networks. Sympathetic neurons have spontaneous action potential activity, which results in tonic stimulation of the heart and vasculature. Therefore, acute sympathetic denervation of the heart and systemic blood vessel usually results in bradycardia and systemic vasodilation. At low resting heart rates, the effects of sympathetic denervation on the heart rate are relatively small because the heart is under a high level of vagal tone. In contrast, sympathetic tone is relatively high in most organ circulations; therefore, sudden removal of sympathetic tone produces significant vasodilation and hypotension.

Parasympathetic activity within the medulla normally inhibits sympathetic activity, and vice versa. Therefore, reciprocal activation of the medullary centers controlling vagal and sympathetic outflow generally occurs. An example of this reciprocity occurs when a person stands up and arterial blood pressure falls. Baroreceptor reflexes cause the medullary centers to increase sympathetic outflow to stimulate the heart (increase heart rate and inotropy) and to constrict the systemic vasculature. These cardiac and vascular responses help to restore normal arterial pressure. As sympathetic fibers are being activated, parasympathetic activity is decreased. This is important because without removal of vagal influences on the heart, the ability of enhanced sympathetic activity to increase heart rate is impaired.

Regions within the hypothalamus can integrate and coordinate cardiovascular responses by providing input to medullary centers. Studies have shown that electrical stimulation of specific hypothalamic regions produces autonomic responses that mimic those that occur during exercise, or the **flight-or-fight response.** These coordinated responses include sympathetic-mediated tachycardia, increased inotropy, catecholamine release, and systemic vasoconstriction.

Input from higher cortical regions can alter autonomic function as well. For example, sudden fear or emotion can sometimes cause vagal activation leading to bradycardia, withdrawal of sympathetic vascular tone, and fainting (**vasovagal syncope**). Fear and anxiety can lead to sympathetic activation that causes tachycardia, increased inotropy, and

hypertension. Chronic sympathetic activation induced by long-term emotional stress can result in sustained hypertension, cardiac hypertrophy, and arrhythmias.

Axons from sympathetic neurons (also termed preganglionic fibers) leave the medulla, travel down the spinal cord, and exit at specific thoracolumbar levels (T1–L2). These fibers then synapse within sympathetic **paravertebral ganglia** (cervical, stellate, and thoracolumbar sympathetic chain) located on either side of the spinal cord, or they synapse within **prevertebral ganglia** located within the abdomen (celiac, superior mesenteric, and inferior mesenteric ganglia) (Fig. 6-4). Postganglionic sympathetic fibers travel to target organs where they innervate arteries and veins; capillaries are not innervated. Small branches of these efferent nerves are found in the adventitia (outer) layer of blood vessels. **Varicosities,** which are small enlargements along the sympathetic nerve fibers, provide the site of neurotransmitter release.

Postganglionic sympathetic fibers traveling to the heart innervate the sinoatrial and atrioventricular nodes, conduction system, and cardiac myocytes, as well as the coronary vasculature. Sympathetic activation increases

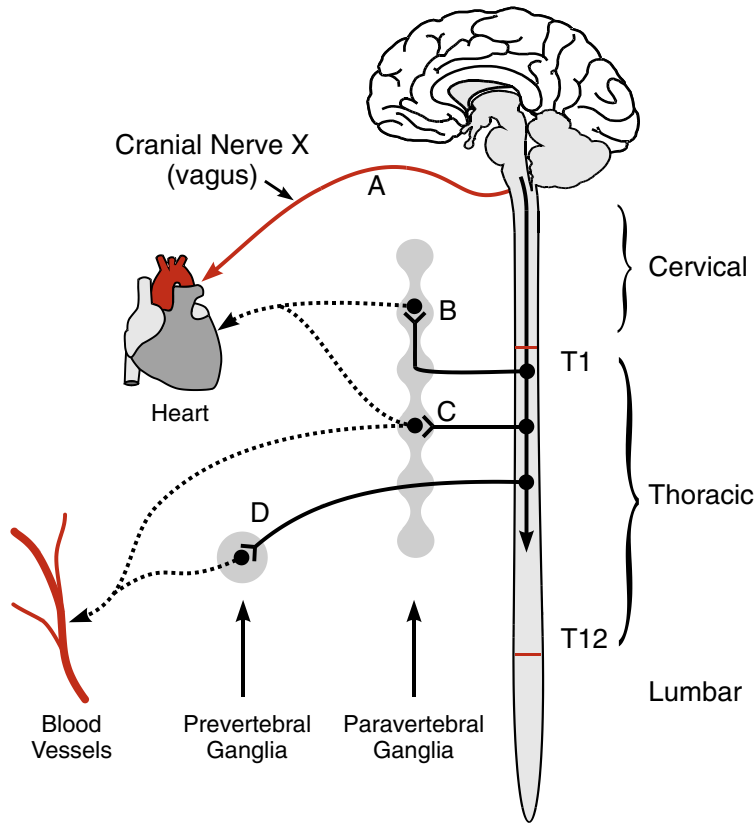

FIGURE 6-4 Organization of sympathetic and vagal innervation of the heart and circulation. The tenth cranial nerve (vagus; parasympathetic) arises from the brainstem. Preganglionic fibers (solid red line, *A*) travel to the heart, where they synapse with cell bodies of short postganglionic fibers that innervate the heart. Preganglionic sympathetic nerves (solid black lines) arise from thoracic (T1–T12) and lumbar segments of the spinal cord. Some of these fibers (*B*) enter the paravertebral ganglia (sympathetic chain) on both sides of the spinal cord, and travel within the ganglia to synapse above (*B*) or below their entry level, or at their level of entry (*C*). Postganglionic fibers (dotted black lines) from the cervical ganglia primarily innervate the heart, whereas those from thoracic ganglia travel to blood vessels and to the heart. Preganglionic fibers from lower thoracic and upper lumbar segments generally synapse in prevertebral ganglia (*D*), from which postganglionic fibers travel to blood vessels.

chronotropy, dromotropy, and inotropy (see Table 6-1). These effects are mediated primarily by norepinephrine binding to β_1-adrenoceptors on the heart (see Figure 6-3). There are also post-junction β_2-adrenoceptors in the heart; however, they are normally less important than β_1-adrenoceptors. Prejunctional β_2-adrenoceptors facilitate norepinephrine release, whereas prejunctional α_2-adrenoceptors inhibit norepinephrine release.

Sympathetic activation constricts both resistance and capacitance vessels, thereby increasing systemic vascular resistance (and arterial blood pressure) and decreasing venous capacitance (which increases venous pressure) (see Table 6-1). Norepinephrine released by sympathetic adrenergic nerves preferentially binds α_1-adrenoceptors to cause smooth muscle contraction and vasoconstriction (see Figure 6-3). Similar responses occur when norepinephrine binds to postjunctional α_2-adrenoreceptors located primarily on small arteries and arterioles, although postjunctional α_1-adrenoceptors are generally the more important α-adrenoceptor subtype. In addition, norepinephrine can bind to prejunctional α_2-adrenoreceptors, which acts as a negative feedback mechanism for modulating norepinephrine release.

Blood vessels possess postjunctional β_2-adrenoceptors. Activation of postjunctional β_2-adrenoceptors by norepinephrine (and, more importantly, by circulating epinephrine) causes vasodilation in the absence of opposing α-adrenoceptor mediated vasoconstriction. To observe this β_2-adrenoceptor induced vasodilation experimentally, one can stimulate vascular sympathetic nerves in the presence of complete α-adrenoceptor blockade. Normally, this small β_2-receptor mediated vasodilator effect of norepinephrine is completely overwhelmed by simultaneous α-adrenoceptor activation, leading to vasoconstriction.

Sympathetic activation of resistance vessels significantly contributes to the vascular tone in many organs. This can be demonstrated by abruptly removing sympathetic influences (e.g., by blocking α-adrenoceptors with drugs). When this is done, blood flow increases, the amount of which depends upon the degree of sympathetic tone and the strength of local autoregulatory mechanisms that will attempt to maintain constant blood flow (see Chapter 7). For example, if α-adrenoceptors in the forearm circulation are blocked pharmacologically, blood flow increases two- or three-fold. Over time, however, intrinsic autoregulatory mechanisms restore normal tone and blood flow.

As described further in Chapter 7, the vascular response to sympathetic activation differs among organs. For example, skeletal muscle, cutaneous, gastrointestinal, and renal circulations are strongly influenced by sympathetic activity. In contrast, the coronary and cerebral circulations have only weak responses to sympathetic stimulation. Sympathetic stimulation of the heart produces only transient coronary vasoconstriction, which is followed by vasodilation produced by metabolic factors associated with increased cardiac mechanical activity. Therefore, generalized sympathetic activation of the circulation increases arterial pressure and reduces organ perfusion throughout the body except in the heart and brain.

Baroreceptor Feedback Regulation of Arterial Pressure

As described above, sympathetic nerves play an important role in regulating systemic vascular resistance and cardiac function, and therefore arterial blood pressure. But, how does the body control the systemic vascular resistance and cardiac output to establish and maintain an arterial blood pressure to ensure adequate organ perfusion?

Arterial blood pressure is regulated through negative feedback systems incorporating pressure sensors (i.e., baroreceptors) found in strategic locations within the cardiovascular system. **Arterial baroreceptors** are found in the carotid sinus (at the bifurcation of external and internal carotids) and in the aortic arch (Fig. 6-5). The sinus nerve (nerve of Hering), a branch of the glossopharyngeal nerve (cranial nerve IX), innervates the carotid sinus. Afferent fibers from the carotid sinus travel in the glossopharyngeal nerve up to the brainstem, where they synapse at the

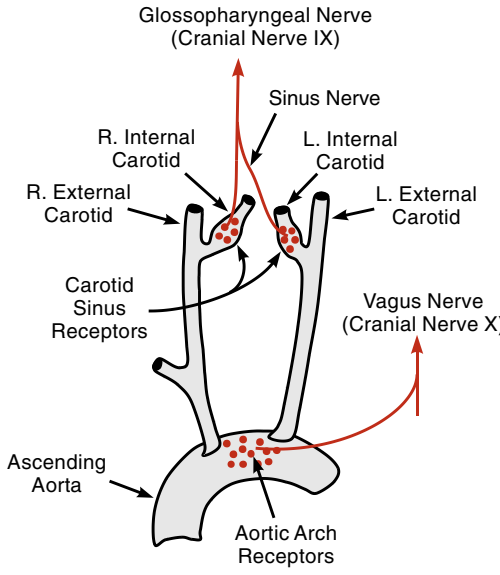

FIGURE 6-5 Location and innervation of arterial baroreceptors. Carotid sinus receptors are located on the internal carotid artery just above the junction with the external carotid artery. These receptors are innervated by the sinus nerve of Hering, which joins the glossopharyngeal nerve (cranial nerve IX) before traveling up to the medulla. Afferent nerves from the aortic arch receptors join the vagus nerve (cranial nerve X), which then travel to the medulla. *R,* right; *L,* left.

nucleus tractus solitarius. The nucleus tractus solitarius modulates the activity of "cardiovascular centers" within the medulla. The aortic arch baroreceptors are innervated by the aortic nerve, which then combines with the vagus nerve (cranial nerve X) before traveling to the nucleus tractus solitarius.

The arterial baroreceptors respond to the stretching of the vessel walls produced by increases in arterial blood pressure (Figure 6-6). Increased arterial pressure increases the firing rate of individual receptors and nerves. Each individual receptor has its own threshold and sensitivity to changes in pressure; therefore, additional receptors are recruited as pressure increases. Overall, the receptors of the carotid sinus respond to pressures ranging from about 60–180 mm Hg. Therefore, if arterial blood pressure decreases from normal, it lowers the firing rate of the carotid sinus baroreceptors; conversely, increased arterial pressure increases receptor firing.

Baroreceptors are sensitive to the rate of pressure change and to a steady or mean pressure. At a given mean arterial pressure, decreasing the arterial pulse pressure decreases firing rate. This is important during conditions such as hemorrhagic shock in which pulse pressure (as well as mean pressure) decreases because of the decline in stroke volume caused by decreased ventricular preload and increased heart rate. Therefore, reduced pulse pressure reinforces the baroreceptor reflex when mean arterial pressure falls. The curve representing the frequency of baroreceptor firing in Figure 6-6 is the integrated receptor firing at a given pulse pressure. At reduce pulse pressures, the curve shifts to the

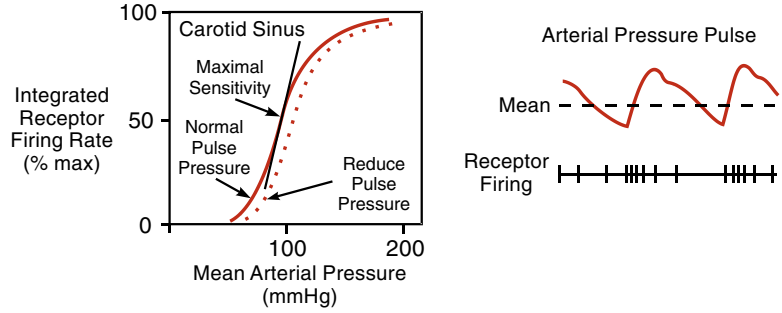

FIGURE 6-6 Effects of arterial pressure on integrated carotid sinus firing rate. Left panel: The threshold for receptor activation occurs at mean arterial pressures of about 60 mm Hg; maximal firing occurs at about 180 mm Hg. Maximal receptor sensitivity occurs at normal mean arterial pressures. The receptor firing-response curve shifts to the right with decreased pulse pressures; therefore, a decrease in pulse pressure at a given mean pressure decreases firing. Right panel: Single receptor firing in response to pulsatile pressure. Receptors fire more rapidly when arterial pressure is rapidly increasing during cardiac systole.

right, thereby decreasing the firing at any given mean arterial pressure.

Maximal carotid sinus sensitivity (the point of greatest slope of the response curve in Figure 6-6) occurs near the "set point" of normal mean arterial pressures (approximately 95 mm Hg in adults). Therefore, small deviations from this set point elicit large changes in baroreceptor firing frequency. This set point, and the entire receptor response curve, is not fixed. Chronic shifts in this curve can occur during hypertension, heart failure, and other disease states. In hypertension, for example, the curve shifts to the right, thereby reducing the firing rate at any given mean arterial pressure. This resetting of the baroreceptor response can occur at the level of the receptors themselves as well as in the brainstem. In arteriosclerosis, the carotid arteries at the region of the carotid sinus become less compliant, and therefore they stretch less in response to changes in arterial blood pressure—this decreases their sensitivity. During exercise, medullary and hypothalamic control centers can modulate autonomic efferent responses at a given level of baroreceptor firing, thereby resetting arterial pressure to a higher level.

Receptors located within the aortic arch function similarly to carotid sinus receptors; however, they have a higher threshold pressure for firing and are less sensitive than the carotid sinus receptors. Therefore, the aortic arch baroreceptors serve as secondary baroreceptors, with the carotid sinus receptors normally being the dominant arterial baroreceptor.

To understand how the baroreceptor reflex operates, consider the events that occur in response to a decrease in arterial pressure (mean, pulse, or both) when a person suddenly stands up (Figure 6-7). When upright posture is suddenly assumed from the supine position, gravity causes venous blood pooling below the heart, particularly in the legs (see Chapter 5). This decreases venous return, central venous pressure, and ventricular preload, leading to a fall in cardiac output and arterial blood pressure. Decreased stretching of baroreceptors results in decreased baroreceptor firing. The "cardiovascular center" within

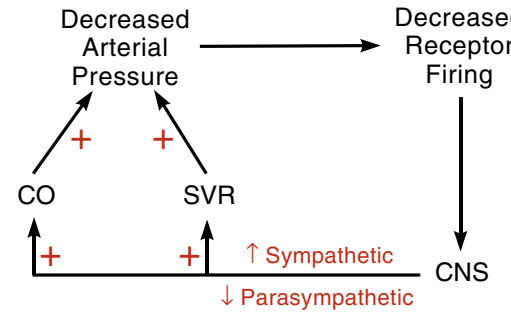

FIGURE 6-7 Baroreceptor feedback loop. A sudden decrease in arterial pressure, as occurs when a person suddenly stands up from a supine position, decreases baroreceptor firing, activating sympathetic nerves and inhibiting parasympathetic (vagal) nerves. This change in autonomic balance increases (+) cardiac output (*CO*) and systemic vascular resistance (*SVR*), which helps to restore normal arterial pressure. *CNS,* central nervous system.

the medulla responds by increasing sympathetic outflow, which increases systemic vascular resistance (vasoconstriction) and cardiac output (increased heart rate and inotropy). Decreased parasympathetic outflow from the medulla contributes to the elevation in heart rate.

Note that *baroreceptor firing normally exerts a tonic inhibitory influence on sympathetic outflow from the medulla.* Therefore, hypotension and decreased baroreceptor firing disinhibits sympathetic outflow (i.e., it increases sympathetic activity) from the medullary centers. The combined effects on systemic vascular resistance and cardiac output increases arterial blood pressure back toward its set point.

The carotid sinus reflex can be activated by rubbing the neck over the carotid sinus (i.e., **carotid sinus massage**). This mechanical stimulation of the receptors increases their firing, which leads to decreased sympathetic and increased parasympathetic outflow from the medulla. This action is sometimes used to abort certain types of arrhythmias by activating the vagus efferents to the heart.

In addition to arterial baroreceptors, stretch receptors are located at the venoatrial junctions of the heart (**cardiopulmonary receptors**) and respond to atrial filling and contraction. These tonically active receptors are

PROBLEM 6-1

How do the carotid sinus baroreceptors respond to occlusion of both common carotid arteries? What are the cardiovascular responses to bilateral carotid occlusion? How would these responses be altered by bilateral vagotomy? How would these responses be altered by the pharmacologic blockade of β_1-adrenoceptors?

The common carotid arteries are below the carotid sinus baroreceptors. Therefore, occlusion of both carotid arteries reduces pressure within the carotid sinuses. This decreases their firing, leading to increased sympathetic and decreased vagal outflow from the medullary cardiovascular centers. This action results in systemic vasoconstriction (increased systemic vascular resistance and decreased venous compliance) and cardiac stimulation (increased heart rate and inotropy). These cardiovascular adjustments will cause arterial pressure to rise.

Bilateral vagotomy enhances the response described above because as arterial pressure rises during carotid occlusion, the aortic arch baroreceptors, which are innervated by the vagus nerve, increase their firing. This partially counteracts the effects of decreased carotid sinus firing. Bilateral vagotomy removes this influence of the aortic arch baroreceptors.

Blockade of β_1-adrenoceptors would prevent the sympathetic-mediated increases in heart rate and inotropy (although some withdrawal of vagal tone may still result in a small tachycardia). The pressor response would still occur because of systemic vasoconstriction (α_1-adrenoceptor mediated); however, it would be blunted significantly because cardiac stimulation would be blocked.

innervated by myelinated vagal afferents. Increased stretch caused by an increase in venous return can sometimes increase heart rate via medullary center activation of sympathetic efferent activity to the SA node. This response, which is called the **Bainbridge reflex,** increases heart rate when the initial heart rate is low.

An increase in blood volume and venous pressure stimulates other types of cardiopulmonary receptors to decrease antidiuretic hormone (ADH, vasopressin) release by the posterior pituitary. Decreased circulating ADH causes diuresis, which leads to a fall in blood volume and venous pressure. If blood volume is lost as a result of dehydration or hemorrhage, these receptors will increase ADH release so that the kidneys excrete less water.

Unmyelinated vagal afferents are found throughout the atria and ventricles. Receptors associated with these vagal afferents respond to stretch such that the firing rate of these receptors is enhanced with increased atrial and ventricular pressures. The effects of these receptors on sympathetic and vagal outflow are similar to on the arterial baroreceptors. Depending upon the circumstances, however, these receptors can either oppose or reinforce arterial baroreceptor function. In heart failure, atrial and ventricular filling pressures are increased, whereas arterial pressure is decreased. Under this condition, increased firing by the atrioventricular receptors opposes the decreased firing by arterial baroreceptors. During hemorrhage, cardiac chamber pressures and arterial pressures are both reduced. This causes the atrioventricular receptors and the arterial baroreceptors to decrease their firing rates and therefore reinforce each other.

Chemoreceptors

Chemoreceptors are specialized cells located on arteries (peripheral chemoreceptors) and within the medulla (central chemoreceptors) that monitor pO_2, pCO_2, and H^+ concentration. Their primary function is to regulate respiratory activity to maintain arterial blood

pO_2, pCO_2, and pH within a narrow physiologic range. Chemoreceptor activity, however, affects cardiovascular function either directly by influencing medullary cardiovascular centers or indirectly through altered pulmonary stretch receptor activity. Impaired respiratory gas exchange, hypoxic environments, cerebral ischemia, and circulatory shock, for example, increase chemoreceptor activity, leading to enhanced sympathetic outflow to the heart and vasculature by activating pressor regions within the medulla.

The **peripheral chemoreceptors** are found in two locations. Small **carotid bodies** are associated with the external carotid arteries near their bifurcation with the internal carotids. Afferent nerve fibers from the carotid body receptors join with the sinus nerve before entering the glossopharyngeal nerve to synapse in the medulla. The carotid bodies increase their firing in response to a fall in arterial pO_2 (hypoxemia) or to an increase in arterial pCO_2 (hypercapnia) and hydrogen ion concentration (acidosis). The threshold pO_2 for activation is about 80 mm Hg (normal arterial pO_2 is about 95 mm Hg). Any elevation of pCO_2 above its normal value of 40 mm Hg, or a decrease in pH below 7.4, also increases receptor firing. In addition, carotid body firing can be stimulated by reduced carotid body perfusion, as occurs during hypotension associated with circulatory shock. This response to reduced perfusion can occur without changes in arterial pO_2, pCO_2, and pH. The mechanism may involve cellular hypoxia resulting from inadequate oxygen delivery to the carotid bodies (i.e., "stagnant hypoxia"). Another set of peripheral chemoreceptors, the **aortic bodies,** are located on the aortic arch, and they function similarly to the carotid bodies. Their afferent connections to the medulla travel with the vagus nerve.

Central chemoreceptors are found in the medulla regions that control cardiovascular and respiratory activity. These receptors increase their firing in response to hypercapnia and acidosis but not directly in response to hypoxia. Carbon dioxide diffusing from the blood into the cerebrospinal fluid forms hydrogen ion by the bicarbonate buffer system, and it is the hydrogen ion rather than the carbon dioxide that stimulates receptor firing.

If a subject breathes a gas mixture containing 10% instead of 21% oxygen, chemoreceptor activation (primarily peripheral) increases respiratory activity and stimulates sympathetic activity to the heart and systemic vasculature, causing arterial blood pressure to increase. If, however, respiratory rate and depth are not allowed to change, the sympathetic-mediated pressor response is accompanied by bradycardia resulting from vagal activation of the heart. This demonstrates that the tachycardia normally found during hypoxemia is secondary to respiratory stimulation and activation of pulmonary stretch receptors. Cardiovascular responses to hypercapnia and acidosis likewise depend in part upon respiratory responses.

Other Autonomic Reflexes Affecting the Heart and Circulation

In addition to the baroreceptor and chemoreceptor reflexes already described, several other reflexes affect cardiovascular function (Table 6-2). An increase in intracranial pressure, which can occur following hemorrhagic stroke or brain trauma, elicits a strong, sympathetic-mediated pressor response (**Cushing reflex**), often accompanied by baroreceptor-mediated bradycardia. It is thought that the high intracranial pressure produces brain ischemia that stimulates medullary centers. Another sympathetic reflex involving the brain occurs when cerebral perfusion falls owing to severe hypotension (a mean arterial pressure less than 60 mm Hg), producing **cerebral ischemia.** This can be thought of as a final effort by the body to restore perfusion pressure to the brain by causing intense constriction of the systemic circulation. Mean arterial pressure can rise to well over 200 mm Hg during severe cerebral ischemia.

Pain also affects cardiovascular function. For example, chest pain associated with coronary ischemia (anginal pain) or myocardial infarction in the anterior left ventricle can cause generalized sympathetic activation, leading to

TABLE 6-2 REFLEXES AFFECTING THE HEART AND CIRCULATION THROUGH CHANGES IN SYMPATHETIC AND PARASYMPATHETIC ACTIVITY

REFLEX	RECEPTOR TYPE	RECEPTOR LOCATION	STIMULUS	SYMPATHETIC ACTIVITY	PARASYMPATHETIC ACTIVITY
Arterial Baroreceptor	Mechano-receptor	Internal Carotids and Aortic Arch	Increased Arterial Pressure	Decreased	Increased
Bainbridge	Mechano-receptor	Venoatrial Junctions	Increased Venous Return	Increased	Decreased
Cardiac	Mechano-receptor	Atria and Ventricles	Increased Chamber Pressure	Decreased	Increased
Peripheral Chemo-receptor	Chemo-receptor	Carotid and Aortic Bodies	Hypoxia, Hypercapnia, Acidosis	Increased	Decreased [1]
Central Chemo-receptors	Chemo-receptor	Medulla	Hypercapnia, Acidosis	Increased	Decreased
Cushing Reflex	Chemo-receptor [2]	Brain	Intracranial Pressure	Increased	Increased
Cerebral Ischemia	Chemo-receptor	Brain	Ischemia	Increased	Decreased
Bezold-Jarisch Reflex	Chemo-receptor	Ventricles and coronary arteries	Chemical, Ischemia	Decreased	Increased
Pain	Nociceptor	Various [3]	Pain	Increased	Decreased
Deep Pain	Nociceptor	Various [4]	Pain	Decreased	Increased
Vasovagal Reflex	Various	Various	Strong Emotion, Pain	Decreased	Increased
Pulmonary Stretch Reflex	Proprio-ceptor	Airways, Respiratory Muscles	Lung Inflation	Decreased	Decreased
Muscle and Joint Reflex	Proprio-ceptor, Chemo-receptor	Muscles	Muscle Movement	Increased	Decreased
Diving Reflex	Thermo-receptor	Face	Water Submersion	Increased	Increased
Temperature Reflex	Thermo-receptor	Skin, Hypo-thalamus	Increased & Decreased Temperature	Increased or Decreased	Insignificant

Mechanoreceptors sense deformation or stretch; *chemoreceptors* respond to chemical stimuli; *nociceptors* respond to pain caused by mechanical, thermal, or chemical stimuli; *proprioceptors* sense position and movement; and *thermoreceptors* respond to either cold or warm temperatures. The *vasovagal reflex* can be triggered by several different stimuli such as pain or strong emotion. [1]Decreased parasympathetic activity to heart contributes to the increase in heart rate seen when respiration is augmented. If respiration is held constant, parasympathetic activity is increased, leading to bradycardia. [2]Brain ischemia caused by high intracranial pressure and reduced cerebral perfusion stimulates chemoreceptors via increased hydrogen ion concentration. [3]Cardiac ischemic pain, as well as other origins of pain, can trigger this reflex. [4]Deep pain arising from viscera and muscle elicits this reflex.

elevated arterial pressure and tachycardia and to sweating (diaphoresis). If cardiac output decreases significantly because of the ischemic injury, arterial pressure may fall despite the enhanced sympathetic activity. Deep pain produced by trauma or visceral distension can produce hypotension (i.e., circulatory shock) caused by enhanced parasympathetic and decreased sympathetic activity. Another example of a pain reflex is the **cold pressor response.** If a person's hand is submerged into ice-cold water, arterial pressure increases as a result of sympathetic activation.

Stimulation of specific types of chemoreceptors within the heart and coronary arteries can produce bradycardia and hypotension mediated by vagus nerve afferents and efferents (**Bezold-Jarisch reflex**). This reflex is sometimes stimulated when dye is injected into coronary arteries during coronary arteriography. Ischemia within the inferoposterior wall of the left ventricle can likewise produce this reflex.

Lung inflation activates **pulmonary stretch receptors** (located in the airways and respiratory muscles) that inhibit medullary sympathetic centers and cause arterial pressure to fall; heart rate increases reflexively. These receptors contribute to the normal cyclical changes in heart rate and arterial pressure associated with respiratory activity.

Limb muscles and tendons also possess receptors that sense tension and length changes (**muscle and joint stretch receptors**). Passive or active movement of joints can stimulate sympathetic activity to the heart and circulation and help to reinforce cardiovascular responses to exercise.

The **diving reflex** is observed in man, although this reflex is far more developed in animals such as seals and ducks. When a person dives under water, the heart rate slows (vagal mediated) and systemic blood flow is reduced owing to peripheral vasoconstriction (sympathetic mediated). This response reduces oxygen consumption by the body and myocardium while preserving coronary and cerebral blood flow. Breath holding enhances this reflex. Thermoreceptors located on the face respond to the cool water and relay this information to the brainstem through afferent facial nerves.

Finally, changes in environmental temperature sensed by cold and warm **thermoreceptors** in the skin can lead to reflex changes in cutaneous blood flow and sweating. Similarly, changes in core temperature, sensed by thermoreceptors located in the hypothalamus, produce changes in sympathetic activity to the skin circulation. For example, a decrease in either skin surface temperature or hypothalamic blood temperature leads to cutaneous vasoconstriction.

HUMORAL CONTROL

In addition to autonomic nerves, many circulating factors (humoral substances) exist that affect cardiac and vascular function. Some of these humoral factors directly influence the heart and blood vessels, whereas others indirectly alter cardiovascular function through changes in blood volume. Major humoral factors include circulating catecholamines, the renin-angiotensin-aldosterone system, atrial natriuretic peptide, and antidiuretic hormone (vasopressin). Although not addressed in this chapter, note that many other hormones and circulating substances (e.g., thyroxine, estrogen, insulin, and growth hormone) have direct or indirect cardiovascular effects.

Circulating Catecholamines

Circulating catecholamines originate from two sources. The adrenal medulla releases catecholamines (80% epinephrine, 20% norepinephrine) when preganglionic sympathetic nerves innervating this tissue are activated. This occurs during times of stress (e.g., exercise, heart failure, blood loss, emotional stress, excitement, or pain). Sympathetic nerves innervating blood vessels are another source of circulating catecholamines, principally norepinephrine. Normally, most of the norepinephrine released by sympathetic nerves is taken back up by the nerves and metabolized (some is taken up by extraneuronal tissues). A small amount of released norepinephrine, however, diffuses into the blood and circulates through-

TABLE 6-3 DIRECT EFFECTS OF LOW PLASMA CONCENTRATIONS OF EPINEPHRINE (EPI) AND NOREPINEPHRINE (NOREPI) ON CARDIAC AND VASCULAR FUNCTION

	EPI	NOREPI
Cardiac		
Heart Rate	+	+ [1]
Inotropy	+	+
Dromotropy	+	+
Vasculature		
Resistance	−/+ [2]	+
Capacitance	−	−

+, increases; –, decreases. [1] Decreases heart rate in vivo owing to baroreceptor reflexes. [2] Some vascular beds constrict, whereas others dilate.

out the body. At times of high levels of sympathetic nerve activation, the amount of norepinephrine spilling over into the blood can increase dramatically.

Circulating **epinephrine** has several direct cardiovascular actions that depend upon the relative distribution of adrenergic receptors in different organs and the relative affinities of the different receptors for epinephrine. Epinephrine binds to β_1, β_2, α_1, and α_2 adrenoceptors; however, the affinity of epinephrine for β-adrenoceptors is much greater than for α-adrenoceptors. The relative receptor affinities explain why, at low plasma concentrations, epinephrine binds preferentially to β-adrenoceptors. Therefore, at low to moderate circulating levels of epinephrine, heart rate, inotropy, and dromotropy are stimulated (primarily β_1-adrenoceptor mediated). Epinephrine at low concentrations binds to β_2-adrenoceptors located on small arteries and arterioles (particularly in skeletal muscle) and causes vasodilation.

If a low dose of epinephrine is injected intravenously while systemic hemodynamics are monitored, heart rate (and cardiac output) will increase, systemic vascular resistance will fall, but mean arterial pressure will change very little (Fig. 6-8; Table 6-3). At high plasma concentrations, the cardiovascular actions of

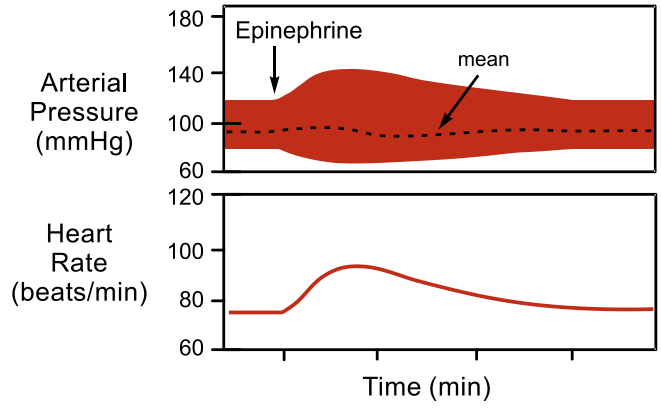

FIGURE 6-8 Effects of intravenous administration of a low dose of epinephrine on arterial pressure and heart rate. A low dose of epinephrine increases heart rate and arterial pulse pressure (it increases systolic and decreases diastolic pressure) with little change in mean arterial pressure. These changes occur because low concentrations of epinephrine preferentially bind to cardiac β_1-adrenoceptors (produces cardiac stimulation) and vascular β_2-adrenoceptors (produces systemic vasodilation). Mean pressure does not change very much because the increase in cardiac output is offset by the decrease in systemic vascular resistance.

PROBLEM 6-2

How would the changes in arterial pressure and heart rate shown in Figure 6-8 be different if β_1-adrenoceptors were blocked before the administration of low-dose epinephrine?

β_1-adrenoceptor activation is responsible for the tachycardia and increased cardiac output produced by epinephrine. Blocking β_1-adrenoceptors would abolish this response. Epinephrine also binds to vascular β_2-adrenoceptors to cause vasodilation; therefore arterial pressure would fall during epinephrine infusion in the presence of β_1-adrenoceptor blockade because the decrease in systemic vascular resistance would not be offset by an increase in cardiac output.

epinephrine are different because epinephrine binds to α-adrenoceptors as well as to β-adrenoceptors. Increasing concentrations of epinephrine result in further cardiac stimulation along with α-adrenoceptor mediated activation of vascular smooth muscle leading to vasoconstriction. This increases arterial blood pressure (pressor response) owing to both an increase in cardiac output and an increase in systemic vascular resistance.

Circulating **norepinephrine** affects the heart and systemic vasculature by binding to β_1, β_2, α_1, and α_2 adrenoceptors; however, the affinity of norepinephrine for β_2 and α_2-adrenoceptors is relatively weak. Therefore, the predominant affects of norepinephrine are mediated through β_1 and α_1-adrenoceptors. If norepinephrine is injected intravenously, it causes an increase in mean arterial blood pressure (systemic vasoconstriction) and pulse pressure (owing to increased stroke volume) and a paradoxical decrease in heart rate after an initial transient increase in heart rate (Fig. 6-9; Table 6-3). The transient increase in heart rate is due to norepinephrine binding to β_1-adrenoceptors in the sinoatrial node, whereas the secondary bradycardia is due to a baroreceptor reflex (vagal-mediated), which is in response to the increase in arterial pressure.

High levels of circulating catecholamines, caused by a catecholamine-secreting adrenal tumor (**pheochromocytoma**), causes tachycardia, arrhythmias, and severe hypertension (systolic arterial pressures can exceed 200 mm Hg).

Other actions of circulating catecholamines include (1) stimulation of renin release with subsequent elevation of angiotensin II (AII) and aldosterone, and (2) cardiac and vascular smooth muscle hypertrophy and remodeling. These actions of catecholamines, in addition to the hemodynamic and cardiac actions already described, make them a frequent therapeutic target for the treatment of hypertension, heart failure, coronary artery disease, and arrhythmias. This has led to the development and use of many different types of α and β-adrenocep-

PROBLEM 6-3

How would the norepinephrine-induced changes in arterial pressure and heart rate shown in Figure 6-9 be different in the presence of bilateral cervical vagotomy?

Bilateral cervical vagotomy would prevent vagal slowing of the heart and denervate the aortic arch baroreceptors. Heart rate (and inotropy) would increase owing to norepinephrine binding to β_1-adrenoceptors on the heart that is now unopposed by the vagus. This, along with aortic arch denervation, would enhance the pressor response of norepinephrine.

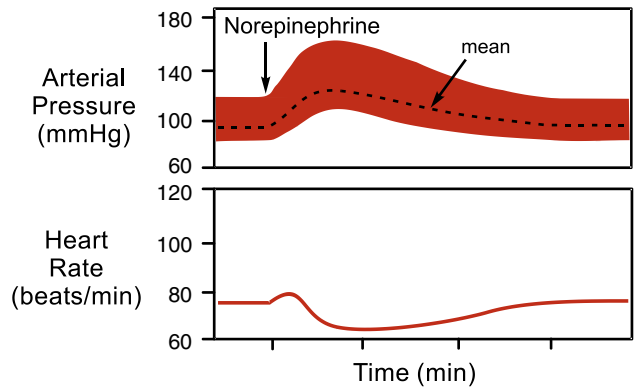

FIGURE 6-9 Effects of intravenous administration of a moderate dose of norepinephrine on arterial pressure and heart rate. Norepinephrine increases mean arterial pressure and arterial pulse pressure; heart rate transiently increases (β_1-adrenoceptor stimulation), then decreases owing to baroreceptor reflex activation of vagal efferents to the heart. Mean arterial pressure rises because norepinephrine binds to vascular α_1-adrenoceptors, which increases systemic vascular resistance.

tor antagonists to modulate the effects of circulating catecholamines as well as the norepinephrine released by sympathetic nerves.

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system plays an important role in regulating blood volume, cardiac and vascular function, and arterial blood pressure. Although the pathways for renin and angiotensin formation have been found in a number of tissues, the most important site for renin formation and subsequent formation of circulating angiotensin is the kidney. Sympathetic stimulation of the kidneys (via β_1-adrenoceptors), renal artery hypotension, and decreased sodium delivery to the distal tubules (usually caused by reduced glomerular filtration rate secondary to reduced renal perfusion) stimulate the release of **renin** into the circulation. The renin is formed within, and released from, **juxtaglomerular cells** associated with afferent and efferent arterioles of renal glomeruli, which are adjacent to the macula densa cells of distal tubule segments that sense sodium chloride concentrations in the distal tubule. Together, these components are referred to as the juxtaglomerular apparatus.

Renin is an enzyme that acts upon **angiotensinogen,** a circulating substrate synthesized and released by the liver, which undergoes proteolytic cleavage to form the decapeptide angiotensin I. Vascular endothelium, particularly in the lungs, has an enzyme, **angiotensin-converting enzyme (ACE),** that cleaves off two amino acids to form the octapeptide, **angiotensin II.**

Angiotensin II has several important functions that are mediated by specific angiotensin II receptors (AT_1) (Figure 6-10). It

1. Constricts resistance vessels, thereby increasing systemic vascular resistance and arterial pressure.
2. Facilitates norepinephrine release from sympathetic nerve endings and inhibits norepinephrine re-uptake by nerve endings, thereby enhancing sympathetic adrenergic affects.
3. Acts upon the adrenal cortex to release aldosterone, which in turn acts upon the kidneys to increase sodium and fluid retention, thereby increasing blood volume.
4. Stimulates the release of vasopressin from the posterior pituitary, which acts upon the kidneys to increase fluid retention and blood volume.
5. Stimulates thirst centers within the brain, which can lead to an increase in blood volume.
6. Stimulates cardiac and vascular hypertrophy.

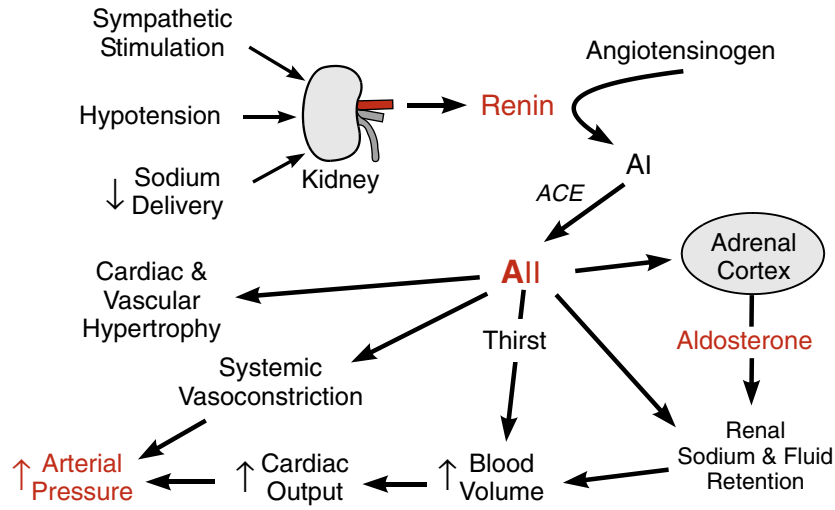

FIGURE 6-10 Formation of angiotensin II and its effects on renal, vascular, and cardiac function. Renin is released by the kidneys in response to sympathetic stimulation, hypotension, and decreased sodium delivery to distal tubules. Renin acts upon angiotensinogen to form angiotensin I (*AI*), which is converted to angiotensin II (*AII*) by angiotensin-converting enzyme (*ACE*). AII has several important actions: it stimulates aldosterone release, which increases renal sodium reabsorption; directly stimulates renal sodium reabsorption; stimulates thirst; produces systemic vasoconstriction; and causes cardiac and vascular smooth muscle hypertrophy. The overall systemic effect of increased AII is increased blood volume, venous pressure, and arterial pressure.

Angiotensin II is continuously produced under basal conditions, and this production can change under different physiologic conditions. For example, when a person exercises, circulating levels of angiotensin II increase. An increase in renin release during exercise probably results from sympathetic stimulation of the kidneys. Changes in body posture likewise alter circulating AII levels, which are increased when a person stands. As with exercise, this results from sympathetic activation. Dehydration and loss of blood volume (hypovolemia) stimulate renin release and angiotensin II formation in response to renal artery hypotension, decreased glomerular filtration rate, and sympathetic activation.

Several cardiovascular disease states are associated with changes in circulating angiotensin II. For example, secondary hypertension caused by renal artery stenosis is associated with increased renin release and circulating angiotensin II. **Primary hyperaldosteronism,** caused by an adrenal tumor that secretes large amounts of aldosterone, increases arterial pressure through its effects on renal sodium retention. This increases blood volume, cardiac output, and arterial pressure. In this condition, renin release and circulating angiotensin II levels are usually depressed because of the hypertension. In heart failure, circulating angiotensin II increases in response to sympathetic activation and decreased renal perfusion. Therapeutic manipulation of the renin-angiotensin-aldosterone system has become important in treating hypertension and heart failure. ACE inhibitors and AT_1 receptor blockers effectively decrease arterial pressure, ventricular afterload, blood volume, and hence ventricular preload, and they inhibit and reverse cardiac and vascular remodeling that occurs during chronic hypertension and heart failure.

Note that local, tissue-produced angiotensin may play a significant role in cardiovascular pathophysiology. Many tissues and organs, including the heart and blood vessels, can produce renin and angiotensin II, which have actions directly within the tissue. This may explain why ACE inhibitors can reduce arterial pressure and cause cardiac and vascular remodeling (e.g., diminish hypertrophy) even in individuals who do not have elevated

circulating levels of angiotensin II. In hypertension and heart failure, for example, tissue ACE activity is often elevated, and this may be the primary target for the pharmacologic actions of ACE inhibitors.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) is a 28-amino acid peptide that is synthesized, stored, and released by atrial myocytes in response to atrial distension, angiotensin II stimulation, endothelin, and sympathetic stimulation (β-adrenoceptor mediated). Therefore, elevated levels of ANP are found during conditions such as hypervolemia and congestive heart failure, both of which cause atrial distension.

ANP is involved in the long-term regulation of sodium and water balance, blood volume, and arterial pressure (Figure 6-11). Most of its actions are the opposite of angiotensin II, and therefore *ANP is a counter-regulatory system for the renin-angiotensin-aldosterone system.* ANP decreases aldosterone release by the adrenal cortex; increases glomerular filtration rate; produces natriuresis and diuresis (potassium sparing); and decreases renin release, thereby decreasing angiotensin II. These actions reduce blood volume, which leads to a fall in central venous pressure, cardiac output, and arterial blood pressure. Chronic elevations of ANP appear to decrease arterial blood pressure primarily by decreasing systemic vascular resistance.

The mechanism of systemic vasodilation may involve ANP receptor-mediated elevations in vascular smooth muscle cGMP (ANP activates particulate guanylyl cyclase). ANP also attenuates sympathetic vascular tone. This latter mechanism may involve ANP acting upon sites within the central nervous system as well as through inhibition of norepinephrine release by sympathetic nerve terminals.

A new class of drugs that are neutral endopeptidase (NEP) inhibitors may be useful in treating heart failure. By inhibiting NEP, the enzyme responsible for the degradation of ANP, these drugs elevate plasma levels of ANP. NEP inhibition is effective in some models of heart failure when combined with

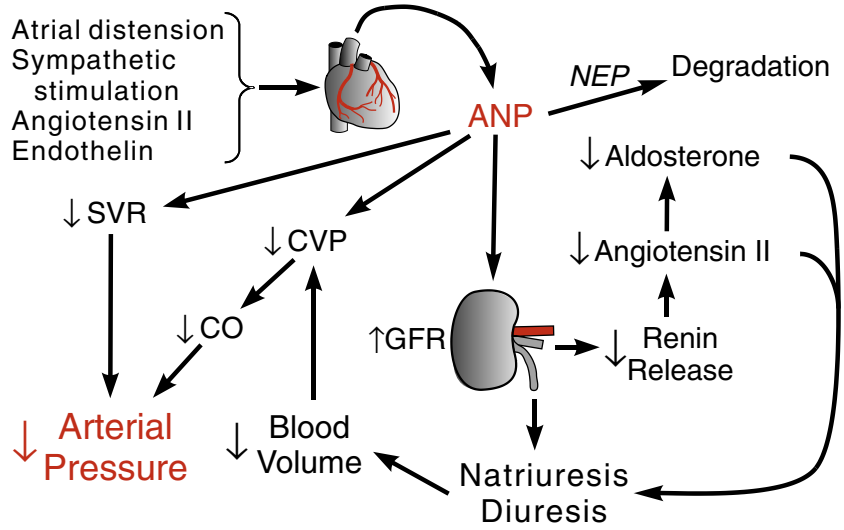

FIGURE 6-11 Formation and cardiovascular/renal actions of atrial natriuretic peptide (*ANP*). ANP, which is released from cardiac atrial tissue in response to atrial distension, sympathetic stimulation, increased angiotensin II, and endothelin, functions as a counter-regulatory mechanism for the renin-angiotensin-aldosterone system. ANP decreases renin release, angiotensin II and aldosterone formation, blood volume, central venous pressure, and arterial pressure. *NEP,* neutral endopeptidase; *GFR,* glomerular filtration rate; *CVP,* central venous pressure; *CO,* cardiac output; *SVR,* systemic vascular resistance.

CASE 6-1

A 56-year old male patient is found to have an arterial pressure of 190/115 mm Hg. Two years earlier he was normotensive. Diagnostic tests reveal bilateral renal artery stenosis. Describe the mechanisms by which this condition elevates arterial pressure.

Bilateral renal artery stenosis reduces the pressure within the afferent arterioles, which causes release of renin. This, in turn, increases circulating angiotensin II, which stimulates aldosterone release. Activation of the renin-angiotensin-aldosterone system causes sodium and fluid retention by the kidneys and an increase in blood volume, which increases cardiac output. Increased vasopressin (stimulated by angiotensin II) contributes to the increase in blood volume. Increased angiotensin II increases systemic vascular resistance by binding to vascular AT_1 receptors and by enhancement of sympathetic activity. These changes in cardiac output and systemic vascular resistance lead to a hypertensive state.

an ACE inhibitor. The reason for this is that NEP inhibition, by elevating ANP, reinforces the effects of ACE inhibition.

Brain-type natriuretic peptide (BNP), a 32-amino acid peptide hormone related to ANP, is synthesized and released by the ventricles in response to pressure and volume overload, particularly during heart failure. BNP appears to have actions that are similar to those of ANP. Recently, circulating BNP has been shown to be a sensitive biomarker for heart failure.

Vasopressin (Antidiuretic Hormone)

Vasopressin (arginine vasopressin, AVP; antidiuretic hormone, ADH) is a nonapeptide hormone released from the posterior pituitary (Figure 6-12). AVP has two principal sites of action: the kidneys and blood vessels. The most important physiologic action of AVP is that it increases water reabsorption by the kidneys by increasing water permeability in the collecting duct, thereby permitting the formation of concentrated urine. This is the

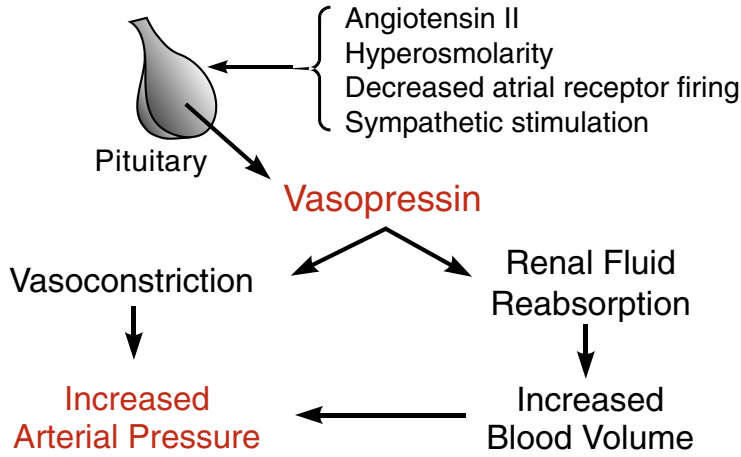

FIGURE 6-12 Cardiovascular and renal effects of arginine vasopressin (AVP). AVP release from the posterior pituitary is stimulated by angiotensin II, hyperosmolarity, decreased atrial receptor firing (usually in response to hypovolemia), and sympathetic activation. The primary action of AVP is on the kidney to increase water reabsorption (antidiuretic effect), which increases blood volume and arterial pressure. AVP also has direct vasoconstrictor actions at high concentrations.

antidiuretic property of AVP, and it leads to an increase in blood volume and arterial blood pressure. This hormone also constricts arterial blood vessels; however, the normal physiologic concentrations of AVP are below its vasoactive range. Studies have shown, nevertheless, that in severe hypovolemic shock, when AVP release is very high, AVP contributes to the compensatory increase in systemic vascular resistance.

Several mechanisms regulate the release of AVP. Specialized stretch receptors within the atrial walls and large veins (cardiopulmonary baroreceptors) entering the atria decrease their firing rate when atrial pressure falls (as occurs with hypovolemia). Afferents from these receptors synapse within the hypothalamus, which is the site of AVP synthesis. AVP is transported from the hypothalamus via axons to the posterior pituitary, from where it is secreted into the circulation. Atrial receptor firing normally inhibits the release of AVP. With hypovolemia and decreased central venous pressure, the decreased firing of atrial stretch receptors leads to an increase in AVP release. AVP release is also stimulated by enhanced sympathetic activity accompanying decreased arterial baroreceptor activity during hypotension. An important mechanism regulating AVP release involves hypothalamic osmoreceptors, which sense extracellular osmolarity. When osmolarity rises, as occurs during dehydration, AVP release is stimulated. Finally, angiotensin II receptors located within the hypothalamus regulate AVP release; an increase in angiotensin II stimulates AVP release.

Heart failure causes a paradoxical increase in AVP. The increased blood volume and atrial pressure associated with heart failure suggest that AVP secretion should be inhibited, but it is not. It may be that sympathetic and renin-angiotensin system activation in heart failure override the volume and low pressure cardiovascular receptors (as well as the osmoregulation of AVP) and cause the increase in AVP secretion. This increase in AVP during heart failure may contribute to the increased systemic vascular resistance and to renal retention of fluid.

In summary, the importance of AVP in cardiovascular regulation is primarily through its effects on volume regulation, which in turn affects ventricular preload and cardiac output through the Frank-Starling relationship. Increased AVP, by increasing blood volume, increases cardiac output and arterial pressure. The vasoconstrictor effects of AVP are probably important only when AVP levels are very high, as occurs during severe hypovolemia.

INTEGRATION OF NEUROHUMORAL MECHANISMS

Autonomic and humoral influences are necessary to maintain a normal arterial blood pressure under the different conditions in which the human body functions. Neurohumoral mechanisms enable the body to adjust to changes in body posture, physical activity, or environmental conditions. The neurohumoral mechanisms act through changes in systemic vascular resistance, venous compliance, blood volume, and cardiac function, and through these actions they can effectively regulate arterial blood pressure (Table 6-4). Although each mechanism has independent cardiovascular actions, it is important to understand that each mechanism also has complex interactions with other control mechanisms that serve to reinforce or inhibit the actions of the other control mechanisms. For example, activation of sympathetic nerves either directly or indirectly increases circulating angiotensin II, aldosterone, adrenal catecholamines, and arginine vasopressin, which act together to increase blood volume, cardiac output, and arterial pressure. These humoral changes are accompanied by an increase in ANP, which acts as a counter-regulatory system to limit the effects of the other neurohumoral mechanisms.

Finally, it is important to note that some neurohumoral effects are rapid (e.g., autonomic nerves and catecholamine effects on cardiac output and pressure), whereas others may take several hours or days because changes in blood volume must occur before alterations in cardiac output and arterial pressure can be fully expressed.

TABLE 6-4 EFFECTS OF NEUROHUMORAL ACTIVATION ON BLOOD VOLUME, CARDIAC OUTPUT AND ARTERIAL PRESSURE

INCREASED	BLOOD VOLUME	CARDIAC OUTPUT	ARTERIAL PRESSURE
Sympathetic Activity	↑	↑	↑
Vagal Activity	—	↓	↓
Circulating Epinephrine	↑	↑	↓↑*
Angiotensin II	↑	↑	↑
Aldosterone	↑	↑	↑
Atrial Natriuretic Peptide	↓	↓	↓
Arginine Vasopressin	↑	↑	↑

↑ = increase; ↓ = decrease. *dependent upon plasma epinephrine concentration.

SUMMARY OF IMPORTANT CONCEPTS

- Autonomic regulation of the heart and vasculature is primarily controlled by special regions within the medulla oblongata of the brainstem that contain the cell bodies of sympathetic and parasympathetic (vagal) efferent nerves.
- The hypothalamus plays an integrative role by modulating medullary neuronal activity (e.g., during exercise).
- Sensory information from peripheral baroreceptors (e.g., carotid sinus baroreceptors) synapse within the medulla at the nucleus tractus solitarius, which modulates the activity of the sympathetic and vagal neurons within the medulla.
- Preganglionic parasympathetic efferent nerves exit the medulla as the tenth cranial nerve and travel to the heart within the left and right vagus nerves. Preganglionic fibers synapse within ganglia located within the heart; short postganglionic fibers innervate the myocardial tissue. Preganglionic sympathetic efferent nerves exit from the spinal cord and synapse within paravertebral or prevertebral ganglia before sending out postganglionic fibers to target tissues in the heart and blood vessels.
- Sympathetic activation increases heart rate, inotropy, and dromotropy through the release of norepinephrine, which binds primarily to postjunctional cardiac β_1-adrenoceptors. Norepinephrine released by sympathetic nerves constricts blood vessels by binding to postjunctional α_1 and α_2-adrenoceptors. The release of norepinephrine from sympathetic nerve terminals is modulated by prejunctional α_2-adrenoceptors, β_2-adrenoceptors and muscarinic (M_2) receptors.
- Parasympathetic activation decreases heart rate, inotropy, and dromotropy, and it produces vasodilation in specific organs through the release of acetylcholine, which binds to postjunctional muscarinic (M_2) receptors.
- Baroreceptors are mechanoreceptors that respond to stretch induced by an increase in pressure or volume. Arterial baroreceptor activity (e.g., carotid sinus and aortic arch receptors) tonically inhibits sympathetic outflow to the heart and blood vessels, and it tonically stimulates vagal outflow to the heart. Decreased arterial pressure, therefore, decreases the firing of arterial baroreceptors, which leads to reflex activation of sympathetic influences acting on the heart and blood vessels and withdrawal of the vagal activity to the heart.
- Peripheral chemoreceptors (e.g., carotid bodies) and central chemoreceptors (e.g., medullary chemoreceptors) respond to decreased pO_2 and pH or increased pCO_2 of the blood. Their primarily function is to regulate respiratory activity, although

chemoreceptor activation generally leads to activation of the sympathetic nervous system to the vasculature, which increases arterial pressure. Heart rate responses depend upon changes in respiratory activity.

- Reflexes triggered by changes in blood volume, cerebral and myocardial ischemia, pain, pulmonary activity, muscle and joint movement, and temperature alter cardiac and vascular function.
- Sympathetic activation of the adrenal medulla stimulates the release of catecholamines, principally epinephrine. This hormone produces cardiac stimulation (via β_1-adrenoceptors), and it either decreases (via vascular β_2-adrenoceptors) or increases (via vascular α_1 and α_2-adrenoceptors) systemic vascular resistance, depending upon the plasma concentration.
- The renin-angiotensin-aldosterone system plays a major role in regulating renal excretion of sodium and water, and therefore it strongly influences blood pressure through changes in blood volume. Renin is released by the kidneys in response to sympathetic stimulation, hypotension, and decreased sodium delivery to distal tubules. Renin acts upon angiotensinogen to form angiotensin I, which is converted to angiotensin II (AII) by angiotensin-converting enzyme (ACE). AII has the following actions: (1) it stimulates aldosterone release from the adrenal cortex, which increases renal sodium reabsorption; (2) it acts on renal tubules to increase sodium reabsorption; (3) it stimulates thirst; (4) it produces systemic vasoconstriction; (5) it enhances sympathetic activity; and (6) it produces cardiac and vascular hypertrophy. The overall systemic effect of increased AII is increased blood volume, venous pressure, and arterial pressure.
- Atrial natriuretic peptide (ANP), which is released by the atria primarily in response to atrial stretch, functions as a counter-regulatory mechanism for the renin-angiotensin-aldosterone system. Therefore, increased ANP reduces blood volume, venous pressure, and arterial pressure.
- Arginine vasopressin (AVP; antidiuretic hormone), which is released by the posterior pituitary when the body needs to reduce renal loss of water, enhances blood volume and increases arterial and venous pressures. At high plasma concentrations, AVP constricts resistance vessels.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. The cell bodies for the preganglionic vagal efferents innervating the heart are found in which region of the brain?
   a. Cortex
   b. Hypothalamus
   c. Medulla
   d. Nucleus tractus solitarius

2. Norepinephrine released by sympathetic nerves
   a. Binds preferentially to β_2-adrenoceptors on cardiac myocytes.
   b. Constricts blood vessels by binding to α_1-adrenoceptors.
   c. Inhibits its own release by binding to prejunctional β_2-adrenoceptors.
   d. Decreases renin release in the kidneys.

3. Stimulating efferent fibers of the right vagus nerve
   a. Decreases systemic vascular resistance.
   b. Increases atrial inotropy.
   c. Increases heart rate.
   d. Releases acetylcholine, which binds to M_2 receptors.

4. A sudden increase in carotid artery pressure
   a. Decreases carotid sinus baroreceptor firing rate.
   b. Increases sympathetic efferent nerve activity to systemic circulation.
   c. Increases vagal efferent activity to the heart.
   d. Results in reflex tachycardia.

5. Which of the following can cause tachycardia?
   a. Face submersion in cold water
   b. Increased blood pCO_2
   c. Increased firing of carotid sinus baroreceptors
   d. Vasovagal reflex

6. Infusion of a low-to-moderate dose of epinephrine following pharmacologic blockade of β-adrenoceptors will
   a. Decrease mean arterial pressure.
   b. Have no significant cardiovascular effects.
   c. Increase heart rate.
   d. Increase systemic vascular resistance.

7. In an experimental protocol, intravenous infusion of acetylcholine was found to decrease mean arterial pressure and increase heart rate. These results can best be explained by
   a. Direct action of acetylcholine on muscarinic receptors at the sinoatrial node.
   b. Increased firing of carotid sinus baroreceptors.
   c. Reflex activation of sympathetic nerves.
   d. Reflex systemic vasodilation.

8. An increase in circulating angiotensin II concentrations
   a. Depresses sympathetic activity.
   b. Increases blood volume.
   c. Inhibits aldosterone release.
   d. Inhibits the release of atrial natriuretic peptide.

9. Atrial natriuretic peptide
   a. Enhances renal sodium retention.
   b. Increases renin release.
   c. Inhibits the release of aldosterone.
   d. Increases blood volume and cardiac output.

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chapter

7

Organ Blood Flow

CD CONTENTS Angina

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Describe the distribution of cardiac output among major organs when a person is at rest.**
2. **Describe how each of the following tissue factors influences blood flow: adenosine, inorganic phosphate, potassium ion, carbon dioxide, hydrogen ion, tissue partial pressure of oxygen, and paracrine hormones such as histamine, prostaglandins, and bradykinin.**
3. **Describe how each of the following endothelial factors influences local blood flow: nitric oxide, endothelial-derived hyperpolarizing factor, endothelin-1, and prostacyclin.**
4. **Explain how extravascular compression alters blood flow in the heart and contracting skeletal muscle.**
5. **Define autoregulation of blood flow, reactive hyperemia and active (functional) hyperemia.**
6. **Describe and contrast the local regulatory mechanisms that may be involved in autoregulation, reactive hyperemia, and active hyperemia in major vascular beds of the body (coronary, cerebral, skeletal muscle, cutaneous, splanchnic, renal, and pulmonary circulations).**
7. **Compare and contrast autonomic control of blood flow in major vascular beds of the body.**
8. **Describe the specialized vascular anatomy in the following organs: brain, heart, intestines and liver, skin, kidneys, and lungs.**

INTRODUCTION

This chapter describes the blood flow to different organs of the body. The first part of the chapter emphasizes local regulatory mechanisms by which organs regulate their own blood flow to meet the metabolic and functional requirements of the organ. The second part of the chapter examines blood flow in specific organs of the body.

DISTRIBUTION OF CARDIAC OUTPUT

We have previously seen that arterial pressure is generated as the heart pumps blood into the systemic circulation. This arterial pressure serves as the driving force for blood flow to all the organ systems. The relative distribution of blood flow to the organs is regulated by the vascular resistance of the individual organs, which is influenced by extrinsic (neurohumoral) and intrinsic (local regulatory) mechanisms as summarized in Chapter 5, Figure 5-9.

Table 7-1 summarizes the distribution of cardiac output when a person is at rest. Most of the cardiac output (approximately 80%) goes to the gastrointestinal tract, kidneys, skeletal muscle, heart and brain, although these organs make up less than 50% of the body mass. This relative distribution of cardiac output, however, changes greatly depending on environmental conditions and the state of physical activity. For example, in a hot, humid environment, the relative blood flow to the skin increases substantially as the body attempts to maintain its core temperature by losing heat to the environment. When a person exercises, the increased cardiac output primarily goes to the active skeletal muscles, heart, and skin (see Chapter 9); at the same time, blood flow decreases to the gastrointestinal and renal circulations. Another example of change in cardiac output distribution occurs following a large meal, when blood flow to the gastrointestinal circulation increases.

Instead of one "normal" blood flow for an organ, there is a range of blood flows. **Basal flow** refers to the flow that is measured under basal conditions (i.e., when a person is in a fasted, resting state and at normal environmental conditions of temperature and humidity). The ratio of basal flow to maximal flow is a measure of the vascular tone, which is the degree of vascular constriction (see Chapter 5). The lower the basal flow relative to the maximal flow, the higher the vascular tone. The difference between basal flow and maximal flow represents the flow capacity or **vasodilator reserve** for the organ. Most organs

TABLE 7-1 BLOOD FLOW IN MAJOR ORGANS OF THE BODY

ORGAN	PERCENT BODY WEIGHT	PERCENT CARDIAC OUTPUT AT REST	NORMAL FLOW (ML/MIN PER 100 G)	MAXIMAL FLOW (ML/MIN PER 100 G)
Heart	0.4	5	80	400
Brain	2	14	55	150
Skeletal muscle	40	18	3	60
Skin	3	4	10	150
Stomach, intestine, liver, spleen, pancreas	6	23	30	250
Kidneys	0.4	20	400	600
Other	48	16	-	-

Normal and maximal flows are approximate values for the whole organ. Many organs (e.g., brain, muscle, kidney, and intestine) have considerable heterogeneity of flow within the organ depending on the type of tissue or region of organ being perfused. The liver receives blood flow from the gastrointestinal venous drainage as well as from the hepatic artery (only hepatic artery flow is included in this table). "Other" includes reproductive organs, bone, fat, and connective tissue.

have a relatively large vasodilator reserve, whereas others, such as the kidneys, have a relatively small vasodilator reserve (see Table 7-1).

The changes that occur in organ blood flow under different conditions depend on the interplay between neurohumoral and local regulatory mechanisms that govern vascular resistance. The neurohumoral mechanisms were discussed in Chapter 6. The following sections focus on the local regulatory mechanisms that affect vascular resistance and organ blood flow.

LOCAL REGULATION OF BLOOD FLOW

Tissues and organs have the ability to regulate, to a varying degree, their own blood flow. This intrinsic ability to regulate blood flow is termed "local regulation" and can occur in the complete absence of any extrinsic neurohumoral influences. For example, if a muscle is removed from the body, perfused under constant pressure with an oxygenated salt solution, and then electrically stimulated to induce muscle contractions, the blood flow increases. The increase in blood flow occurs in the absence of neurohumoral influences, and therefore is a local or intrinsic mechanism.

The mechanisms responsible for local regulation originate from within the blood vessels (e.g., endothelial factors, myogenic mechanisms) and from the surrounding tissue (i.e., tissue factors), many of which are related to tissue metabolism or other biochemical pathways (e.g., arachidonic acid metabolites and bradykinin). Mechanical factors (e.g., compressive forces during muscle contraction) can also influence vascular resistance and thereby alter blood flow.

Tissue Factors

Tissue factors are substances produced by the tissue surrounding blood vessels (Fig. 7-1). These substances act on the blood vessel to produce either relaxation or contraction of the smooth muscle, thereby altering resistance and blood flow. In some cases, these substances indirectly act on the vascular smooth muscle by affecting endothelial function or by altering the release of norepinephrine by sympathetic nerves. Some of these vasoactive substances are tissue metabolites that are products of cellular metabolism or activity (e.g., adenosine, CO_2, H^+, K^+, lactate). In addition, different cell types surrounding blood vessels can release vasoactive substances referred to as local, paracrine hormones (e.g., histamine,

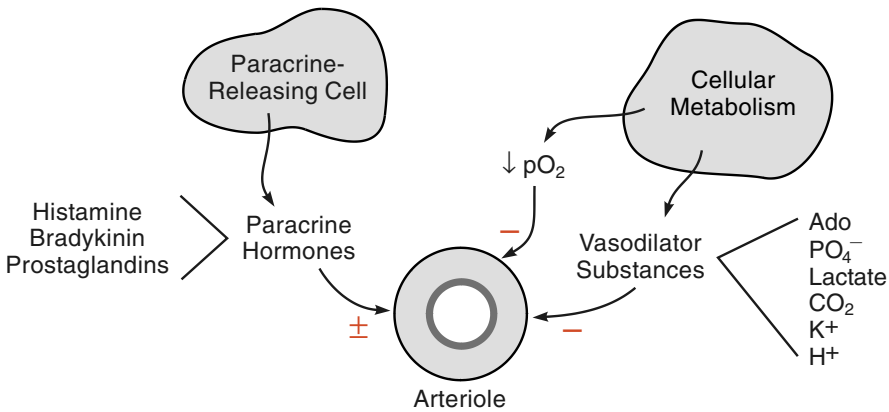

FIGURE 7-1 Vasoactive substances derived from tissue cells around arterioles. Increased tissue metabolism leads to formation of metabolites that dilate (-) nearby arterioles. Increased oxygen consumption decreases the tissue partial pressure of oxygen (pO_2), which dilates arterioles. Some cells release locally acting, paracrine hormones (or their precursors), which can either constrict (+) or dilate (-) arterioles. *Ado,* adenosine; PO_4^-, inorganic phosphate; CO_2, carbon dioxide; K^+, potassium ion; H^+, hydrogen ion.

bradykinin, and prostaglandins). A **paracrine hormone** is a substance released by one cell that acts on another nearby cell by diffusing through the interstitial fluid. This is in contrast to **endocrine hormones** that circulate in the blood to reach distant target cells or **autocrine substances** that affect the same cell from which they are released.

Increases or decreases in metabolism alter the release of some of these vasoactive substances; thus, metabolic activity is closely coupled to blood flow in most organs of the body. For example, an increase in tissue metabolism, as occurs during muscle contraction or during changes in neuronal activity in the brain, leads to an increase in blood flow. Extensive evidence shows that the actively metabolizing cells surrounding arterioles release vasoactive substances that cause vasodilation. This is termed the **metabolic theory of blood flow regulation.** These vasoactive substances, which are linked to tissue metabolism, ensure that the tissue is adequately supplied by oxygen and that products of metabolism (e.g., CO_2, H^+, lactic acid) are removed. Several substances have been implicated in metabolic regulation of blood flow. Their relative importance depends on the tissue in which they are formed as well as different conditions that might cause their release.

1. **Adenosine** is a potent vasodilator in most organs (although adenosine constricts renal vessels). It is formed by the action of 5'-nucleotidase, an enzyme that dephosphorylates cellular adenosine monophosphate (AMP). The AMP is derived from hydrolysis of intracellular adenosine triphosphate (ATP) and adenosine diphosphate (ADP). Adenosine formation increases during hypoxia and increased oxygen consumption, both of which lead to increased ATP hydrolysis. Small amounts of ATP hydrolysis can lead to large increases in adenosine formation because intracellular concentrations of ATP are about a thousand-fold greater than adenosine concentrations. Experimental evidence supports the idea that adenosine formation is a particularly important mechanism for regulating coronary blood flow when myocardial oxygen consumption increases or during hypoxic conditions.
2. **Inorganic phosphate** is released by the hydrolysis of adenine nucleotides (ATP, ADP, and AMP). Inorganic phosphate may have some vasodilatory activity in contracting skeletal muscle, but its importance is far less than that of adenosine, potassium, and nitric oxide in regulating skeletal muscle blood flow.
3. **Carbon dioxide** formation increases during states of increased oxidative metabolism. CO_2 concentrations in the tissue and vasculature can also increase when blood flow is reduced, which reduces the washout of CO_2. As a gas, CO_2 readily diffuses from parenchymal cells to the vascular smooth muscle of blood vessels, where it causes vasodilation. Considerable evidence indicates that CO_2 plays a significant role in regulating cerebral blood flow through the formation of H^+.
4. **Hydrogen ion** increases when CO_2 increases or during states of increased anaerobic metabolism (e.g., during ischemia or hypoxia) when acid metabolites such as lactic acid are produced. Increased H^+ causes local vasodilation, particularly in the cerebral circulation.
5. **Potassium ion** is released by contracting cardiac and skeletal muscle. Muscle contraction is initiated by membrane depolarization, which results from a cellular influx of Na^+ and an efflux of K^+. Normally, the Na^+/K^+-ATPase pump is able to restore the ionic gradients (see Chapter 2); however, the pump does not keep up with rapid depolarizations (i.e., there is a time lag) during muscle contractions, and a small amount of K^+ accumulates in the extracellular space. Small increases in extracellular K^+ around blood vessels cause hyperpolarization of the vascular smooth muscle cells, possibly by stimulating the electrogenic Na^+/K^+-ATPase pump and increasing K^+ conductance through potassium channels. Hyperpolarization leads to smooth muscle relaxation. Potassium ion appears to play a significant role in caus-

ing the increase in blood flow in contracting skeletal muscle.

6. **Oxygen** levels within the blood vessel and surrounding tissue are also important in local regulation of blood flow. Decreased tissue partial pressure of oxygen (pO_2) resulting from reduced oxygen supply or increased oxygen utilization by tissues causes vasodilation. Hypoxia-induced vasodilation may be direct (inadequate O_2 to sustain smooth muscle contraction) or indirect via the production of vasodilator metabolites (e.g., adenosine, lactic acid, H^+). Although hypoxia causes vasodilation in nearly all vascular beds, there is a notable exception—it causes vasoconstriction in the pulmonary circulation.
7. **Osmolarity** changes in the blood and in the tissue interstitium have been implicated in local blood flow regulation. It is well known that intra-arterial infusions of hyperosmolar solutions can produce vasodilation. The molecules making up the hyperosmolar solution need not be vasoactive. Tissue ischemia and increased metabolic activity raise the osmolarity of the tissue interstitial fluid and venous blood. Therefore, it has been suggested that nonspecific changes in osmolarity may play a role in the regulation of blood flow.

Several tissue factors involved in regulating blood flow are not directly coupled to tissue metabolism. These include paracrine hormones such as histamine, bradykinin, and products of arachidonic acid (eicosanoids). **Histamine,** released by tissue mast cells in response to injury, inflammation, and allergic responses, causes arteriolar vasodilation, venous constriction in some vascular beds, and increased capillary permeability. Both H_1 and H_2 histamine receptors are involved in the vascular effects of histamine. **Bradykinin** is formed from the action of kallikrein (a proteolytic enzyme) acting on alpha$_2$-globulin (kininogen), which is found in blood and tissues. Like histamine, bradykinin is a powerful dilator of arterioles. It acts on vascular bradykinin receptors, which stimulate nitric oxide formation by the vascular endothelium, thereby producing vasodilation. In addition, bradykinin stimulates prostacyclin formation, which produces vasodilation. One of the enzymes responsible for breaking down bradykinin is angiotensin-converting enzyme (ACE) (see Chapter 6, Fig. 6-10). Therefore, ACE inhibition not only decreases angiotensin II, it also increases bradykinin, which is believed to be partly responsible for the vasodilation accompanying ACE inhibition. **Arachidonic acid metabolites** such as prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2) are vasodilators, whereas other eicosanoids such as $PGF_{2\alpha}$, thromboxanes, and leukotrienes are generally vasoconstrictors. Drugs that block the formation of these eicosanoids (e.g., cyclo-oxygenase inhibitors such as aspirin or ibuprofen) alter vascular control by these substances.

Endothelial Factors

The vascular endothelium serves an important paracrine role in the regulation of smooth muscle tone and organ blood flow. As described in Chapter 3, the vascular endothelium produces vasoactive substances that have significant effects on vascular smooth muscle. Circulating (endocrine) and paracrine hormones, shearing forces, hypoxia, and many different drugs can stimulate the formation and release of endothelial substances (Fig. 7-2). Among their many actions, two of these substances, **nitric oxide** and **prostacyclin,** are powerful vasodilators, (see Nitric Oxide and Prostaglandins in Chapter 3 on CD). In contrast, **endothelin-1** is a powerful vasoconstrictor [see CD3 – endothelin]. Although all three of these endothelial-derived substances have important actions on the vascular smooth muscle, nitric oxide appears to be the most important in terms of regulating blood flow under normal physiologic conditions. If nitric oxide synthesis is inhibited pharmacologically using nitric oxide synthase (NOS) inhibitors, vasoconstriction occurs in most vascular beds. This demonstrates that there normally is a basal release of nitric oxide that inhibits vascular tone; there-

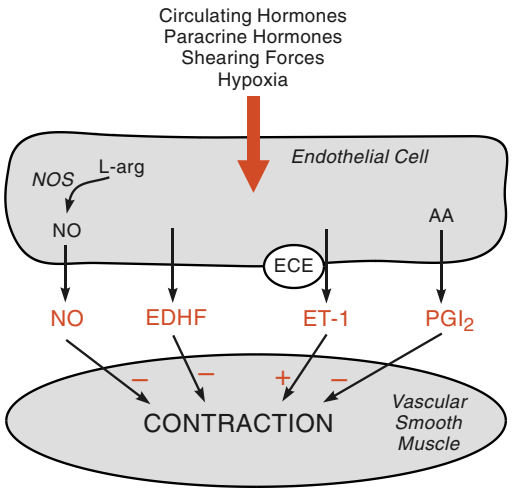

FIGURE 7-2 Endothelial-derived vasoactive factors. Nitric oxide (NO) formed by nitric oxide synthase (*NOS*) acting on L-arginine (*L-arg*), endothelial-derived hyperpolarizing factor (*EDHF*), and prostacyclin (PGI_2) derived from arachidonic acid (*AA*) inhibit (-) smooth muscle contraction and cause vasodilation. Endothelin-1 (*ET-1*) formed by endothelin-converting enzyme (*ECE*) causes smooth muscle contraction (+). The formation and release of these substances are influenced by circulating and paracrine hormones, shearing forces acting on the endothelium, hypoxia, and many different drugs.

fore, blocking nitric oxide formation leads to an increase in tone.

Nitric oxide is involved in what is termed **flow dependent vasodilation.** Experimental studies have shown that an increase in vessel flow (actually an increase in shearing forces acting on the vascular endothelium) stimulates endothelial nitric oxide production, which causes vasodilation. Flow-dependent vasodilation is particularly important as a mechanism for increasing coronary blood flow when cardiac activity and metabolism are increased. Impaired nitric oxide synthesis or decreased bioavailability, as occurs during coronary artery disease, limits the ability of coronary blood flow to increase when cardiac activity and oxygen demand are increased. Other disorders such as hypertension, cerebrovascular disease, and diabetes are associated with impaired endothelial control of vascular function as well.

Another endothelial factor is **endothelial-derived hyperpolarizing factor (EDHF).** Some substances (e.g., acetylcholine, bradykinin) that stimulate nitric oxide production stimulate EDHF as well. The identity of this factor is not known for certain, but its release causes smooth muscle hyperpolarization and relaxation.

Smooth Muscle (Myogenic) Mechanisms

Myogenic mechanisms originate within the smooth muscle of blood vessels, particularly in small arteries and arterioles. When the lumen of a blood vessel is suddenly expanded, as occurs when intravascular pressure is suddenly increased, the smooth muscle responds by contracting in order to restore the vessel diameter and resistance. Conversely, a reduction in intravascular pressure results in smooth muscle relaxation and vasodilation. Electrophysiologic studies have shown that vascular smooth muscle cells depolarize when stretched, leading to contraction.

Myogenic behavior has not been observed in all vascular beds, but it has been noted in the intestinal and renal circulations, and may be present to a small degree in skeletal muscle. It is difficult to evaluate myogenic mechanisms in vivo because changes in pressure are usually associated with changes in flow that trigger metabolic mechanisms, which usually dominate over myogenic mechanisms. For example, increasing venous pressure to a vascular bed should activate myogenic mechanisms to produce vasoconstriction because elevated venous pressures are transmitted back to the precapillary resistance vessels; however, the reduction in blood flow associated with the increase in venous pressure (which reduces perfusion pressure) activates tissue metabolic mechanisms that cause vasodilation. In most organs, conducting such an experiment usually results in vasodilation because the metabolic vasodilator response overrides the myogenic vasoconstrictor response, if present.

Extravascular Compression

Mechanical compressive forces can affect vascular resistance and blood flow within organs.

Sometimes this occurs during normal physiologic conditions; at other times, compressive forces can be the result of pathologic mechanisms. The pressure that distends the wall of a blood vessel is the transmural pressure (inside minus outside pressure). Therefore, if the pressure outside of the vessel increases, then the transmural pressure decreases. At very high extravascular pressures, a vessel can completely collapse. Therefore, veins, which have a relatively low intravascular pressure, are more likely to collapse when extravascular pressure is elevated; however, arteries can also become significantly compressed when extravascular pressure is elevated to very high levels.

Several examples of mechanical compression affecting organ blood flow exist. During cardiac systole or skeletal muscle contraction (particularly tetanic contractions), vascular resistance is greatly increased and blood flow is impeded by mechanical compression. Lung inflation and deflation alter pulmonary vascular transmural pressures (see Fig. 5-12) and thereby have substantial effects on pulmonary vascular resistance. Excessive distension of the gastrointestinal tract can increase vascular resistance to the point at which tissues become ischemic. Blood vessels in organs such as the brain or kidneys, which are surrounded by a rigid cranium or capsule, are particularly susceptible to increases in extravascular pressure that occur with edema, vascular hemorrhage (e.g., cerebral stroke), or the growth of a tumor.

Autoregulation of Blood Flow

Autoregulation *is the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure.* For example, if perfusion pressure is decreased to an organ by partial occlusion of the artery supplying the organ, blood flow will initially fall, then return toward normal levels over the next few minutes. This autoregulatory response occurs in isolated, perfused organs, which are not subject to neural or humoral influences. Therefore, it is a local or intrinsic response of the organ.

When perfusion pressure (arterial – venous pressure; $P_A - P_V$) initially decreases, blood flow (F) falls because of the following relationship between pressure, flow, and resistance (R):

$$F = \frac{(P_A - P_V)}{R}$$

The reductions in flow and perfusion pressure are thought to activate metabolic or myogenic mechanisms that cause arteriolar vasodilation and a fall in resistance (R). As resistance decreases, blood flow increases despite the presence of a reduced perfusion pressure. This autoregulatory response is shown in the left panel of Figure 7-3. For example, if perfusion pressure is reduced from 100 mm Hg to 70 mm Hg, it causes flow to decrease initially by approximately 30%. Over the next few minutes, however, flow begins to increase back toward control as the organ blood flow is autoregulated (red lines). Blood flow increases because vascular resistance falls as the resistance vessels dilate.

If the perfusion pressure to an organ is increased and decreased over a wide range of pressures and the steady-state autoregulatory flow response is measured, then the relationship between steady-state flow and perfusion pressure can be plotted as shown in the right panel of Figure 7-3. The red line represents the autoregulatory range in which flow changes relatively little despite a large change in perfusion pressure. The "flatness" of the autoregulation curve varies considerably among organs; the flatter the relationship, the better the autoregulation. Coronary, cerebral, and renal circulations show a high degree of autoregulation, whereas skeletal muscle and gastrointestinal circulations show only a moderate degree of autoregulation. The cutaneous circulation displays virtually no autoregulation.

Autoregulation has limits even in organs that display a high degree of autoregulation. When the perfusion pressure falls below 60–70 mm Hg in the cerebral and coronary circulations, the resistance vessels become maximally dilated and their ability to autoregulate is lost. Furthermore, at very high perfusion pressures (approximately 170 mm Hg in

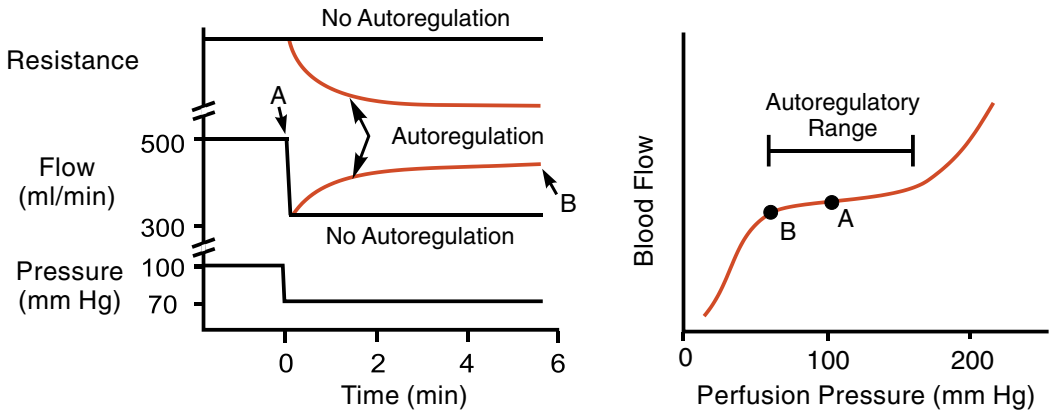

FIGURE 7-3 Autoregulation of blood flow. The left panel shows that decreasing perfusion pressure from 100 mm Hg to 70 mm Hg at point *A* results in a transient decrease in flow. If no autoregulation occurs, resistance remains unchanged and flow remains decreased. With autoregulation (*red line*), the initial fall in pressure leads to a decrease in vascular resistance, which causes flow to increase to a new steady-state level despite the reduced perfusion pressure (point *B*). The right panel shows steady-state, autoregulatory flows plotted against different perfusion pressures. Points *A* and *B* represent the control flow and autoregulatory steady-state flow, respectively, from the left panel. The autoregulatory range is the range of pressures over which flow shows little change. Below or above the autoregulatory range, flow changes are approximately proportional to the changes in perfusion pressure. The autoregulatory range as well as the flatness of the autoregulatory response curve varies among organs.

Fig. 7-3), the upper limit of the autoregulatory range is reached and the vessels undergo no further constriction with increases in perfusion pressure; therefore, flow increases as pressure increases. The autoregulatory response can be modulated by neurohumoral influences and disease states. For example, sympathetic stimulation and chronic hypertension can shift the cerebral autoregulatory range to the right as described later in this chapter.

Autoregulation may involve both metabolic and myogenic mechanisms. If the perfusion pressure to an organ is reduced, the initial fall in blood flow leads to a fall in tissue pO_2 and the accumulation of vasodilator metabolites. These changes cause the resistance vessels to dilate in an attempt to restore normal flow. A reduction in perfusion pressure may also be sensed by the smooth muscle in resistance vessels, which responds by relaxing (myogenic response), leading to an increase in flow.

Under what conditions does autoregulation occur, and why is it important? In hypotension caused by blood loss, despite baroreceptor reflexes that lead to constriction of much of the systemic vasculature, blood flow to the brain and myocardium will not decline appreciably (unless the arterial pressure falls below the autoregulatory range). This is because of the strong capacity of these organs to autoregulate and their ability to escape sympathetic vasoconstrictor influences. The autoregulatory response helps to ensure that these critical organs have an adequate blood flow and oxygen delivery even in the presence of systemic hypotension.

Other situations occur in which systemic arterial pressure does not change, but in which autoregulation is very important nevertheless. Autoregulation can occur when a distributing artery (e.g., coronary artery) to an organ becomes partially occluded. This arterial stenosis increases resistance and the pressure drop along the vessel length. This reduces pressure in small distal arteries and arterioles, which are the primary vessels for regulating blood flow within an organ. These resistance vessels dilate in response to the reduced pressure and blood flow caused by the upstream stenosis. This autoregulatory response helps to maintain normal blood flow in the presence of upstream stenosis, and it is particularly important in organs such as the brain and heart in which partial occlusion of large arteries can lead to significant reductions

PROBLEM 7-1

An experiment was conducted using an isolated perfused organ (e.g., intestinal segment) in which arterial and venous pressures were controlled while blood flow was measured. When venous pressure was suddenly raised from 0 mm Hg to 15 mm Hg while arterial pressure was maintained at 100 mm Hg, flow decreased by 25%. Calculate the percentage change that occurred in vascular resistance in response to venous pressure elevation. Discuss the involvement of metabolic and myogenic mechanisms in this response.

The initial perfusion pressure was 100 mm Hg (mean arterial pressure minus venous pressure). Elevating the venous pressure to 15 mm Hg reduced the perfusion pressure to 85 mm Hg. According to the equation relating blood flow, perfusion pressure and vascular resistance ($F = \Delta P/R$), flow would decrease by 15% with a 15% decrease in perfusion pressure (assuming that resistance does not change). However, in this case, flow decreased by 25% indicating that resistance increased by 13.3% ($R = \Delta P/F$). The metabolic theory for autoregulation states that as perfusion pressure and flow are reduced, an accumulation of vasodilator metabolites decreases resistance in an attempt to restore flow; however, resistance did not decrease in this experiment. The myogenic theory states that increased transmural pressure causes vascular smooth muscle to contract, thereby increasing resistance and decreasing flow. Increasing venous pressure in this experiment increased the transmural pressure in arterioles, causing them to constrict and increase their resistance. Therefore, increasing venous pressure produces opposite and competing responses between these two mechanisms. Because vascular resistance increased in this experiment, we can conclude that the myogenic (vasoconstrictor) mechanism was dominant over the metabolic (vasodilator) mechanism. These results have been observed experimentally in organs such as the intestine.

in oxygen delivery, thereby leading to tissue hypoxia and organ dysfunction.

Reactive and Active Hyperemia

Reactive hyperemia *is the transient increase in organ blood flow that occurs following a brief period of ischemia, usually produced by temporary arterial occlusion.* Figure 7-4 shows the effects of a 2-minute arterial occlusion on blood flow. During the occlusion period, blood flow goes to zero. When the occlusion is released, blood flow rapidly increases above normal levels (hyperemia) that lasts for several minutes. In most tissues, experiments have suggested that the hyperemia occurs because during the occlusion period, tissue hypoxia and a build-up of vasoactive metabolites dilate arterioles and decrease vascular resistance. When the occlusion is released and perfusion pressure is restored, flow becomes elevated because of the reduced vascular resistance. During the hyperemia, oxygen becomes replenished and vasodilator metabolites are washed out of the tissue, causing the resistance vessels to regain their normal

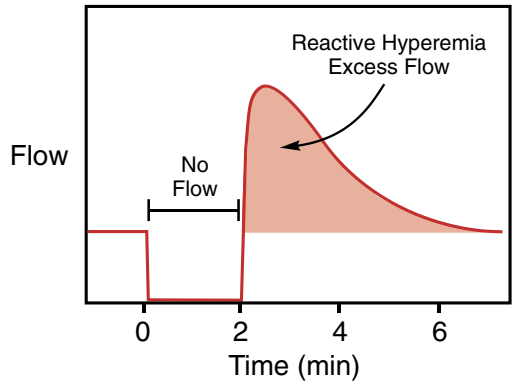

FIGURE 7-4 Reactive hyperemia. Arterial occlusion (ischemia) followed by reperfusion results in a transient increase in blood flow (reactive hyperemia). The magnitude and duration of the reactive hyperemia are directly related to the duration of ischemia.

vascular tone and thereby return flow to normal levels. The longer the period of occlusion, the greater the metabolic stimulus for vasodilation leading to increases in peak flow and duration of hyperemia. Maximal vasodilation, as indicated by a maximal peak hyperemic flow, may occur following less than one minute of complete arterial occlusion, or it may require several minutes of occlusion depending on the vascular bed and its metabolic activity. For example, in the beating heart (high metabolic activity), maximal reactive hyperemic responses are seen with coronary occlusions of less than one minute, whereas in resting skeletal muscle (low metabolic activity), several minutes of ischemia are necessary to elicit a maximal vasodilator response. Myogenic mechanisms may also contribute to reactive hyperemia in some tissues because arterial occlusion decreases the pressure in arterioles, which can lead to myogenic-mediated vasodilation.

Several examples of reactive hyperemia exist. The application of a tourniquet to a limb, and then its removal, results in reactive hyperemia. During surgery, arterial vessels are often clamped for a period of time; release of the arterial clamp results in reactive hyperemia. Transient coronary artery occlusions (e.g., coronary vasospasm) result in subsequent reactive hyperemia within the myocardium supplied by the coronary vessel.

Active hyperemia *is the increase in organ blood flow that is associated with increased metabolic activity of an organ or tissue.* With increased metabolic activity, vascular resistance decreases owing to vasodilation and vascular recruitment (particularly in skeletal muscle). Active hyperemia occurs during muscle contraction (also termed **exercise** or **functional hyperemia**), increased cardiac activity, increased mental activity, and increased gastrointestinal activity during food absorption.

In Figure 7-5, the left panel shows the effects of increasing tissue metabolism for 2 minutes on mean blood flow in a rhythmically contracting skeletal muscle. Within seconds of initiating contraction and the increase in metabolic activity, blood flow increases. The vasodilation is thought to be owing to a combination of tissue hypoxia and the generation of vasodilator metabolites such as potassium ion, carbon dioxide, nitric oxide, and adenosine. This increased blood flow (i.e., hyperemia) is maintained throughout the period of increased metabolic activity and then subsides as normal metabolism is restored. The amplitude of the active hyperemia is closely related to the increase in metabolic activity (e.g., oxygen consumption) as shown in the right panel. At high levels of metabolic activity, the vasculature becomes maximally dilated, resulting in a maximal increase in blood flow. Active hyperemia is important because it increases oxy-

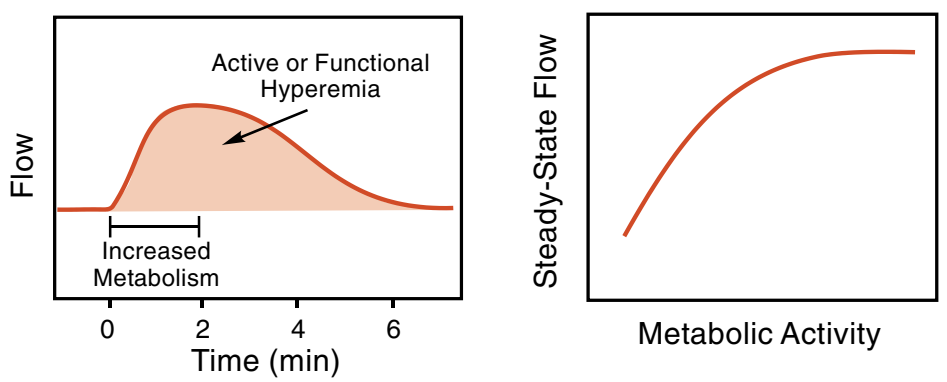

FIGURE 7-5 Active hyperemia. The left panel shows that increasing metabolism for 2 minutes transiently increases blood flow (active or functional hyperemia). The right panel shows that the steady-state increase in blood flow during active hyperemia is directly related to the increase in metabolic activity until the vessels become maximally dilated and flow can no longer increase.

gen delivery to tissues at a time of increased oxygen demand. Furthermore, the increased blood flow enhances the removal of metabolic waste products from the tissue.

The vasodilatory capacity during active hyperemia differs considerably among organs. In skeletal muscle, blood flow can increase more than twenty- to fifty-fold during exercise. Cerebral blood flow, in contrast, increases no more than two-fold at maximal metabolic activity. The reason for this difference is that resting skeletal muscle has a high degree of vascular tone in contrast to the cerebral circulation, which has a relatively low degree of vascular tone because of its higher metabolic rate under basal conditions.

SPECIAL CIRCULATIONS

Coronary Circulation

The two major branches of the coronary circulation are the left main and right main coronary arteries (Fig. 7-6). These vessels arise from coronary ostia, which are small openings in the wall of the ascending aorta just distal to the aortic valve. The **left main coronary artery** is relatively short in length (~1 cm). After coursing behind the pulmonary artery trunk, it divides into the **left anterior descending artery,** which travels along the interventricular groove on the anterior surface of the heart, and the **circumflex artery,** which travels posteriorly along the groove between the left atrium and ventricle. These branches of the left coronary artery supply blood primarily to the left ventricle and atrium. The **right main coronary artery** travels between the right atrium and ventricle (left atrioventricular groove) toward the posterior regions of the heart. This vessel and its branches serve the right ventricle and atrium, and in most individuals, the inferoposterior region of the left ventricle. Significant variation is possible among individuals in the anatomical arrangement and distribution of flow by the coronary vessels.

The major coronary vessels lie on the epicardial surface of the heart and serve as low-resistance distribution vessels. These

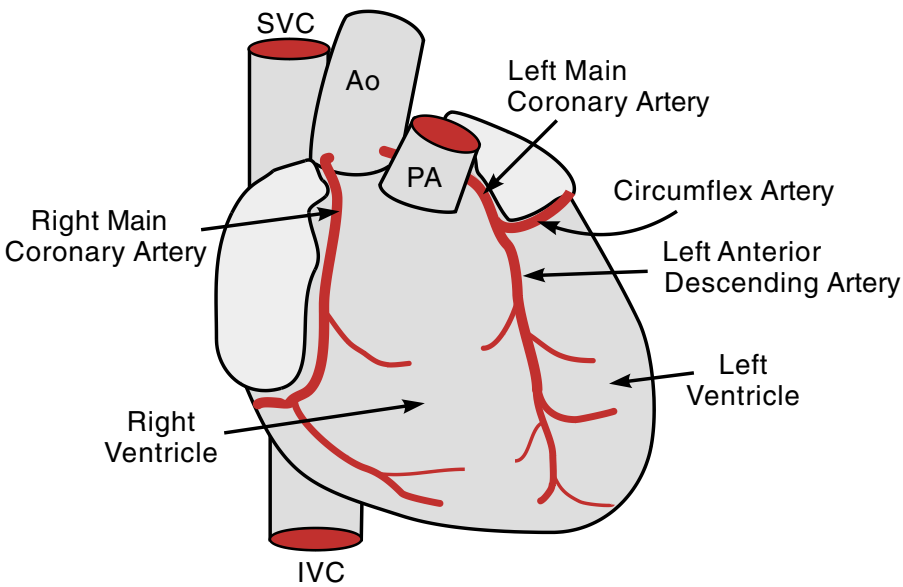

FIGURE 7-6 Anterior view of the heart showing the major coronary arteries. The left main artery arises from the aorta (*Ao*) just distal to the aortic valve, travels behind the pulmonary artery (*PA*), and then branches into the circumflex artery (courses along the left atrioventricular groove) and left anterior descending artery (courses along the interventricular groove), both of which primarily supply blood to the left ventricle. The right coronary artery arises from the aorta and travels between the right atrium and ventricle toward the posterior regions of the heart to supply the right ventricle and atrium and the inferoposterior wall of the left ventricle. *SVC,* superior vena cava; *IVC,* inferior vena cava.

epicardial arteries give off smaller branches that dive into the myocardium and become the microvascular resistance vessels that regulate coronary blood flow. The resistance vessels give rise to a dense capillary network so that each cardiac myocyte is closely associated with several capillaries. The high capillary-to-fiber density ensures short diffusion distances to maximize oxygen transport into the cells and removal of metabolic waste products (e.g., CO_2, H^+) (see Chapter 8).

Coronary veins are located adjacent to coronary arteries. These veins drain into the **coronary sinus** located on the posterior aspect of the heart. Blood flow from the coronary sinus empties into the right atrium. Some drainage also occurs directly into the cardiac chambers through the anterior cardiac veins and **thebesian vessels.**

Coronary blood flow is not steady as in most other organs. When flow is measured within a coronary artery, it is found to decrease during cardiac systole and increase during diastole (Fig. 7-7). Therefore, *most of the blood flow to the myocardium occurs during diastole.* The reason that coronary flow is influenced by the cardiac cycle is that during systole, the contraction of the myocardium compresses the microvasculature within the ventricular wall, thereby increasing resistance and decreasing flow. During systole, blood flow is reduced to the greatest extent within the innermost regions of the ventricular wall (i.e., in the subendocardium) because this is where the compressive forces are greatest. (This results in the subendocardial regions being more susceptible to ischemic injury when coronary artery disease or reduced aortic pressure is present.) As the ventricle begins to relax in early diastole, the compressive forces are removed and blood flow is permitted to increase. Blood flow reaches a peak in early diastole and then falls passively as the aortic pressure falls toward its diastolic value. Therefore, it is the aortic pressure during diastole that is most crucial for perfusing the coronaries. This explains why increases in heart rate can reduce coronary perfusion. At high heart rates, the length of diastole is greatly shortened, which reduces the time for coronary perfusion. This is not a problem when the coronary arteries are normal, because they dilate with increased heart rate and metabolism; however, if the coronaries are diseased and their vasodilator reserve is limited, increases in heart rate can limit coronary flow and lead to myocardial ischemia and anginal pain.

The mechanical forces affecting coronary flow are greatest within the left ventricle because this chamber develops pressures that are several-fold greater than those developed by

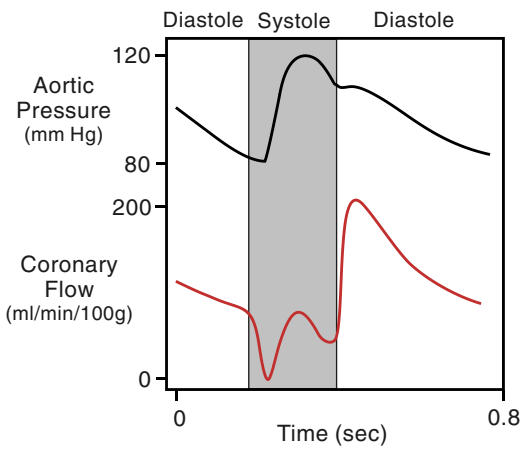

FIGURE 7-7 Pulsatile nature of coronary blood flow measured in the left coronary artery. Flow is lower during systole because of mechanical compression of intramuscular coronary vessels. Flow is maximal early in diastole, and then it falls as aortic pressure declines.

the right ventricle. The right ventricle, and to a lesser extent the atria, show some effects of contraction and relaxation on blood flow within their musculature, but it is much less apparent than that observed in the left ventricle.

Mean coronary blood flow (averaged over several cardiac cycles) can range from 80 mL/min per 100 g of tissue at resting heart rates to over 400 mL/min per 100 g during exercise (see Table 7-1). Therefore, the coronary vasculature normally has a relatively high vasodilator reserve capacity.

Coronary blood flow is primarily regulated by tissue metabolism. Adenosine has been shown to be important in dilating the coronary vessels when the myocardium becomes hypoxic or when cardiac metabolism increases during increased cardiac work. Experimental studies have shown that inhibiting adenosine formation, enhancing its breakdown to inosine, or blocking vascular adenosine receptors impairs coronary vasodilation under these conditions. In addition, nitric oxide has been shown to be important in coronary vessels, particularly in producing flow-dependent vasodilation.

Coronary vessels are innervated by both sympathetic and parasympathetic nerves. Unlike most other vascular beds, activation of sympathetic nerves to the heart causes only transient vasoconstriction (α_1-adrenoceptor mediated) followed by vasodilation. The vasodilation occurs because sympathetic activation of the heart also increases heart rate and inotropy through β_1-adrenoceptors, which leads to the production of vasodilator metabolites that inhibit the vasoconstrictor response and cause vasodilation. This is termed **functional sympatholysis.** If β_1-adrenoceptors are blocked experimentally, sympathetic stimulation of the heart causes coronary vasoconstriction. Parasympathetic stimulation of the heart (i.e., vagal nerve activation) elicits modest coronary vasodilation owing to the direct effects of released acetylcholine on the coronaries. However, if parasympathetic activation of the heart results in a significant decrease in myocardial oxygen demand, local metabolic mechanisms increase coronary vascular tone (i.e., cause vasoconstriction). Therefore, parasympathetic activation of the heart generally results in a decrease in coronary blood flow, although the direct effect of parasympathetic stimulation of the coronary vessels is vasodilation.

Coronary blood flow is crucial for the normal function of the heart. Because of the high oxygen consumption of the beating heart (see Chapter 4) and the fact that the heart relies on oxidative metabolism (see Chapter 3), coronary blood flow (oxygen delivery) and the metabolic activity of the heart need to be tightly coupled. This is all the more important because, as discussed in Chapter 4, the beating heart extracts more than half of the oxygen from the arterial blood; therefore, there is relatively little oxygen extraction reserve. In coronary artery disease, chronic narrowing of the vessels or impaired vascular function reduces maximal coronary blood flow (i.e., there is reduced vasodilator reserve). When this occurs, coronary flow fails to increase adequately as myocardial oxygen demands increase (Fig. 7-8). This leads to cardiac hypoxia and impaired contractile function.

The relationship between coronary blood flow and the metabolic demand of the heart is often discussed in terms of the myocardial **oxygen supply/demand ratio.** The oxygen supply is the amount of oxygen delivered to the myocardium in the arterial blood, which is the product of the coronary blood flow and

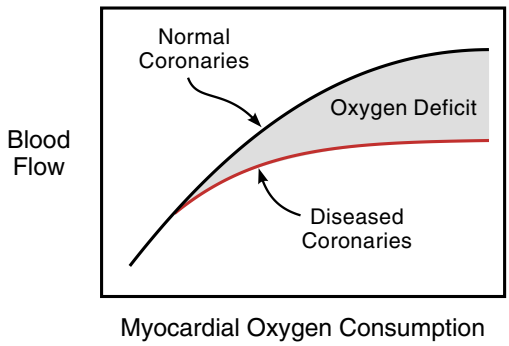

FIGURE 7-8 Relationship between coronary blood flow and myocardial oxygen consumption. Coronary blood flow increases as myocardial oxygen consumption increases. However, if the coronary vessels are diseased and have increased resistance owing to stenosis, blood flow (and therefore oxygen delivery) will be limited at higher oxygen consumptions leading to an oxygen deficit and myocardial hypoxia.

CASE 7-1

A patient with known coronary artery disease (multiple vessel stenosis) is also hypertensive. Explain why blood pressure-lowering drugs that produce reflex tachycardia should be not be used in such a patient.

It is important to control arterial pressure in patients with coronary artery disease because hypertension increases ventricular afterload and myocardial oxygen demand. However, it is important to lower arterial pressure using drugs that do not cause a reflex tachycardia for two reasons. First, reflex tachycardia (baroreceptor-mediated) increases myocardial oxygen demand and offsets the beneficial effects of reducing afterload (see Chapter 4). Second, tachycardia further impairs coronary perfusion because the duration of diastole relative to systole decreases at elevated heart rates. This reduces the time available for coronary perfusion during diastole, which is the time when the greatest amount of coronary perfusion occurs. It is common in clinical practice to give either a β-blocker or calcium-channel blocker to a patient with both coronary artery disease and hypertension, because both types of drugs lower pressure and prevent reflex tachycardia.

arterial oxygen content. If blood flow is in the units of mL blood/min and arterial oxygen content is expressed in mL O_2/mL blood, oxygen delivery has the units of mL O_2/min. The oxygen demand of the heart is the myocardial oxygen consumption, which is the product of coronary blood flow and the difference between the arterial and venous oxygen contents. A decrease in the oxygen supply/demand ratio causes tissue hypoxia, which can result in chest pain (**angina pectoris**) (see Angina on CD). This can occur by a decrease in oxygen supply (decreased coronary blood flow or arterial oxygen content), an increase in myocardial oxygen consumption, or a combination of the two. One of the therapeutic goals for people who have coronary artery disease and anginal pain is to increase the oxygen supply/demand ratio either by improving coronary flow (e.g., coronary bypass grafts or coronary stent placement) or by decreasing myocardial oxygen consumption by reducing heart rate, inotropy, and afterload (see Chapter 4).

Coronary artery disease is a leading cause of death. Both structural and functional changes occur when coronary arteries become diseased. Atherosclerotic processes decrease the lumen diameter, causing stenosis. This commonly occurs in the large epicardial arteries, although the disease also afflicts small vessels. The large coronary arteries ordinarily represent only a very small fraction of total coronary vascular resistance. Therefore, stenosis in these vessels needs to exceed a 60% to 70% reduction in lumen diameter (i.e., exceed the critical stenosis) to have significant effects on resting blood flow and maximal flow capacity (see Chapter 5 and Stenosis on CD).

In addition to narrowing the lumen and increasing resistance to flow, atherosclerosis causes endothelial damage and dysfunction. This leads to reduced nitric oxide and prostacyclin formation, which can precipitate coronary vasospasm and thrombus formation, leading to increased vascular resistance and decreased flow. Loss of these endothelial factors impairs vasodilation, which decreases the vasodilator reserve capacity. When coronary flow is compromised by coronary artery disease either at rest or during times of increased metabolic demand (e.g., during exercise), the myocardium becomes hypoxic, which can impair mechanical function, precipitate arrhythmias, and produce angina.

When coronary oxygen delivery is limited by disease, collateral vessels can play an important adjunct role in supplying oxygen to the heart. Conditions of chronic stress (e.g., chronic hypoxia or exercise training) can cause

new blood vessels to form by **angiogenesis.** Collateralization increases myocardial blood supply by increasing the number of parallel vessels, thereby reducing vascular resistance within the myocardium. This helps to supply blood flow to ischemic regions caused by vascular stenosis or thrombosis.

Cerebral Circulation

The brain is a highly oxidative organ that consumes almost 20% of resting total-body oxygen consumption. To deliver adequate oxygen, the cerebral blood flow needs to be relatively high, about 50–60 mL/min per 100 g tissue weight (see Table 7-1). Although the brain represents only about 2% of body weight, it receives approximately 14% of the cardiac output.

The brain circulation is supplied by four principal arteries: the left and right **carotid arteries** and the left and right **vertebral arteries** (Fig. 7-9). The vertebral arteries join together on the ventral surface of the pons to form the **basilar artery,** which then travels up the brainstem to join the carotid arteries through interconnecting arteries, forming the **Circle of Willis.** Arterial vessels originating from the vertebral and basilar arteries as well as the Circle of Willis distribute blood flow to different regions of the brain. This interconnecting network of arterial vessels at the brainstem provides a safety mechanism for cerebral perfusion. If, for example, a carotid artery becomes partly occluded and flow is reduced through that artery, increased flow through the other interconnecting arteries can help improve perfusion of the affected portion of the brain.

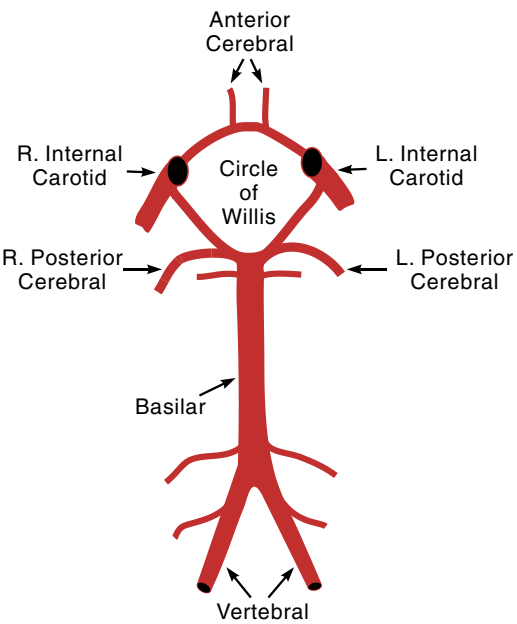

FIGURE 7-9 Major cerebral arteries perfusing the brain. This view is of the ventral surface of the brain and brainstem. The carotid and vertebral arteries are the major source of cerebral blood flow and are interconnected through the Circle of Willis and basilar artery. *L,* left; *R,* right.

Because the cerebral circulation is located within a rigid cranium, changes in intracranial pressure can have significant effects on cerebral perfusion (Fig. 7-10). For example, cerebral vascular hemorrhage, brain edema caused by cerebral trauma, or tumor growth can increase intracranial pressure, which can lead to vascular compression and reduced cerebral blood flow. The venous vessels are most susceptible to compression because of their low intravascular pressure. Because intracranial pressure is normally greater than the venous pressure outside the cranium and the venous vessels can easily collapse, the effective perfusion pressure of the brain is not the mean arterial pressure minus central venous pressure, but rather the mean arterial pressure minus the intracranial pressure. Intracranial pressure normally ranges from 0–10 mm Hg; however, if it becomes elevated (e.g., 20 mm Hg or greater), and especially if there is systemic hypotension, the effective cerebral perfusion pressure and blood flow can be significantly reduced.

Like the coronary circulation, the cerebral blood flow is tightly coupled to oxygen consumption. Therefore, cerebral blood flow increases (active or functional hyperemia) when neuronal activity and oxygen consumption are increased. Changes in neuronal activity in specific brain regions lead to increases in blood flow to those regions.

The brain shows excellent autoregulation between mean arterial pressures of about 60 mm Hg and 130 mm Hg (Fig. 7-11). This is

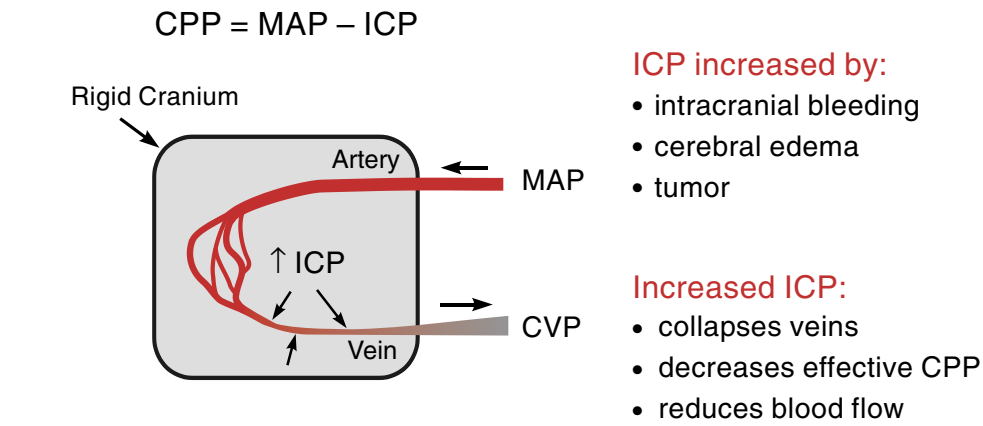

FIGURE 7-10 Effects of intracranial pressure (*ICP*) on cerebral blood flow. ICP is the pressure within the rigid cranium (gray area of figure). Increased ICP decreases transmural pressure (inside minus outside pressure) of blood vessels (particularly veins), which can cause vascular collapse, increased resistance, and decreased blood flow. Therefore, the effective cerebral perfusion pressure (*CPP*) is mean arterial pressure (*MAP*) minus ICP. *CVP,* central venous pressure.

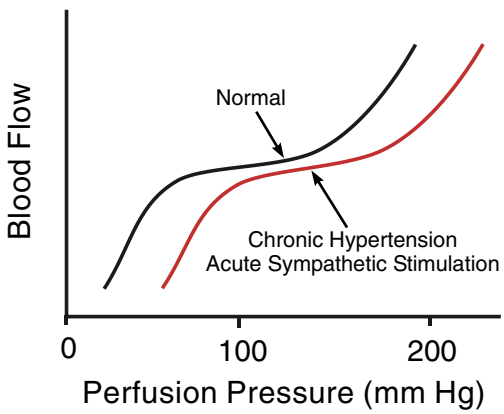

FIGURE 7-11 Autoregulation of cerebral blood flow. Cerebral blood flow shows excellent autoregulation between mean arterial pressures of 60 mm Hg and 130 mm Hg. The autoregulatory curve shifts to the right with chronic hypertension or acute sympathetic activation. This shift helps to protect the brain from the damaging effects of elevated pressure.

important because cerebral function relies on a steady supply of oxygen and cannot afford to be subjected to a reduction in flow caused by a fall in arterial pressure. If mean arterial pressure falls below 60 mm Hg, cerebral perfusion becomes impaired, which results in depressed neuronal function, mental confusion, and loss of consciousness. When arterial pressure is above the autoregulatory range (e.g., in a hypertensive crisis), blood flow and pressures within the cerebral microcirculation increase. This may cause endothelial and vascular damage, disruption of the blood-brain barrier, and hemorrhagic stroke. With chronic hypertension, the autoregulatory curve shifts to the right (see Fig. 7-11), which helps to protect the brain at higher arterial pressures. However, this rightward shift then makes the brain more susceptible to reduced perfusion when arterial pressure falls below the lower end of the rightward-shifted autoregulatory range.

Metabolic mechanisms play a dominant role in the control of cerebral blood flow. Considerable evidence indicates that changes in carbon dioxide are important for coupling tissue metabolism and blood flow. Increased oxidative metabolism increases carbon dioxide production, which causes vasodilation. It is thought that the carbon dioxide diffuses into the cerebrospinal fluid, where hydrogen ion is formed by the action of carbonic anhydrase; the hydrogen ion then causes vasodilation. In addition, carbon dioxide and hydrogen ion increase when perfusion is reduced because of impaired washout of carbon dioxide. Adenosine, nitric oxide, potassium ion, and myogenic mechanisms have also been implicated in the local regulation of cerebral blood flow.

Cerebral blood flow is strongly influenced by the partial pressure of carbon dioxide and, to a lesser extent, oxygen in the arterial blood (Fig. 7-12). Cerebral blood flow is highly sensitive to small changes in arterial partial pressure of CO_2 (pCO_2) from its normal value of about 40 mm Hg, with increased pCO_2 (hypercapnea) causing pronounced vasodilation and decreased pCO_2 (hypocapnea) causing vasoconstriction. Hydrogen ion appears to be responsible for the changes in vascular resistance when changes occur in arterial pCO_2. The importance of CO_2 in regulating cerebral blood flow can be demonstrated when a person hyperventilates, which decreases arterial pCO_2. When this occurs, a person becomes "light headed" as the reduced pCO_2 causes cerebral blood flow to decrease. Severe arterial hypoxia (hypoxemia) increases cerebral blood flow. Arterial pO_2 is normally about 95–100 mm Hg. If the pO_2 falls below 50 mm Hg (severe arterial hypoxia), it elicits a strong vasodilator response in the brain, which helps to maintain oxygen delivery despite the reduction in arterial oxygen content. As described in Chapter 6, decreased arterial pO_2 and increased pCO_2 stimulate chemoreceptors, which activate sympathetic efferents to the systemic vasculature to cause vasoconstriction; however, the direct effects of hypoxia and hypercapnea override the weak effects of sympathetic activation in the brain so that cerebral vasodilation occurs and oxygen delivery is enhanced.

Although sympathetic nerves innervate larger cerebral vessels, activation of these nerves has relatively little influence on cerebral blood flow. Maximal sympathetic activation increases cerebral vascular resistance by no more than 20% to 30%, in contrast to an approximately 500% increase occurring in skeletal muscle. The reason, in part, for the weak sympathetic response by the cerebral vasculature is that metabolic mechanisms are dominant in regulating flow; therefore, functional sympatholysis occurs during sympathetic activation. This is crucial to preserve normal brain function; otherwise, every time a person stands up or exercises, both of which cause sympathetic activation, cerebral perfusion would decrease. Therefore, baroreceptor reflexes have little influence on cerebral blood flow. Sympathetic activation shifts the autoregulatory curve to the right, similar to what occurs with chronic hypertension.

In recent years, we have learned that neuropeptides originating in the brain significantly influence cerebral vascular tone, and they may be involved in producing headaches (e.g., migraine and cluster headaches) and

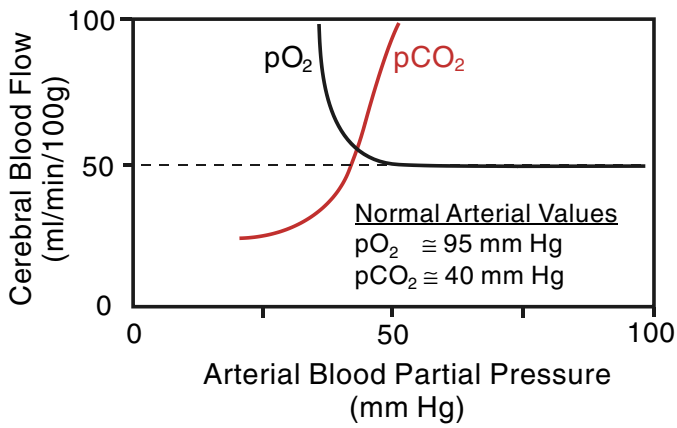

FIGURE 7-12 Effects of arterial partial pressure of oxygen and carbon dioxide on cerebral blood flow. An arterial partial pressure of oxygen (pO_2) of less than 50 mm Hg (normal value is about 95 mm Hg) causes cerebral vasodilation and increased flow. A reduction in arterial partial pressure of carbon dioxide (pCO_2) below its normal value of 40 mm Hg decreases flow, whereas pCO_2 values greater than 40 mm Hg increase flow. Therefore, cerebral blood flow is more sensitive to changes from normal arterial pCO_2 values than from normal arterial pO_2 values.

cerebral vascular vasospasm during strokes. Parasympathetic cholinergic fibers innervating the cerebral vasculature release nitric oxide and **vasoactive intestinal polypeptide (VIP).** These substances, along with acetylcholine, produce localized vasodilation. Other nerves appear to release the local vasodilators **calcitonin gene-related peptide (CGRP)** and **substance-P.** Sympathetic adrenergic nerves can release **neuropeptide-Y (NPY)** in addition to norepinephrine, which causes localized vasoconstriction.

Skeletal Muscle Circulation

The primary function of skeletal muscle is to contract and generate mechanical forces to provide support to the skeleton and produce movement of joints. This mechanical activity consumes large amounts of energy and therefore requires delivery of considerable amounts of oxygen and substrates, as well as the efficient removal of metabolic waste products. Both oxygen delivery and metabolic waste removal functions are performed by the circulation.

The circulation within skeletal muscle is highly organized. Arterioles give rise to capillaries that generally run parallel to the muscle fibers, with each fiber surrounded by three to four capillaries. When the muscle is not contracting, relatively little oxygen is required and only about one-fourth of the capillaries are perfused. In contrast, during muscle contraction and active hyperemia, all the anatomical capillaries may be perfused, which increases the number of flowing capillaries around each muscle fiber (termed **capillary recruitment**). This anatomical arrangement of capillaries and the ability to recruit capillaries decreases diffusion distances, leading to an efficient exchange of gasses and molecules between the blood and the myocytes, particularly under conditions of high oxygen demand.

In resting humans, almost 20% of cardiac output is delivered to skeletal muscle. This large cardiac output to muscle occurs not because blood flow is exceptionally high in resting muscle, but because skeletal muscle makes up about 40% of the body mass. In the resting, noncontracting state, muscle blood flow is about 3 mL/min per 100 g. This resting flow is much less than that found in organs such as the brain and kidneys, in which "resting" flows are about 55 and 400 mL/min per 100 g, respectively.

When muscles contract during exercise, blood flow can increase more than twenty-fold. If muscle contraction is occurring during whole-body exercise (e.g., running), more than 80% of cardiac output can be directed to the contracting muscles. Therefore, skeletal muscle has a very large flow reserve (or capacity) relative to its blood flow at rest, indicating that the vasculature in resting muscle has a high degree of tone (see Table 7-1). This resting tone is brought about by the interplay between vasoconstrictor (e.g., sympathetic adrenergic and myogenic influences) and vasodilator influences (e.g., nitric oxide production, and tissue metabolites). In the resting state, the vasoconstrictor influences dominate, whereas during muscle contraction, vasodilator influences dominate to increase oxygen delivery to the contracting muscle fibers and remove metabolic waste products that accumulate.

The blood flow response to skeletal muscle contraction depends on the type of contraction. With rhythmic or phasic contraction of muscle (Fig. 7-13, top panel), as occurs during normal locomotory activity, mean blood flow increases during the period of muscle activity. However, if blood flow is measured without filtering or averaging, the flow is found to be phasic—flow decreases during contraction and increases during relaxation phases of the muscle activity because of mechanical compression of the vessels. In contrast, a sustained muscle contraction (e.g., lifting and holding a heavy weight) decreases mean blood flow during the period of contraction, followed by a postcontraction hyperemic response when the contraction ceases (see Fig. 7-13, bottom panel).

The precise mechanisms responsible for dilating skeletal muscle vasculature during contraction are not clearly understood. However, considerable evidence indicates that increases in interstitial adenosine and K^+

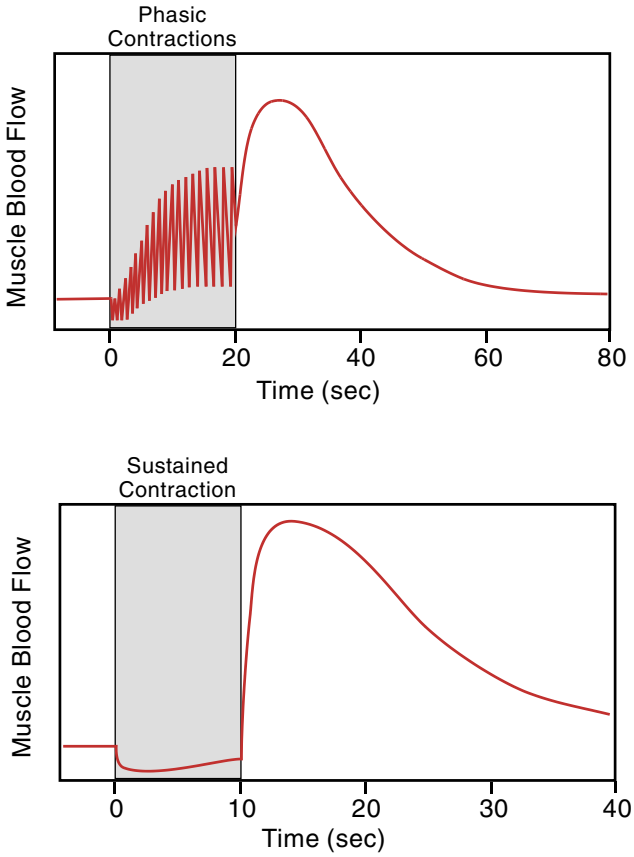

FIGURE 7-13 Skeletal muscle active hyperemia following phasic and sustained (tetanic) contractions. The top panel shows that phasic contractions cause flow to decrease during contraction and increase during relaxation, although the net effect is an increase in flow during contraction. When contractions cease, a further increase in flow occurs because mechanical compression of the vasculature is removed. The bottom panel shows that sustained, tetanic contractions generate high intramuscular forces that compress the vasculature and reduce flow. When contraction ceases, a large hyperemia follows.

during muscle contraction contribute to the vasodilation. Tissue hypoxia, particularly when blood flow is mechanically compromised during forceful sustained muscle contractions, may provide a signal for vasodilation. Evidence also exists that increased endothelial release of nitric oxide contributes to the dilation of the vasculature. Other suggested mechanisms include increased levels of lactic acid, CO_2, and H^+ and hyperosmolarity. Another mechanism that facilitates blood flow during coordinated contractions of groups of muscles (as occurs during normal physical activity such as running) is the skeletal muscle pump (see Chapter 5). Regardless of the mechanisms involved in producing active hyperemia, the outcome is that there is a close correlation between the increase in oxygen consumption and the increase in blood flow during muscle contraction.

Skeletal muscle vasculature is innervated primarily by sympathetic adrenergic fibers. The norepinephrine released by these fibers binds to α-adrenoceptors and causes vasoconstriction. Under resting conditions, a significant portion of the vascular tone is generated by sympathetic activity, so that if a resting muscle is suddenly denervated or the α-adrenoceptors are blocked pharmacologically by a drug such as phentolamine, blood flow will transiently increase two to three-fold until local regulatory mechanisms reestablish a

new steady-state flow. Activation of the sympathetic adrenergic nervous system (e.g., baroreceptor reflex in response to hypovolemia) can dramatically reduce blood flow in resting muscle. When this reduction in blood flow occurs, the muscle extracts more oxygen (the arterial-venous oxygen difference increases) and activates anaerobic pathways for ATP production. However, prolonged hypoperfusion of muscle caused by intense sympathetic activation eventually leads to vasodilator mechanisms dominating over the sympathetic vasoconstriction, leading to **sympathetic escape** and partial restoration of blood flow.

Recent evidence suggests that increased muscle blood flow seen under some conditions of generalized sympathetic activation (e.g., during exercise or mental stress) may involve circulating catecholamines stimulating β_2-adrenoceptors and locally released nitric oxide.

Evidence exists, at least in nonprimate species such as cats and dogs, for sympathetic cholinergic innervation of skeletal muscle resistance vessels. The neurotransmitter for these fibers is acetylcholine, which binds to muscarinic receptors to produce vasodilation. This branch of the autonomic nervous system has little or no influence on blood flow under resting conditions; however, activation of these fibers in anticipation of exercise and during exercise can contribute to the increase in blood flow associated with exercise. There is no convincing evidence, however, for similar active, neurogenic vasodilator mechanisms existing in humans.

Cutaneous Circulation

The nutrient and oxygen requirements of the skin are quite low relative to other organs; therefore, cutaneous blood flow does not primarily serve a metabolic support role. Instead, the primary role of blood flow to the skin is to allow heat to be exchanged between the blood and the environment to help regulate body temperature. Therefore, the cutaneous circulation is under the control of hypothalamic thermoregulatory centers that adjust the sympathetic outflow to the cutaneous vasculature. At normal body and ambient temperatures, the skin circulation is subjected to a high degree of sympathetic adrenergic tone. If core temperature begins to rise (e.g., during physical exertion), the hypothalamus decreases sympathetic outflow to the skin, which causes cutaneous vasodilation and increased blood flow. This enables more warm blood to circulate in the sub-epidermal layer of the skin so that more heat energy can be conducted through the skin to the environment. Conversely, if core temperature decreases, the hypothalamus attempts to retain heat by increasing sympathetic outflow to the skin, which decreases cutaneous blood flow and prevents heat loss to the environment. The sympathetic control of the cutaneous circulation is so powerful that cutaneous blood flow can range from more than 30% of cardiac output to less than 1%.

The microvascular network that supplies skin is unique among organs. Small arteries arising from the subcutaneous tissues give rise to arterioles that penetrate into the dermis and give rise to capillaries that loop underneath the epidermis (Fig. 7-14). Blood flows from these capillary loops into venules and then into an extensive, interconnecting **venous plexus.** Most of the cutaneous blood volume is found in the venous plexus, which is a prominent feature in the nose, lips, ears, toes, and fingers—especially the fingertips. The blood in the venous plexus is also responsible for skin coloration in lightly pigmented individuals. The venous plexus receives blood directly from the small subcutaneous arteries through special interconnecting vessels called **arteriovenous (AV) anastomoses.**

The resistance vessels supplying the subepidermal capillary loops and the AV anastomoses are richly innervated by sympathetic adrenergic fibers. Constriction of these vessels during hypothalamic-mediated sympathetic activation decreases blood flow through the capillary loops and the venous plexus. In addition to sympathetic neural control, the resistance vessels and AV anastomoses are very sensitive to α-adrenoceptor-mediated vasoconstriction induced by circulating catecholamines.

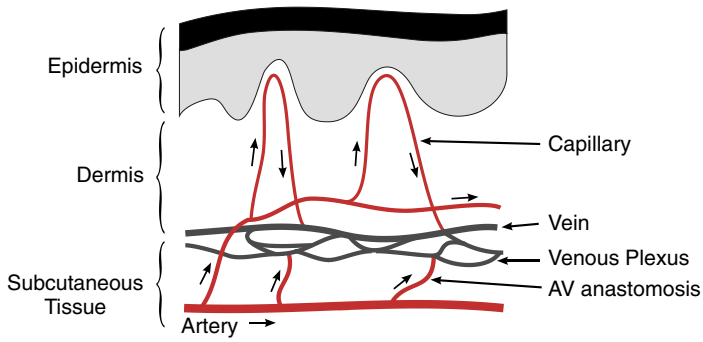

FIGURE 7-14 Anatomy of the cutaneous circulation. Arteries within the subcutaneous tissue give rise to either arterioles that travel into the dermis and give rise to capillary loops, or to arteriovenous (AV) anastomoses that connect to a plexus of small veins in the subdermis. The venous plexus also receives blood from the capillary loops. Sympathetic stimulation constricts the resistance vessels and AV anastomoses, thereby decreasing dermal blood flow.

Although the AV anastomoses are almost exclusively controlled by sympathetic influences, the resistance vessels respond to both metabolic influences and sympathetic influences and therefore demonstrate local regulatory phenomena such as reactive hyperemia and autoregulation. These local regulatory responses, however, are relatively weak compared to those observed in most other organs.

The cutaneous resistance vessels also respond to local paracrine influences, particularly during sweating and tissue injury. Activation of cutaneous sweat glands by sympathetic cholinergic nerves produces vasodilation in addition to the formation of sweat. It is thought that local formation of bradykinin is partly responsible for this vasodilation. Bradykinin may stimulate the formation of nitric oxide to cause vasodilation during sweating. Moreover, evidence suggests that an unidentified vasodilator substance (a co-transmitter) is released by sympathetic cholinergic nerves. Tissue injury from mechanical trauma, heat, or chemicals releases paracrine substances such as histamine and bradykinin, which increase blood flow and cause localized edema by increasing microvascular permeability. If the skin is firmly stroked with a blunt object, the skin initially blanches owing to localized vasoconstriction. This is followed within a minute by the formation of a red line that spreads away from the site of injury (red flare); both the red line and red flare are caused by an increase in blood flow. Localized swelling (wheal formation) may then follow, caused by increased microvascular permeability and leakage of fluid into the interstitium. The red line, flare, and wheal are called the **triple response.** Both paracrine hormones and **local axon reflexes** are believed to be involved in the triple response. The vasodilator neurotransmitter involved in local axon reflexes has not been identified. This neurogenic-mediated vasodilation is called "active vasodilation" in contrast to vasodilation that occurs during withdrawal of sympathetic adrenergic influences, called "passive vasodilation."

Local changes in skin temperature selectively alter blood flow to the affected region. For example, if a heat source is placed on a small region of the skin on the back of the hand, blood flow will increase only to the region that is heated. This response appears to be mediated by local axon reflexes and local formation of nitric oxide instead of by changes in sympathetic discharge mediated by the hypothalamus. Localized cooling produces vasoconstriction through local axon reflexes. If tissue is exposed to extreme cold, a phenomenon called **cold-induced vasodilation** may occur following an initial vasoconstrictor response, especially if the exposed body region is a hand, foot, or face. This phenomenon causes light-colored skin to appear red, and it explains the rosy cheeks, ears, and nose a person may exhibit when exposed to very cold air temperatures. With continued exposure, alternating

periods of dilation and constriction may occur. The mechanism for cold-induced vasodilation is not clear, but it probably involves changes in local axon reflexes and impaired ability of the vessels to constrict because of hypothermia.

Splanchnic Circulation

The splanchnic circulation includes blood flow to the gastrointestinal tract, spleen, pancreas, and liver. Blood flow to these combined organs represents 20% to 25% of cardiac output (see Table 7-1). Three major arteries arising from the abdominal aorta supply blood to the stomach, intestine, spleen, and liver—the celiac, superior mesenteric, and inferior mesenteric arteries. The following describes blood flow to the intestines and liver.

Several branches arising from the superior mesenteric artery supply blood to the intestine. These and subsequent branches travel through the mesentery that supports the intestine. Small arterial branches enter the outer muscular wall of the intestine and divide into several smaller orders of arteries and arterioles, most of which enter into the submucosa from which arterioles and capillaries arise to supply blood to the intestinal villi. Water and nutrients transported into the villi enter the blood and are carried away by the portal venous circulation.

Intestinal blood flow is closely coupled to the primary function of the intestine, i.e., the absorption of water, electrolytes, and nutrients from the intestinal lumen. Therefore, intestinal blood flow increases when food is present within the intestine. Blood flow to the intestine in the fasted state is about 30 mL/min per 100 g; following a meal, flow can exceed 250 mL/min per 100 g. This functional hyperemia is stimulated by gastrointestinal hormones such as gastrin and cholecystokinin, as well as by glucose, amino acids, and fatty acids that are absorbed by the intestine. Evidence exists that submucosal arteriolar vasodilation during functional hyperemia is mediated by hyperosmolarity and nitric oxide.

The intestinal circulation is strongly influenced by the activity of sympathetic adrenergic nerves. Increased sympathetic activity during exercise or in response to decreased baroreceptor firing (e.g., during hemorrhage or standing) constricts both arterial resistance vessels and venous capacitance vessels. Because the intestinal circulation receives such a large fraction of cardiac output, sympathetic stimulation of the intestine causes a substantial increase in total systemic vascular resistance. Additionally, the large blood volume contained within the venous vasculature is mobilized during sympathetic stimulation to increase central venous pressure.

Parasympathetic activation of the intestine increases motility and glandular secretions. Increased motility per se does not cause large increases in blood flow, but flow nevertheless increases. This may involve metabolic mechanisms or local paracrine influences such as the formation of bradykinin and nitric oxide.

Venous blood leaving the gastrointestinal tract, spleen, and pancreas drains into the hepatic portal vein, which supplies approximately 75% of the hepatic blood flow. The remainder of the hepatic blood flow is supplied by the hepatic artery, which is a branch of the celiac artery. Note that in this arrangement, most of the liver circulation is in series with the gastrointestinal, splenic, and pancreatic circulations. Therefore, changes in blood flow in these vascular beds have a significant influence on hepatic flow.

Terminal vessels from the hepatic portal vein and hepatic artery form sinusoids within the liver, which function as capillaries. The pressure within these sinusoids is very low, just a few mm Hg above central venous pressure. This is important because the sinusoids are very permeable (see Chapter 8). Changes in central venous and hepatic venous pressure are almost completely transmitted to the sinusoids. Therefore, elevations in central venous pressure during right ventricular failure can cause substantial increases in sinusoid pressure and fluid filtration, leading to hepatic edema and accumulation of fluid within the abdominal cavity (ascites).

The liver circulation does not show autoregulation; however, decreases in hepatic portal flow result in reciprocal increases in hepatic artery flow, and vice versa. Sympathetic

nerve activation constricts vessels derived from both the hepatic portal system and hepatic artery. The most important effect of sympathetic activation is on venous capacitance vessels, which contain a significant fraction (approximately 15%) of the venous blood volume in the body. The liver, like the gastrointestinal circulation, functions as an important venous reservoir.

The spleen is an important venous reservoir containing hemoconcentrated blood in some animals (e.g., dogs). Stressful conditions in the dog (e.g., blood loss) can cause splenic contraction, which can substantially increase circulating blood volume and hematocrit.

Renal Circulation

Approximately 20% of the cardiac output perfuses the kidneys although the kidneys represent only about 0.4% of total body weight. Renal blood flow, therefore, is about 400 mL/min per 100 g of tissue weight, which is the highest of any major organ within the body (see Table 7-1). Only the pituitary and carotid bodies have higher blood flows per unit tissue weight. Whereas blood flow in many organs is closely coupled to tissue oxidative metabolism, this is not the case for the kidneys, in which the blood flow greatly exceeds the need for oxygen delivery. The very high blood flow results in a relatively low extraction of oxygen from the blood (about 1 to 2 mL O_2/mL blood) despite the fact that renal oxygen consumption is high (approximately 5 mL O_2/min per 100 g). The reason for renal blood flow being so high is that the primary function of the kidneys is to filter blood and form urine. The kidney comprises three major regions: the cortex (the outer layer that contains glomeruli for filtration), the medulla (the middle region that contains renal tubules and capillaries involved in concentrating the urine), and the hilum (the inner region where the renal artery and vein, nerves, lymphatics, and ureter enter or leave the kidney). Because most of the filtering takes place within the cortex, about 90% of the total renal blood flow supplies the cortex, with the remainder supplying the medullary regions.

The vascular organization within the kidneys is very different from most organs. The abdominal aorta gives rise to renal arteries that distribute blood flow to each kidney. The renal artery enters the kidney at the hilum and gives off several branches (**interlobar arteries**) that travel in the kidney toward the cortex. Subsequent branches (**arcuate and interlobular arteries**) then form **afferent arterioles,** which supply blood to each glomerulus (Fig. 7-15). As the afferent arteriole enters the glomerulus, it gives rise to a cluster of **glomerular capillaries,** from which fluid is filtered into Bowman's capsule and into the renal proximal tubule. The glomerular capillaries then form an **efferent arteriole** from which arise **peritubular capillaries** that surround the renal tubules. Efferent arterioles associated with **juxtamedullary nephrons** located in the inner cortex near the outer medulla give rise to very long capillaries (**vasa recta**) that loop down deep within the medulla. The capillaries are involved with countercurrent exchange and the maintenance of medullary osmotic gradients. Capillaries eventually form venules and then veins, which join together to exit the kidney as the renal vein. Therefore, within the kidney, a capillary bed (glomerular capillaries) is located between the two principal sites of resistance (afferent and efferent arterioles). Furthermore, a second capillary bed (peritubular capillaries) is in series with the glomerular capillaries and is separated by the efferent arteriole.

The vascular arrangement within the kidney is very important for filtration and reabsorption functions of the kidney. Changes in afferent and efferent arteriole resistance affect not only blood flow, but also the hydrostatic pressures within the glomerular and peritubular capillaries. Glomerular capillary pressure, which is about 50 mm Hg, is much higher than that in capillaries found in other organs. This high pressure drives fluid filtration (see Chapter 8). The peritubular capillary pressure, however, is low (about 10–20 mm Hg). This is important because it permits fluid reabsorption to limit water loss and urine excretion. About 20% of the plasma entering the

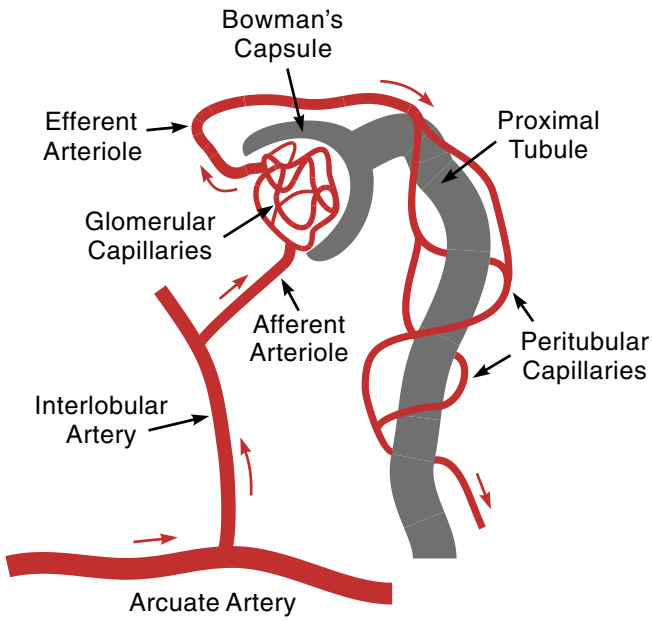

FIGURE 7-15 Renal vascular anatomy. Small vessels derived from branches of the renal artery form arcuate arteries and interlobular arteries, which then become afferent arterioles that supply blood to the glomerulus. As the afferent arteriole enters the glomerulus, it gives rise to a cluster of glomerular capillaries, from which fluid is filtered into Bowman's capsule and into the renal proximal tubule. The glomerular capillaries then form an efferent arteriole from which arise peritubular capillaries that surround the renal tubules.

kidney is filtered. If significant reabsorption did not occur, a high rate of urine formation would rapidly lead to hypovolemia and hypotension and an excessive loss of electrolytes. Figure 7-16 shows the effects of afferent and efferent arteriole constriction on blood flow and glomerular capillary pressure. If the afferent arteriole constricts, distal pressures, glomerular filtration, and blood flow are reduced (see Fig. 7-16, Panel B). In contrast, although efferent arteriole constriction reduces flow and peritubular capillary pressure, it increases glomerular capillary pressure and glomerular filtration (see Fig. 7-16, Panel D).

The renal circulation exhibits strong autoregulation between arterial pressures of about 80–180 mm Hg. Autoregulation of blood flow is accompanied by autoregulation of glomerular filtration so that filtration remains essentially unchanged over a wide range of arterial pressures. For this to occur, glomerular capillary pressure must remain unchanged when arterial pressure changes. This takes place because the principal site for autoregulation is the afferent arteriole. If arterial pressure falls, the afferent arteriole dilates, which helps to maintain the glomerular capillary pressure and flow despite the fall in arterial pressure.

Two mechanisms have been proposed to explain renal autoregulation: myogenic mechanisms and tubuloglomerular feedback. Myogenic mechanisms were described earlier in this chapter. Briefly, a reduction in afferent arteriole pressure is sensed by the vascular smooth muscle, which responds by relaxing; an increase in pressure induces smooth muscle contraction. The **tubuloglomerular feedback** mechanism is poorly understood, and the actual mediators have not been identified. It is believed, however, that changes in perfusion pressure alter glomerular filtration and therefore tubular flow and sodium delivery to the macula densa of the juxtaglomerular apparatus, which then signals the afferent arteriole to constrict or dilate. The macula densa of the juxtaglomerular apparatus is a group of specialized cells of the distal tubule

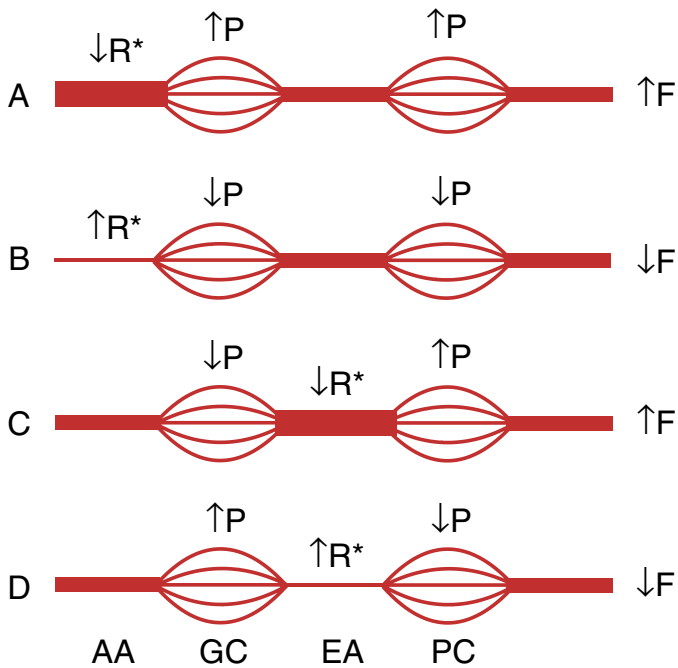

FIGURE 7-16 Effects of renal afferent and efferent arteriole resistances on blood flow and renal capillary pressures. *Panel A:* Decreased afferent arteriole (*AA*) resistance increases glomerular capillary (*GC*) and peritubular capillary (*PC*) pressures and increases flow (*F*). *Panel B:* Increased AA resistance decreases GC and PC pressures and decreases F. *Panel C:* Decreased efferent arteriole (*EA*) resistance decreases GC pressure, increases PC pressure, and increases F. *Panel D:* Increased EA resistance increases GC pressure, decreases PC pressure, and decreases F. *,arteriole undergoing resistance change; *R,* resistance; *P,* pressure.

that lie adjacent to the afferent arteriole as the distal tubule loops up back toward the glomerulus. These cells sense solute osmolarity, particularly sodium chloride. Some investigators have proposed that adenosine (which is a vasoconstrictor in the kidney), locally produced angiotensin II (a vasoconstrictor), or vasodilators such as nitric oxide, prostaglandin E_2, and prostacyclin are involved in tubuloglomerular feedback and autoregulation. Locally produced angiotensin II strongly influences efferent arteriole tone. Thus, inhibition of angiotensin II formation by an angiotensin-converting enzyme (ACE) inhibitor dilates the efferent arteriole, which decreases glomerular capillary pressure and reduces glomerular filtration under some conditions (e.g., renal artery stenosis). Drugs that inhibit prostaglandin and prostacyclin biosynthesis (cyclo-oxygenase inhibitors) alter renal hemodynamics and function, particularly with long-term use.

The renal circulation responds strongly to sympathetic adrenergic stimulation. Under normal conditions, relatively little sympathetic tone on the renal vasculature occurs; however, with strenuous exercise or in response to severe hemorrhage, increased renal sympathetic nerve activity can virtually shut down renal blood flow. Because renal blood flow receives a relatively large fraction of cardiac output and therefore contributes significantly to systemic vascular resistance, renal vasoconstriction can serve an important role in maintaining arterial pressure under these conditions; however, intense renal vasoconstriction seriously impairs renal perfusion and function, and it can lead to renal failure.

Pulmonary Circulation

Two separate circulations perfusing respiratory structures exist: the pulmonary circulation, which is derived from the pulmonary

artery and supplies blood flow to the alveoli for gas exchange, and the bronchial circulation, which is derived from the thoracic aorta and supplies nutrient flow to the trachea and bronchial structures. The pulmonary circulation receives all of the cardiac output of the right ventricle, whereas the bronchial circulation receives about 1% of the left ventricular output.

The pulmonary circulation is a low-resistance, low-pressure, high-compliance vascular bed. Although the pulmonary circulation receives virtually the same cardiac output as the systemic circulation, the pulmonary pressures are much lower. The pulmonary artery systolic and diastolic pressures are about 25 mm Hg and 10 mm Hg, respectively. The mean pulmonary artery pressure is therefore about 15 mm Hg. If we assume that the left atrial pressure averages 8 mm Hg, the perfusion pressure for the pulmonary circulation (mean pulmonary artery pressure minus left atrial pressure) is only about 7 mm Hg. This is considerably lower than the perfusion pressure for the systemic circulation (about 90 mm Hg). Because the flow is essentially the same, but the perfusion pressure is much lower in the pulmonary circulation, the pulmonary vascular resistance must be very low. In fact, pulmonary vascular resistance is generally ten- to fifteen-fold lower than systemic vascular resistance. The reason for the much lower pulmonary vascular resistance is that the vessels are larger in diameter, shorter in length, and have many more parallel elements than the systemic circulation.

Pulmonary vessels are also much more compliant than systemic vessels. Because of this, an increase in right ventricular output does not cause a proportionate increase in pulmonary artery pressure. The reason for this is that the pulmonary vessels passively distend as the pulmonary artery pressure increases, which lowers their resistance. Increased pressure also recruits additional pulmonary capillaries, which further reduces resistance. This high vascular compliance and ability to recruit capillaries are important mechanisms for preventing pulmonary vascular pressures from rising too high when cardiac output increases (e.g., during exercise).

Increased pulmonary vascular pressure can have two adverse consequences. First, increased pulmonary artery pressure increases the afterload on the right ventricle, which can impair ejection, and with chronic pressure elevation, cause right ventricular failure. Second, an increase in pulmonary capillary pressure increases fluid filtration (see Chapter 8), which can lead to pulmonary edema. Pulmonary capillary pressures are ordinarily about 10 mm Hg, which is less than half the value found in most other organs.

Because of their low pressures and high compliance, pulmonary vascular diameters are strongly influenced by gravity and by changes in intrapleural pressure during respiration. When a person stands up, gravity increases hydrostatic pressures within vessels located in the lower regions of the lungs, which distends these vessels, decreases resistance, and increases blood flow to the lower regions. In contrast, vessels located in the upper regions of the lungs have reduced intravascular pressures; this increases resistance and reduces blood flow when a person is standing. Changes in intrapleural pressure during respiration (see Chapter 5) alter the transmural pressure that distends the vessels. For example, during normal inspiration, the fall in intrapleural pressure increases vascular transmural pressure, which distends nonalveolar vessels, decreases resistance, and increases regional flow. The opposite occurs during a forced expiration, particularly against a high resistance (e.g., Valsalva maneuver). The capillaries associated with the alveoli are compressed as the alveoli fill with air during inspiration. With very deep inspirations, this capillary compression can cause an increase in overall pulmonary resistance.

The primary purpose of the pulmonary circulation is to perfuse alveoli for the exchange of blood gasses. Gas exchange depends, in part, on diffusion distances and the surface area available for exchange. The capillary-alveolar arrangement is such that diffusion distances are minimized and surface area is max-

TABLE 7-2 COMPARISON OF VASCULAR CONTROL MECHANISMS IN DIFFERENT VASCULAR BEDS

CIRCULATORY BED	SYMPATHETIC CONTROL	METABOLIC CONTROL	AUTOREGULATION
Coronary	+[1]	+++	+++
Cerebral	+	+++	+++
Skeletal muscle	++	+++	++
Cutaneous	+++	+	+
Intestinal	+++	++	++
Renal	++	+	+++
Pulmonary	+	+[2]	+

+++, strong; ++, moderate, +, weak. [1] Sympathetic vasoconstriction in the coronaries is overridden by metabolic vasodilation during sympathetic activation of the heart. [2] Hypoxia causes vasoconstriction, the opposite of all other organs.

imized. Pulmonary capillaries differ from their systemic counterparts in that they form thin interconnecting sheets around and between adjacent alveoli, which greatly increase their surface area and reduce diffusion distances.

Unlike other organs, alveolar or arterial hypoxia causes pulmonary vasoconstriction. The mechanism is not known; however, evidence suggests that endothelin, reactive oxygen species, leukotrienes, and thromboxanes may be involved. This **hypoxic vasoconstriction,** especially in response to regional variations in ventilation, helps to maintain normal ventilation-perfusion ratios in the lung. Maintenance of normal ventilation-perfusion ratios is important because high blood flow to hypoxic regions, for example, would decrease the overall oxygen content of the blood leaving the lungs.

Sympathetic adrenergic innervation of the pulmonary vasculature occurs, and sympathetic activation increases pulmonary vascular resistance and pulmonary artery pressure. Sympathetic activation also decreases pulmonary vascular compliance and mobilizes pulmonary blood volume to the systemic circulation.

Summary of Special Circulations

Perfusion pressure and vascular resistance determine blood flow in organs. Under normal circumstances, the perfusion pressure remains fairly constant owing to baroreceptor mechanisms. Therefore, the primary means by which blood flow changes within an organ is by changes in vascular resistance, which is influenced by extrinsic factors (e.g., sympathetic nerves and hormones) and intrinsic factors (e.g., tissue metabolites and endothelial-derived substances). Basal vascular tone is determined by the net effect of the extrinsic and intrinsic factors acting on the vasculature. Resistance can either increase or decrease from the basal state by alterations in the relative contribution of extrinsic and intrinsic factors. Table 7-2 summarizes the relative importance of sympathetic and metabolic control mechanisms and the intrinsic autoregulatory capacity of several major organ vascular beds.

SUMMARY OF IMPORTANT CONCEPTS

- The relative distribution of blood flow to organs is regulated by the vascular resistance of the individual organs, which is determined by extrinsic (neurohumoral) and intrinsic (local regulatory) mechanisms.
- Important local mechanisms regulating organ blood flow include the following: (1) tissue factors such as adenosine, K^+, O_2, CO_2, and H^+; (2) paracrine hormones such as bradykinin, histamine, and prostaglandins; (3) endothelial factors such as

nitric oxide, endothelin-1, and prostacyclin; and (4) myogenic mechanisms intrinsic to the vascular smooth muscle.

- The following local factors produce vasodilation in most tissues: adenosine, K^+, H^+, CO_2, hypoxia, bradykinin, histamine, prostaglandin E_2, prostacyclin, and nitric oxide. The following local factors produce vasoconstriction: endothelin-1 and the myogenic response to vascular stretch.
- Mechanical compression of blood vessels strongly influences blood flow in the coronary circulation and in contracting skeletal muscle.
- Autoregulation, which is the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure, is important in organs such as the heart, brain, and kidneys; the gastrointestinal and skeletal muscles circulations show moderate autoregulation.
- In organs such as the heart, brain, skeletal muscle, and gastrointestinal tract, blood flow is tightly coupled to oxidative metabolism; therefore, an increase in tissue oxygen consumption leads to an increase in blood flow. This is called active or functional hyperemia.
- Blood flow in the following organs is moderately to strongly influenced by sympathetic vasoconstrictor mechanisms: resting skeletal muscle, kidneys, gastrointestinal circulation, and skin (related to thermoregulation).
- Vascular control mechanisms linked to oxidative metabolism (metabolic mechanisms) are particularly strong in the heart, brain, and skeletal muscle.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. Which of the following causes vasodilation in most vascular beds?
    a. Decreased tissue pCO_2
    b. Increased tissue pO_2
    c. Increased interstitial K^+
    d. Increased release of endothelin-1
2. Two minutes after perfusion pressure to the kidney is suddenly reduced from 100 mm Hg to 70 mm Hg, which of the following will occur?
    a. Afferent arterioles will be dilated.
    b. Renal blood flow will be reduced by 30%.
    c. Renal vascular resistance will be increased.
    d. The kidney will become hypoxic.
3. If a coronary artery is occluded for one minute and then the occlusion is released,
    a. A period of active hyperemia follows.
    b. Coronary flow will increase because of vasoconstriction occurring during the ischemia.
    c. Endothelial release of nitric oxide will contribute to the reactive hyperemia.
    d. Interstitial adenosine concentrations will increase and constrict coronary arterioles.
4. Which one of the following organ circulations is most strongly constricted during sympathetic activation resulting from a baroreceptor reflex when a person suddenly stands up?
    a. Brain
    b. Heart
    c. Intestine
    d. Skin

Match the organs listed in questions 5–10 with answers "a" through "i" below. Each question may have more than one correct answer.

Answers:

a. Blood flow is primarily regulated by CO_2 and H^+.
b. Capillary beds found between two in-series arterioles
c. Hypoxic vasoconstriction
d. Highest capillary pressure
e. Highest arterial-venous oxygen difference

f. Abundant arterial-venous anastomoses
g. Largest organ mass
h. Receives most of its blood supply directly from other organs
i. Controlled primarily by hypothalamic thermoregulatory centers

5. Skin circulation _____
6. Renal circulation _____
7. Coronary arteries _____
8. Pulmonary circulation _____
9. Cerebral circulation _____
10. Skeletal muscle circulation _____

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chapter

Exchange Function of the Microcirculation

8

CD CONTENTS

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Describe the principal mechanisms by which each of the following moves across the capillary endothelium: lipid-insoluble substances, lipid-soluble substances, fluid, and electrolytes.**
2. **Write out and explain Fick's First Law for diffusion.**
3. **Name three different types of capillaries; know the organs in which they are found, and describe their differences in permeability to macromolecules and fluid.**
4. **Describe the factors that determine oxygen's rate of exchange between the microcirculation and tissue.**
5. **Describe how changes in tissue (interstitial) and plasma hydrostatic and oncotic pressures affect transcapillary fluid movement.**
6. **Explain how changes in each of the following affect capillary pressure: arterial and venous pressures, precapillary and postcapillary resistances.**
7. **Explain what determines the rate of fluid movement across capillaries for a given net driving force of hydrostatic and oncotic pressures.**
8. **Explain why changes in venous pressure have a greater affect on capillary pressure than do changes in arterial pressure.**
9. **Explain why oncotic pressure (colloid osmotic pressure) rather than total osmotic pressure governs fluid exchange across the capillary.**
10. **Describe the significance of the reflection coefficient for proteins in terms of how it affects the oncotic pressure generated by proteins.**
11. **Describe the function of lymphatics in the maintenance of interstitial fluid volume.**
12. **Describe how changes in capillary hydrostatic pressure, plasma oncotic pressure, capillary permeability, and lymphatic function can lead to tissue edema.**

INTRODUCTION

The microcirculation consists of small arteries, arterioles, capillaries, venules, small veins, and small lymphatic vessels found within organs and tissues (see Chapter 5, Fig. 5-1). These vessels have several important functions. First, the small arteries and arterioles are the principal sites of resistance within the systemic circulation and therefore play a major role in the regulation of arterial blood pressure and blood flow within organs (see Chapter 5). Second, venules and small veins have an important capacitance function and therefore determine the distribution of blood volume within the body. Third, the microcirculation allows passage of leukocytes from the blood into the extravascular space. Fourth, the microcirculation is the exchange site of gases, nutrients, metabolic wastes, and thermal energy between the blood and tissues. Capillaries are quantitatively the most important site for exchange because of their physical structure (small volume-to-surface area ratio and thin walls), large number, and enormous surface area available for exchange. This chapter focuses on the exchange function of capillaries.

MECHANISMS OF EXCHANGE

Fluid, electrolytes, gases, and small and large molecular weight substances transverse the capillary endothelium by several different mechanisms: diffusion, bulk flow, vesicular transport, and active transport (Fig. 8-1). ***Diffusion*** *is the movement of a molecule from a high concentration to a low concentration.* This mechanism of exchange is particularly important for gases (O_2 and CO_2) and other lipid-soluble substances (e.g., steroid hormones, anesthetics). Fluid and electrolytes also are exchanged across the endothelium, in part, by diffusion.

The movement of a substance by diffusion is described by **Fick's First Law** of diffusion (Equation 8-1), in which the movement of a molecule per unit time (flux J_S; moles/sec) equals the diffusion constant (D) of the barrier (e.g., capillary wall) multiplied by the surface area (A) available for diffusion and the concentration gradient ($\Delta C/\Delta X$), which is the

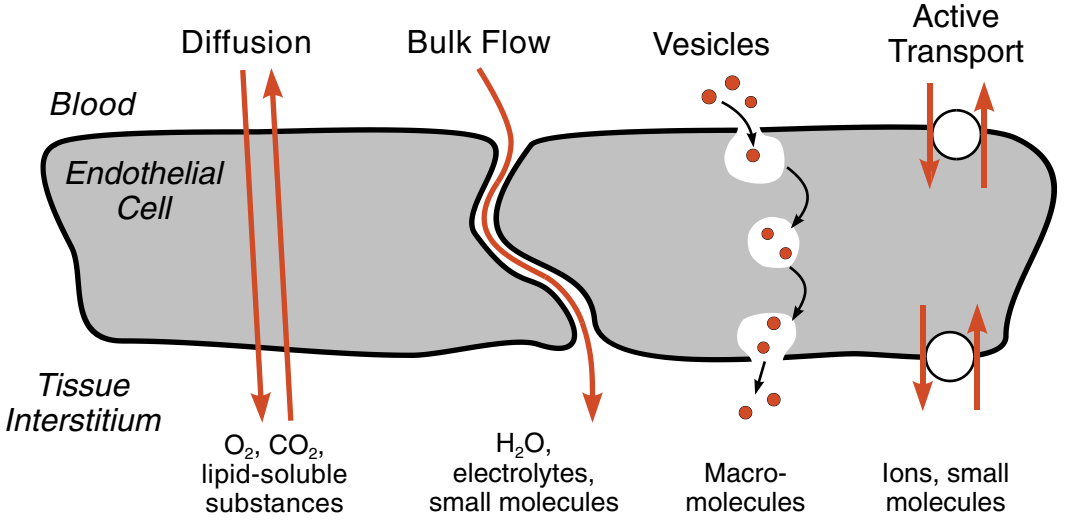


FIGURE 8-1 Mechanisms of exchange across the capillary endothelium. Lipid-soluble substances like oxygen and carbon dioxide readily exchange across capillary endothelial cells by diffusion. Water and electrolytes move across the endothelium primarily by bulk flow through intercellular clefts ("pores"). Vesicular transport mechanisms move large molecules across the endothelium. Active transport mechanisms move ions and other small molecules across the endothelium.

concentration difference across the barrier (ΔC) divided by the diffusion distance (ΔX).

Eq. 8-1 $$J_s = DA\frac{\Delta C}{\Delta X}$$

*The **diffusion constant** is a value that represents the ease with which a specific substance can cross the capillary wall (or other barrier) by diffusion.* The diffusion constant of a capillary wall is different for different substances. For example, the diffusion constant for oxygen is very high compared to glucose.

Therefore, Equation 8-1 tells us that *the rate of diffusion is directly related to the concentration difference, the diffusion constant, and the area available for diffusion, and it is inversely related to the diffusion distance.* The diffusion distance (ΔX) in Equation 8-1 is sometimes combined with the diffusion constant (D) and called the permeability coefficient (P). This simplifies Equation 8-1 to $J_s = PS(\Delta C)$ in which S is the surface area available for exchange. The combined value of the permeability coefficient times the surface area has been calculated for different substances in many organs and tissues; it is called the **PS product.**

A second mechanism for exchange is **bulk flow.** This mechanism is important for the movement of water and lipid-insoluble substances across capillaries. *Bulk flow of fluid and electrolytes and of small molecules occurs through intercellular clefts between endothelial cells* (see Fig. 8-1). These extracellular pathways are sometimes referred to as "pores."

The physical structure of capillaries varies considerably among organs; these differences greatly affect exchange by bulk flow. Some capillaries (e.g., skeletal muscle, skin, lung, and brain) have a very "tight" endothelium and continuous basement membrane (termed **continuous capillaries**), which reduces bulk flow across the capillary wall. In contrast, some vascular beds have **fenestrated capillaries** (e.g., in exocrine glands, renal glomeruli, and intestinal mucosa), which have perforations (fenestrae) in the endothelium, resulting in relatively high permeability and bulk flow. **Discontinuous capillaries** (found in the liver, spleen, and bone marrow) have large intercellular gaps, as well as gaps in the basement membrane, and therefore have the highest permeability.

Bulk flow follows Poiseuille's equation for hydrodynamic flow (see Chapter 5, Equation 5-6). Changes in pressure gradients (either hydrostatic or colloid osmotic) across a capillary alter fluid movement across the capillary. In addition, changes in the size and number of "pores" or intercellular clefts alter exchange. Pore size and path length are analogous to vessel radius and length in Poiseuille's equation; they are major factors in the resistance to bulk flow across capillaries. In some organs, precapillary sphincters (circular bands of smooth muscle at the entrance to capillaries) can regulate the number of perfused capillaries. An increase in perfused capillaries increases the surface area available for fluid exchange and the net movement of fluid across capillaries by bulk flow.

Vesicular transport is a third mechanism by which exchange occurs between blood and tissue. This mechanism is particularly important for the translocation of macromolecules (e.g. proteins) across capillary endothelium. Compared to diffusion and bulk flow, vesicular transport plays a relatively minor role in transcapillary exchange (except for macromolecules). Evidence exists, however, that vesicles can sometimes fuse together, creating a channel through a capillary endothelial cell, thereby permitting bulk flow to occur.

Active transport is a fourth mechanism of exchange. Some molecules (e.g., ions, glucose, amino acids) are actively transported across capillary endothelial cells; however, this is not normally thought of as a mechanism for exchange between plasma and interstitium, but rather as a mechanism for exchange between an individual cell and its surrounding milieu.

EXCHANGE OF OXYGEN AND CARBON DIOXIDE

Oxygen diffuses from the blood to the tissues to support mitochondrial respiration. The lipid solubility of oxygen enables it to readily diffuse through tissues; however, the distance

that oxygen is able to diffuse within a tissue is limited by cellular utilization of oxygen. For example, as oxygen diffuses out of a capillary in skeletal muscle, the muscle cells adjacent to the capillary take up the oxygen for use by the mitochondria. Consequently, little oxygen diffuses all the way through one cell to reach another. Therefore, in tissues having a high demand for oxygen, it is essential that the capillary density is great enough to provide short diffusion distances.

Large amounts of oxygen diffuse across the capillaries not only because of their thin walls and high diffusion constant for oxygen, but more importantly, because of their large surface area available for diffusion. It has been observed that significant amounts of oxygen also diffuse out of arterioles. Some of this oxygen diffuses through arteriolar walls into the surrounding cells, and in some cases, it diffuses from arterioles into the venules that often are found adjacent to arterioles. Normally, systemic arterial blood is fully saturated with oxygen and has a pO_2 of about 95 mm Hg. Direct measurements of pO_2 in small arterioles (20–80 μ diameter) of some tissues reveal that the pO_2 is only 25–35 mm Hg, which corresponds to a 30% to 60% loss of oxygen content of the blood. Therefore, substantial amounts of oxygen diffuse out of the blood before the blood reaches the capillaries; however, capillaries are the most important site for tissue oxygenation because the relatively high capillary density ensures that diffusion distances between the blood and tissue cells are short.

Because oxygen diffusion follows Fick's First Law (Equation 8-1), the rate of oxygen diffusion can be enhanced by increasing arterial pO_2, decreasing tissue pO_2, or increasing the area available for diffusion (i.e., increasing the number of flowing vessels, particularly capillaries). For a single capillary having a fixed diffusion constant, diffusion length, and surface area, the rate of oxygen diffusion (JO_2) primarily depends on the concentration difference of oxygen (expressed as pO_2 difference) between the capillary blood and the tissue surrounding the capillary (the pO_2 difference is 20 mm Hg in Figure 8-2).

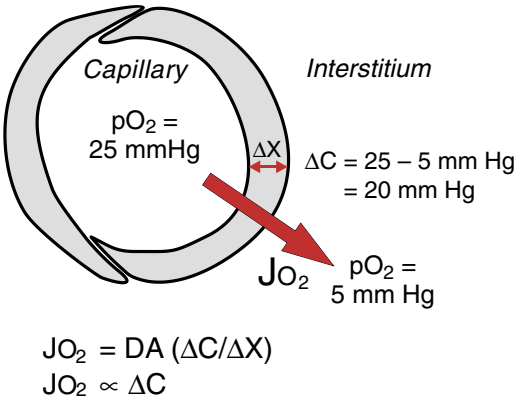


FIGURE 8-2 Diffusion of oxygen (JO_2) from capillaries into the tissue follows Fick's First Law of diffusion. Because the diffusion constant (D), the area for exchange (A), and the diffusion distance (ΔX) remain relatively constant in a single capillary, the diffusion of oxygen is governed primarily by the difference in partial pressure of oxygen (pO_2) between the blood and tissue (ΔC), which is 20 mm Hg in this example. Increasing the pO_2 difference increases the rate of diffusion.

Therefore, increasing capillary blood pO_2 (as occurs when a person breathes pure oxygen) or decreasing tissue pO_2 (as occurs with increased tissue oxygen consumption) increases the rate of oxygen diffusion into the tissue. Capillary pO_2 is also increased by dilation of resistance vessels. This increases microvascular blood flow, thereby delivering more oxygen to the capillaries per unit time, which results in higher pO_2 values in the capillary blood. If vasodilation is accompanied by an increase in the number of flowing capillaries (as occurs during skeletal muscle contraction), this increases the surface area available for oxygen diffusion and further enhances oxygen transport into the tissue.

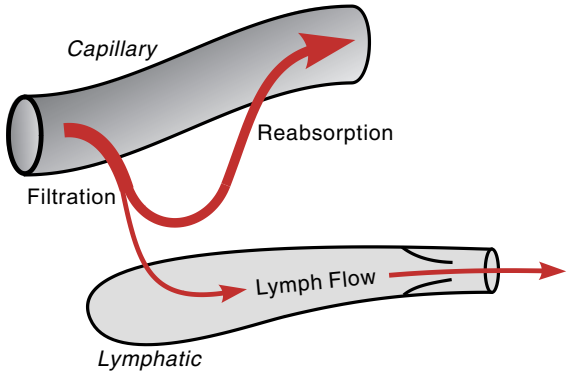
Carbon dioxide is a by-product of oxidative metabolism and must be removed from the tissue and transported to the lungs by the blood. Like oxygen, carbon dioxide is very lipid-soluble and readily diffuses from cells into the blood. In fact, its diffusion constant is about 20 times greater than oxygen in aqueous solutions. The removal of carbon dioxide from tissues is not diffusion-limited; its removal depends primarily on the blood flow. Therefore, reduced tissue perfusion leads to an increase in tissue and venous pCO_2.

TRANSCAPILLARY FLUID EXCHANGE

The body is comprised of two basic fluid compartments: intravascular and extravascular. The intravascular compartment contains fluid (i.e., blood) within the cardiac chambers and blood vessels of the body. The extravascular system is everything outside of the intravascular compartment. The extravascular compartment is made up of many subcompartments such as the cellular, interstitial, and lymphatic subcompartments and a specialized system containing cerebrospinal fluid within the central nervous system.

Fluid readily exchanges between the intravascular and extravascular compartments. Fluid leaves blood vessels (primarily capillaries) and enters the tissue interstitium of the extravascular compartment. This is called **fluid filtration** (Fig. 8-3). It is estimated that about 1% of the plasma is filtered into the interstitium in a typical organ. The interstitial fluid is exchanged with the fluid found within the subcompartments of the extracellular compartment. It is crucial that a steady state is achieved in which the same volume of fluid that leaves the vasculature is returned to the vasculature; otherwise the extravascular compartment would swell with fluid (i.e., become edematous).

There are two routes by which fluid is returned to the blood. First, **fluid reabsorption** returns most of the filtered fluid to the blood at the venular end of capillaries or at postcapillary venules (see Fig. 8-3). The rate of reabsorption is less than filtration; therefore a second mechanism is required to maintain fluid balance. This second mechanism involves lymphatic vessels. These specialized vessels, similar in size to venules, comprise an endothelium with intercellular gaps surrounded by a highly permeable basement membrane. Terminal lymphatics end as blind sacs within the tissue. The terminal lymphatics take up the excess fluid (including electrolytes and macromolecules) and transport it into larger lymphatics that leave the tissue. It is estimated that 5% to 10% of capillary filtration is transported out of tissues by the lymphatics. The larger lymphatics have smooth muscle cells that undergo spontaneous vasomotion that serves to "pump" the lymph. Vasomotion is spontaneous rhythmic contraction and relaxation of the lymphatic vessels. Evidence exists that as a lymphatic vessel fills with fluid, the increased pressure stretches the vessel and induces a myogenic contraction. Sympathetic nerves can modulate this vasomotion. Lymphatic vessels contain one-



Filtration = Reabsorption + Lymph Flow

FIGURE 8-3 Capillary filtration, reabsorption, and lymph flow. Fluid filters out of the arteriolar end of the capillary and into the interstitium. Most of this fluid is reabsorbed at the venular end of the capillary, with the rest of the fluid entering terminal lymphatics to be carried away from the tissue and eventually returned to the blood. Fluid exchange is in balance (i.e., at a steady state) when filtration equals reabsorption plus lymph flow.

way valves that direct lymph away from the tissue and eventually back into the systemic circulation via the thoracic duct and subclavian veins. Approximately 2–4 L/day of lymph are returned to the circulation by this manner.

In the steady state, the rate of fluid entering the tissue interstitium by filtration is the same as that of the fluid leaving the tissue by capillary reabsorption and lymph flow. That is, filtration equals reabsorption plus lymph flow. When this balance is altered, the volume and pressure of fluid within the interstitium changes. For example, if net filtration transiently increases and lymph flow does not increase to the same extent, interstitial volume and pressure will increase, causing edema. Factors that cause edema are discussed in the last section of this chapter.

Physical Mechanisms Governing Fluid Exchange

The movement of fluid across a capillary is determined by several physical factors: the hydrostatic pressure, oncotic pressure, and physical nature of the barrier (i.e., the permeability of the capillary wall) separating the fluid in the blood from the fluid within the interstitium. As described earlier, the movement of fluid can be related to Poiseuille's equation for hydrodynamic flow (see Equation 5-6), or in more simplified terms, to the general hydrodynamic equation (Equation 5-3) that relates flow (F), driving pressure (ΔP), and resistance (R) (i.e., $F = \Delta P/R$). A more common way to express this hydrodynamic equation for transcapillary fluid exchange is to substitute vascular conductance (C) for resistance, which are reciprocally related (i.e., $F = C \cdot \Delta P$). Fluid flux is the number of molecules of water (or volume) per unit time that moves across the exchange barrier; therefore, fluid flux can be expressed in similar units as flow. If net fluid flux (J) is substituted for flow, net driving force (NDF) is substituted for driving pressure (ΔP), and filtration constant (K_F) and surface area (A) are substituted for vascular conductance, the following relationship is obtained (Equation 8-2):

Eq. 8-2 $$J = K_F \cdot A\ (NDF)$$

Equation 8-2 and Figure 8-4 show that net fluid movement (fluid flux, J) is directly related to the filtration constant (K_F), the surface area available for fluid exchange (A), and the net driving force (NDF). *At a given NDF (assuming that the NDF is not equal to zero), the amount of fluid filtered or reabsorbed per unit time is determined by the filtration constant and surface area available for exchange.*

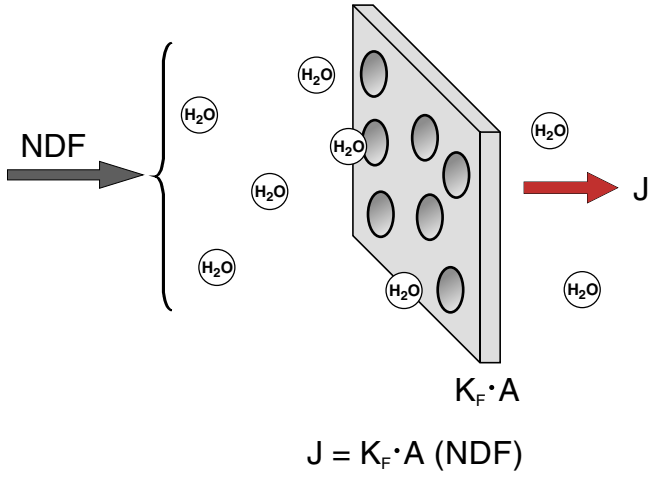


FIGURE 8-4 Factors determining fluid movement. The rate of fluid movement (flux, *J*) across the capillary endothelium, designated as water molecules in this figure, is determined by the net driving force (*NDF*), the capillary filtration constant (K_F), and the capillary surface area (*A*) available for exchange.

The filtration constant is determined by the physical properties of the barrier (i.e., size and number of "pores" and the thickness of the capillary barrier), and therefore it represents the permeability of the capillaries. For example, fenestrated capillaries have a higher K_F (i.e., permeability) than continuous capillaries. Furthermore, paracrine substances such as histamine, bradykinin, and leukotrienes increase K_F. The surface area (A) is primarily related to the length, diameter, and number of vessels (capillaries and postcapillary venules) available for exchange. The surface area is dynamic in vascular beds such as skeletal muscle. In that tissue, the number of perfused capillaries can increase several-fold during exercise. In experimental studies using whole organs, K_F and A are combined and called the **capillary filtration coefficient** (CFC).

The direction of fluid movement (filtration or reabsorption) in Equation 8-2 depends on whether the NDF is positive (filtration) or negative (reabsorption). If the NDF is zero, no net fluid movement occurs even if K_F and A are very large.

The NDF is determined by hydrostatic and oncotic forces. Two hydrostatic and two oncotic pressures affect transcapillary fluid exchange: capillary hydrostatic pressure, tissue (interstitial) hydrostatic pressure, capillary (plasma) oncotic pressure, and tissue (interstitial) oncotic pressure (Fig. 8-5). These physical forces are sometimes referred to as **Starling forces** in honor of Ernest Starling, who pioneered much of the early research on capillary fluid exchange. The net hydrostatic pressure driving fluid out of the capillary (filtration) is the intracapillary pressure minus the interstitial hydrostatic pressure ($P_c - P_i$). The net oncotic pressure drawing fluid into the capillary (reabsorption) is the capillary plasma oncotic pressure minus the interstitial oncotic pressure ($\pi_c - \pi_i$).

Capillary hydrostatic pressure (P_C) drives fluid out of the capillary, and it is highest at the arteriolar end of the capillary and lowest at the venular end. Depending on the organ, the pressure may drop along the length of the capillary (axial or longitudinal pressure gradient) by 15–30 mm Hg owing to capillary resistance. Because of this pressure gradient along the capillary length, filtration is favored at the arteriolar end of the capillary where capillary hydrostatic pressure is greatest.

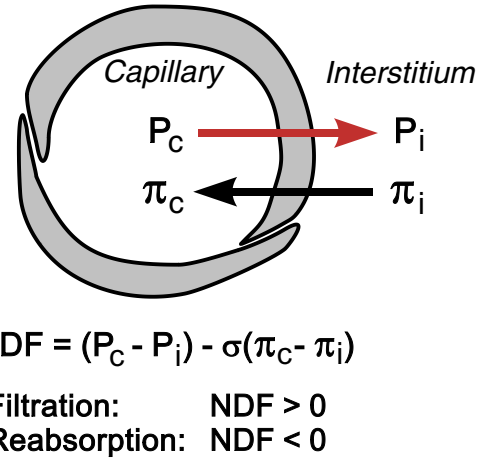


FIGURE 8-5 Net driving force for fluid movement across capillaries. Hydrostatic and oncotic pressures within the capillary (P_c, π_c) and the tissue interstitium (P_i, π_i) determine the net driving force (*NDF*) for fluid movement out of the capillary (filtration) or into the capillary (reabsorption). The hydrostatic pressure difference favors filtration (red arrow) because P_c is greater than P_i. The oncotic pressure difference favors reabsorption (black arrow) because π_c is greater than π_i. The oncotic pressure difference is multiplied by the reflection coefficient (σ), a factor that represents the permeability of the capillary to the proteins responsible for generating the oncotic pressure.

The average capillary hydrostatic pressure is determined by arterial and venous pressures (P_A and P_V), and by the ratio of post-to-precapillary resistances (R_V/R_A). An increase in either arterial or venous pressure increases capillary pressure; however, the effects of elevations in venous pressure are much greater than those of an equivalent elevation in arterial pressure. The reason for this is that postcapillary resistance is much lower than precapillary resistance. In most organs, the precapillary resistance is five to ten times greater than postcapillary resistance; therefore, R_V/R_A ranges from 0.1 to 0.2. If we assume that $R_V/R_A = 0.2$, the following relationship (Equation 8-3) can be derived (for details, see Capillary Pressure on CD):

Eq. 8-3

$$P_C = \frac{\left(\frac{R_V}{R_A}\right) P_A + P_V}{1 + \left(\frac{R_V}{R_A}\right)} \Rightarrow P_C = \frac{0.2P_A + P_V}{1.2}$$

Equation 8-3 shows that increasing venous pressure by 20 mm Hg increases mean capillary pressure by 16.7 mm Hg. In contrast, increasing arterial pressure by 20 mm Hg increases mean capillary pressure by only 3.3 mm Hg. The reason for this difference is that the high precapillary resistance blunts the effects of increased arterial pressure on the downstream capillaries. Therefore, mean capillary hydrostatic pressure is more strongly influenced by changes in venous pressure than by changes in arterial pressure. This has significant clinical implication. Conditions that increase venous pressure (e.g., right ventricular failure, cirrhosis of the liver, venous thrombosis) can lead to edema in peripheral organs and tissues by increasing capillary hydrostatic pressure and capillary fluid filtration.

Tissue (interstitial) hydrostatic pressure (P_i) is the pressure within the tissue interstitium that is exerted against the outside wall of the capillary, and therefore opposes

PROBLEM 8-1

In an experimental study, the control mean arterial and venous pressures perfusing an organ are 90 mm Hg and 10 mm Hg, respectively, and the post-to-precapillary resistance ratio is 0.20. After inducing heart failure, the mean arterial pressure falls to 80 mm Hg, and the venous pressure increases to 20 mm Hg. Furthermore, the post-to-precapillary resistance ratio decreases to 0.15. Calculate the increase in mean capillary pressure caused by the heart failure.

Use Equation 8-3 to calculate the mean capillary pressure for both the control condition and the condition during heart failure. The difference represents the increase in capillary pressure caused by the heart failure.

$$\text{Control: } P_C = \frac{\left(\frac{R_V}{R_A}\right) P_A + P_V}{1 + \left(\frac{R_V}{R_A}\right)} = \frac{0.2(90) + 10}{1.2} = 23.3 \text{ mm Hg}$$

$$\text{Heart Failure: } P_C = \frac{0.15(80) + 20}{1.15} = 27.8 \text{ mm Hg}$$

Therefore, capillary pressure increased by 4.5 mm Hg.

Note: This problem illustrates the relationship between capillary pressure, arterial and venous pressures, and precapillary and postcapillary resistances. In an actual experimental study, unlike this problem, the capillary pressure would be measured and the precapillary and postcapillary resistances would be calculated because these resistances can only be known if capillary, arterial, and venous pressures are first known. The ratio of post-to-precapillary resistances can be calculated from:

$$\frac{R_V}{R_A} = \frac{(P_C - P_V)}{(P_A - P_C)}$$

This calculation assumes that the precapillary flow equals the postcapillary flow, which generally is an acceptable assumption (see Capillary Pressure on CD).

the capillary hydrostatic pressure. This pressure is determined by the interstitial fluid volume and the compliance of the tissue (see Interstitial Compliance on CD). In many tissues under normal states of hydration, tissue hydrostatic pressure is subatmospheric by a few millimeters of mercury (mm Hg), whereas in others it is slightly positive by a few mm Hg. Increased tissue fluid volume, as occurs during states of enhanced capillary fluid filtration or lymphatic blockage, increases tissue hydrostatic pressure. In contrast, dehydration reduces tissue hydrostatic pressure.

Capillary plasma oncotic pressure (π_c) is the osmotic pressure within the capillary that is determined by the presence of proteins. Because this is an osmotic force within the plasma, it opposes filtration and promotes reabsorption. Because the capillary barrier is readily permeable to ions, the ions have no significant effect on osmotic pressure within the capillary (see Osmosis and Osmotic Pressure on CD). Instead, the osmotic pressure is principally determined by plasma proteins that are relatively impermeable. Rather than being called "osmotic" pressure, this pressure is referred to as the "oncotic" pressure or "colloid osmotic" pressure because it is generated by macromolecular colloids. Albumin, the most abundant plasma protein, generates about 70% of the oncotic pressure; globulins and fibrinogen generate the remainder of the oncotic pressure. The plasma oncotic pressure typically is 25–30 mm Hg. The oncotic pressure increases along the length of the capillary, particularly in capillaries having high net filtration (e.g., renal glomerular capillaries). This occurs because the filtered fluid leaves behind proteins, increasing the plasma protein concentration.

When oncotic pressure is determined, it is measured across a semipermeable membrane—i.e., a membrane that is permeable to fluid and electrolytes but not permeable to large protein molecules. In most capillaries, however, the endothelial barrier has a finite permeability to proteins. The actual permeability to proteins depends on the type of capillary and on the nature of the proteins (size, shape, and charge). Because of this finite permeability, the effective oncotic pressure generated across the capillary membrane is less than that calculated from the protein concentration. The **reflection coefficient** (σ) across a capillary is the effective oncotic pressure divided by the oncotic pressure, calculated from the concentration difference of the proteins across the capillary wall. If the capillary is impermeable to protein, $\sigma = 1$. If the capillary is freely permeable to protein, $\sigma = 0$. Continuous capillaries have a high σ (greater than 0.9), whereas discontinuous capillaries, which are very "leaky" to proteins, have a relatively low σ. In the latter case, plasma and tissue oncotic pressures may have a negligible influence on the NDF. Therefore, the effective oncotic pressure is the oncotic pressure calculated from the protein concentrations multiplied by the reflection coefficient for capillaries in a particular tissue.

The **tissue (or interstitial) oncotic pressure** (π_i), a force that promotes filtration, is determined by the interstitial protein concentration and the reflection coefficient of the capillary wall for those proteins. The protein concentration is influenced, in part, by the amount of fluid filtration into the interstitium. For example, increased capillary filtration into the interstitium decreases interstitial protein concentration and reduces the oncotic pressure. This effect of filtration on protein concentration serves as a mechanism to limit excessive capillary filtration. The interstitial oncotic pressure, which is typically about 5 mm Hg, acts on the capillary fluid to enhance filtration and oppose reabsorption.

Together, the hydrostatic and oncotic forces are related to the NDF as shown in Equation 8-4. The net hydrostatic pressure, which normally promotes filtration, is represented by ($P_c - P_i$). The net oncotic pressure, which promotes reabsorption, is represented by $\pi_c - \pi_i$), multiplied by the reflection coefficient (σ). This equation shows that the NDF is increased by increases in P_c and π_i and decreased by increases in P_i and π_c.

Eq. 8-4 $$NDF = (P_c - P_i) - \sigma(\pi_c - \pi_i)$$

If the above expression for NDF is incorporated into Equation 8-2, the following equation is derived:

Eq. 8-5 $J = K_F \cdot A[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$

The expression in brackets represents the NDF. If the NDF is positive, filtration occurs, and if it is negative, reabsorption occurs. For a given NDF, the rate of fluid movement (J) is determined by the product of K_F and A.

Capillary Exchange Model

Capillary fluid exchange can be modeled as shown in Figure 8-6. This model assumes that the following values remain constant along capillary length: P_i = 1 mm Hg, π_c = 25 mm Hg, π_i = 6 mm Hg, and σ = 1. According to Equation 8-4, if P_c is 30 mm Hg at the entrance to the capillary and falls linearly to 15 mm Hg at the end of the capillary, the NDF changes from +10 at the entrance of the capillary to –5 at the end of the capillary. Filtration occurs along most of the length of the capillary wherever NDF is greater than zero. Reabsorption occurs where NDF is less than zero, which is near the venular end of the capillary. Net fluid movement is zero at the point along the capillary where NDF = 0. The rate of filtration or reabsorption (J) depends on the product of K_F and A, and the NDF.

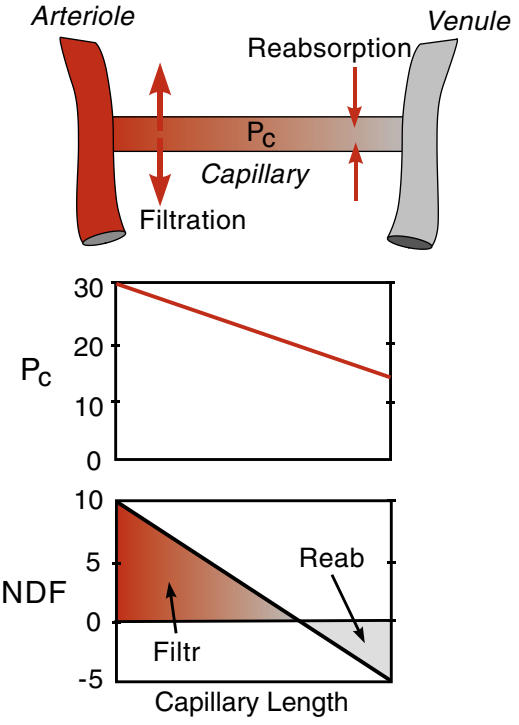


FIGURE 8-6 Model of capillary fluid exchange. Assuming that P_i = 1, π_c = 25, π_i = 6 mm Hg, and σ = 1, and assuming that capillary hydrostatic pressure (P_c) at the beginning and end of the capillary are 30 mm Hg and 15 mm Hg, respectively, the net driving force [NDF = $(P_c - P_i) - (\pi_c - \pi_i)$] is positive along most of the length of the capillary, which causes filtration (*Filtr*) to occur. Near the venular end of the capillary, the *NDF* is less than zero and reabsorption (*Reab*) occurs.

PROBLEM 8-2

Given that P_c = 22 mm Hg, P_i = –3 mm Hg, π_c = 26 mm Hg, π_i = 6 mm Hg, and σ = 0.9, answer the following questions:

a) What is the net driving force for transcapillary fluid exchange?

b) Is filtration or reabsorption occurring?

c) If the product of K_F and A is doubled, what will happen to the net rate of fluid movement across the capillary, assuming that the net driving force does not change?

Answer:

a) The net driving force, NDF = $[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$. Substituting the given values, the NDF = 7 mm Hg.

$$NDF = [22 - (-3)] - 0.9\,[(26 - 6)] = 7 \text{ mm Hg}$$

b) Because the NDF is greater than zero, filtration is occurring.

c) The net rate of fluid movement, $J = K_F \cdot A$ (NDF). Therefore, if the product of K_F and A is doubled, then J (the filtration in this problem) is doubled because the NDF $\neq$ 0.

This model is highly simplified because it assumes that P_i, π_c, and π_i remain constant, which does not occur in vivo. As fluid leaves the arteriolar end of the capillary, π_c increases, P_i increases, and π_i decreases. These changes oppose the filtration. For most capillaries, the fraction of fluid filtered from the capillary (filtration fraction) is less than 1%, so P_i, π_c, and π_i do not change appreciably. Renal capillaries, however, are different because the filtration fraction in these capillaries is very high (approximately 20%), which leads to significant increases in plasma oncotic pressure. In non-renal capillaries, if capillary permeability is increased, or if capillary hydrostatic pressure is increased to high levels by venous occlusion or heart failure, the increase in filtration can lead to significant changes in P_i, π_c, and π_i in a manner that opposes and therefore limits the net filtration of fluid.

Lymphatics (not shown in Fig. 8-6) pick up excess filtered fluid and transport it out of the tissue. When net filtration increases, lymphatic flow also increases. The lymphatics, therefore, along with the dynamic changes in P_c, P_i, π_c, and π_i help to maintain a proper state of interstitial hydration and thereby prevent edema from occurring.

EDEMA FORMATION

When the fluid volume within the interstitial compartment increases because filtration exceeds the rate of capillary reabsorption plus lymphatic flow, the interstitial compartment increases in volume, leading to tissue swelling (i.e., edema). The change in interstitial pressure that results from an increase in interstitial volume depends on the compliance of the interstitial compartment. For example, edema in the brain causes large increases in interstitial pressure because of the rigid cranium (i.e., low compliance). Soft, highly compliant tissues such as the skin and subcutaneous tissues can undergo considerable swelling before substantial increases in tissue pressure occur.

Edema can damage organs and, in some cases, cause death. For example, cerebral edema following brain trauma can lead to cellular death because the increased interstitial pressure damages neurons and causes tissue ischemia by compressing blood vessels. Even in tissues that are relatively compliant, such as skin and skeletal muscle, severe edema can lead to tissue necrosis. Pulmonary edema can be life threatening because gas exchange is impaired.

Table 8-1 lists some of the many causes of edema. Every cause of edema can be related to one or more of the following:

- Increased capillary hydrostatic pressure
- Increased capillary permeability
- Decreased plasma oncotic pressure
- Lymphatic obstruction

The most common cause of edema is elevated capillary pressure, such as occurs during heart failure or venous obstruction. Both conditions increase venous pressure, which is transmitted back to the capillaries, causing an increase in fluid filtration. Localized edema in tissues is commonly caused by injury or inflammation (e.g., sprained ankle, bee sting), which causes the release of local paracrine substances (e.g., histamine, bradykinin, and leukotrienes) that increase capillary and venular permeability. Some of these substances (e.g., histamine) also increase capillary pressure by dilating arterioles and constricting venules.

The treatment for edema involves modifying one or more of the physical factors that regulates fluid movement. For example, in pulmonary or systemic edema secondary to heart failure, diuretics are given to the patient to reduce blood volume and venous pressure, therefore reducing capillary hydrostatic pressure. A patient suffering from ankle edema following an injury will be instructed to keep that foot elevated whenever possible to diminish the effects of gravity on capillary pressure and to use a tight fitting elastic stocking or bandage around the ankle to increase tissue hydrostatic pressure (which opposes filtration). Drugs (e.g., antihistamines) are sometimes used to block the release or action of paracrine substances that increase capillary permeability following tissue injury or inflammation.

TABLE 8-1 CAUSES OF EDEMA

Increased Capillary Pressure
- Increased venous pressure
  - Heart failure
  - Increased blood volume
  - Venous obstruction (thrombosis or compression)
  - Incompetent venous valves
  - Gravity
- Increased arterial pressure
  - Hypertension
- Decreased arterial resistance
  - Vasodilation (physiologic or pharmacologic)

Increased Capillary Permeability
- Vascular damage (e.g., burns, trauma)
- Inflammation

Decreased Plasma Oncotic Pressure
- Reduced plasma proteins (e.g., malnutrition, burns, liver dysfunction)

Lymphatic Blockage (Lymphedema)
- Tissue injury
- Inflammation of lymphatics
- Lymphatic invasion by parasites (e.g., filariasis)

SUMMARY OF IMPORTANT CONCEPTS

- Diffusion is the primary mechanism for the exchange of gasses and lipid-soluble substances across the capillary barrier. With diffusion, the rate of molecular movement (flux, J) is directly related to the diffusion constant of the substance (D), the surface area available for diffusion (A), and the concentration difference across the capillary wall (ΔC). It is inversely related to the diffusion distance (thickness of diffusion barrier, ΔX) as shown by Fick's First Law of diffusion: $J_S = DA(\Delta C \Delta X)$.
- The exchange of water and electrolytes across capillaries (and postcapillary venules) occurs primarily through bulk flow through intercellular clefts ("pores") between endothelial cells. Bulk flow is governed by the same factors that determine the blood flow through vessels; these factors are described by Poiseuille's equation (see Chapter 5).
- The net driving force (NDF) that determines fluid movement is the net hydrostatic pressure across the capillary wall (capillary minus interstitial hydrostatic pressures, $P_c - P_i$) minus the opposing effective oncotic pressure gradient across the capillary wall (capillary minus interstitial oncotic pressures, $\pi_c - \pi_i$, multiplied by the reflection coefficient [σ]). Therefore, the NDF = $(P_c - P_i) - \sigma(\pi_c - \pi_i)$.
- Changes in capillary hydrostatic pressure significantly alter fluid exchange. Capillary pressure is determined by arterial and venous pressures and by the ratio of precapillary and postcapillary resistances. Changes in venous pressure have a much greater quantitative influence on capillary pressure than do similar changes in arterial pressure.
- Filtration occurs when the NDF is greater than zero, which generally occurs at the arteriolar end of the capillary. Reabsorption occurs when the NDF is less than zero, which generally occurs at the venular end of the capillary where capillary hydrostatic pressure is lower.
- The net fluid flux (J) is directly related to the NDF, the capillary filtration constant (K_F), and the surface area (A) available for fluid exchange; therefore, $J = K_F \cdot A$ (NDF). At a given NDF, the greater the filtration constant or the greater the capillary surface area, the greater the net amount of fluid movement across the capillary.
- Fluid balance within a tissue is achieved when capillary filtration equals the sum of capillary reabsorption and lymphatic flow.

An increase in tissue fluid volume (edema) occurs when the rate of fluid filtration exceeds the sum of the rate of fluid reabsorption and lymphatic flow.

- Edema can occur when increased capillary hydrostatic pressure, increased capillary permeability, decreased plasma oncotic pressure, or lymphatic blockage occurs.

Review Questions

Please refer to the appendix for the answers to the review questions.

For each question, choose the one best answer:

1. Which of the following mechanisms is most important quantitatively for the exchange of electrolytes across capillaries?
   a. Bulk flow
   b. Diffusion
   c. Osmosis
   d. Vesicular transport

2. Oxygen exchange between blood and tissues is enhanced by
   a. Decreased arteriolar flow.
   b. Decreased arteriolar pO_2.
   c. Decreased tissue pO_2.
   d. Decreased number of flowing capillaries.

3. Net capillary fluid filtration is enhanced by
   a. Decreased capillary plasma oncotic pressure.
   b. Decreased venous pressure.
   c. Increased precapillary resistance.
   d. Increased tissue hydrostatic pressure.

4. If capillary hydrostatic pressure = 15 mm Hg, capillary oncotic pressure = 28 mm Hg, tissue interstitial pressure = −5 mm Hg, and tissue oncotic pressure = 6 mm Hg (assume that $\sigma = 1$), these Starling forces will result in
   a. Net filtration.
   b. Net reabsorption.
   c. No net fluid movement.

5. If capillary filtration is enhanced by histamine during tissue inflammation,
   a. Lymphatic flow will increase.
   b. Capillary filtration fraction will decrease.
   c. The capillary filtration constant will be lower than normal.
   d. Tissue interstitial pressure will decrease.

6. Edema can result from
   a. Increased arteriolar resistance.
   b. Increased plasma protein concentration.
   c. Reduced venous pressure.
   d. Obstructed lymphatic.

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chapter

9

Cardiovascular Integration and Adaptation

CD CONTENTS

Pulmonary Capillary Wedge Pressure
Pressure Natriuresis

LEARNING OBJECTIVES

Understanding the concepts presented in this chapter will enable the student to:

1. **Describe the mechanical, metabolic, and neurohumoral mechanisms that lead to changes in cardiac output, central venous pressure, systemic vascular resistance, mean arterial pressure, and arterial pulse pressure during exercise.**
2. **Describe how exercise affects blood flow to the following organs: brain, heart, active skeletal muscle, nonactive muscle, skin, gastrointestinal tract, and kidneys.**
3. **Explain the mechanisms that enable ventricular stroke volume to increase during exercise at high heart rates.**
4. **Describe how each of the following influences the cardiovascular responses to exercise: type of exercise (dynamic versus static), body posture, physical conditioning, altitude, temperature and humidity, age, and gender.**
5. **Describe the effects of pregnancy on blood volume, central venous pressure, ventricular stroke volume, heart rate, systemic vascular resistance, and arterial pressure.**
6. **Describe the mechanisms by which each of the following conditions can lead to hypotension: hemorrhage, dehydration, heart failure, cardiac arrhythmias, changing from supine to standing position, and autonomic dysfunction.**

7. **Describe the autonomic and hormonal compensatory mechanisms that are activated to restore arterial pressure following hemorrhage.**
8. **Explain why the baroreceptor reflex is a short-term compensatory mechanism, whereas renal mechanisms are considered long-term for restoring arterial pressure following hemorrhage.**
9. **Describe how each of the following positive feedback mechanisms can lead to irreversible shock and death following severe hemorrhage: cardiac depression, vascular sympathetic escape, metabolic acidosis, cerebral ischemia, rheological factors, and systemic inflammatory responses.**
10. **Describe how altered renal function and changes in systemic vascular resistance can lead to hypertension.**
11. **Describe the mechanisms by which each of the following conditions can lead to secondary hypertension: renal artery stenosis, renal disease, primary hyperaldosteronism, pheochromocytoma, aortic coarctation, pregnancy, hyperthyroidism, and Cushing's syndrome.**
12. **Describe the physiologic rationale for using the following drug classes in the treatment of essential hypertension: diuretics, β-adrenoceptor blockers, α-adrenoceptor blockers, calcium-channel blockers, and angiotensin-converting enzyme inhibitors.**
13. **Define systolic and diastolic ventricular failure and show how these two types of failure affect ventricular pressure-volume loops.**
14. **Describe how the following serve as compensatory mechanisms in heart failure: ventricular dilation and hypertrophy, increased sympathetic activity, activation of the renin-angiotensin-aldosterone system, enhanced vasopressin secretion, and increased blood volume.**
15. **Compare cardiovascular function at rest and cardiovascular responses at maximal exercise in a normal subject and in a heart failure patient.**
16. **Describe the physiologic rationale for using the following drug classes in the treatment of heart failure: diuretics, vasodilators, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-adrenoceptor blockers, and positive inotropic drugs.**

INTRODUCTION

Previous chapters emphasized physiologic concepts concerning cardiac and vascular function at the cellular and organ level. In addition, they examined mechanisms, such as baroreceptors and circulating hormones, that regulate overall cardiovascular function. This chapter integrates all the components of the cardiovascular system and shows how they work together to maintain normal perfusion of organs under conditions of increased organ demand for blood flow (e.g., during exercise and pregnancy) or during abnormal stressful conditions such as hemorrhage. This chapter also examines some of the changes that occur in cardiovascular function during pathologic conditions such as hypertension and heart failure.

CARDIOVASCULAR RESPONSES TO EXERCISE

The cardiovascular system must be able to respond to a wide range of demands placed on it by the body. Previous chapters focused on cardiovascular function in normal resting states; however, physical activity, is (or should be!) a normal, regular event in the daily activity of humans. Physical movement is associated with increases in the metabolic activity of contracting muscles. This increased metabolic activity is largely oxidative; therefore, the cardiovascular system needs to increase blood flow and oxygen delivery to the contracting muscles.

The cardiovascular responses to physical activity are summarized in Table 9-1. Contracting muscles undergo metabolic vasodilation (see Chapter 7). If large muscle

TABLE 9-1 SUMMARY OF CARDIOVASCULAR CHANGES DURING EXERCISE

↑ **Cardiac output**
- ↑ heart rate (↑ sympathetic adrenergic and ↓ parasympathetic activity)
- ↑ stroke volume (↑ CVP; ↑ inotropy; ↑ lusitropy)

↑ **Mean arterial pressure and pulse pressure**
- CO increases more than SVR decreases
- ↑ stroke volume increases pulse pressure

↑ **Central venous pressure**
- venous constriction (↑ sympathetic adrenergic activity)
- muscle pump activity
- abdominothoracic pump

↓ **Systemic vascular resistance**
- metabolic vasodilation in active muscle and heart
- cutaneous vasodilation (↓ sympathetic adrenergic activity)
- vasoconstriction in splanchnic, nonactive muscle, and renal circulation (↑ sympathetic adrenergic activity)

CVP, central venous pressure; *CO,* cardiac output; *SVR,* systemic vascular resistance.

groups are involved in the physical activity (e.g., running, bicycling), the metabolic vasodilation in these muscles causes a large fall in systemic vascular resistance. Ordinarily, this would cause arterial pressure to fall; however, during physical activity, arterial pressure increases because cardiac output increases at the same time that systemic vascular resistance begins to fall. Furthermore, increased sympathetic activity (see Chapter 6) leads to vasoconstriction in the gastrointestinal tract, nonactive muscles, and kidneys, which helps to limit the fall in systemic vascular resistance as well as shift blood flow to the active muscles. Venous return to the heart is augmented by venous constriction and by the skeletal muscle and abdominothoracic pumps (see Chapter 5). Enhanced venous return enables the cardiac output to increase by preventing a fall in cardiac preload that would otherwise occur as heart rate and inotropy increase (see Chapter 4). Therefore, all the cardiovascular changes occurring during physical activity ensure that active muscles are supplied with increased blood flow and oxygen while maintaining normal, or even elevated, arterial pressures.

Mechanisms Involved in Cardiovascular Response to Exercise

Four fundamental mechanisms are responsible for cardiovascular changes during physical activity: mechanical, metabolic, autonomic, and hormonal. When a person suddenly begins to run, cardiac output increases before metabolic and neurohumoral mechanisms are activated. This initial increase in cardiac output results primarily from the skeletal muscle pump system, which enhances venous return and increases cardiac output by the Frank-Starling mechanism. Within a few seconds of the initiation of muscle contraction, metabolic mechanisms in the contracting muscle dilate resistance vessels and increase blood flow. A few seconds following the onset of running, changes occur in the autonomic nervous system (Fig. 9-1). Hypothalamic centers coordinate a pattern of increased sympathetic and decreased parasympathetic (vagal) outflow

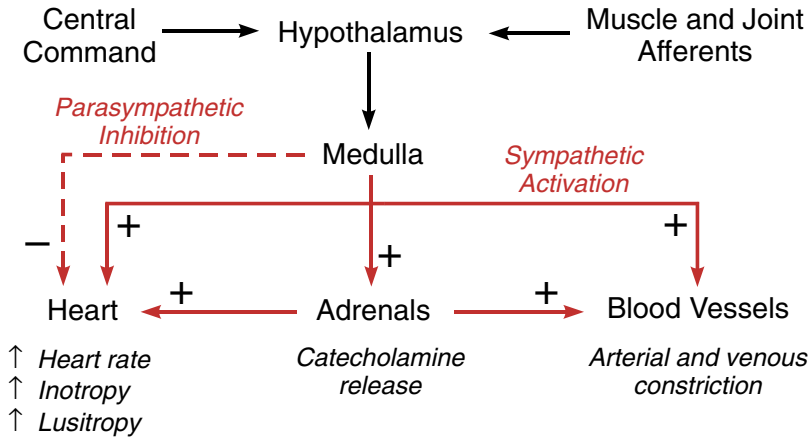

FIGURE 9-1 Summary of adrenergic and cholinergic control mechanisms during exercise. The hypothalamus functions as an integrative center that receives information from the brain and muscle and joint receptors, then modulates sympathetic and parasympathetic (vagal) outflow from the medulla. Sympathetic nerves are activated (+) and parasympathetic nerves are inactivated (-) during exercise, leading to adrenal release of catecholamines, cardiac stimulation, and vasoconstriction.

from the medullary cardiovascular centers (see Chapter 6). This leads to an increase in heart rate, inotropy, and lusitropy, which increases cardiac output. Increased sympathetic efferent activity constricts resistance and capacitance vessels in the splanchnic circulation and nonactive muscles to help maintain arterial pressure and central venous pressure. In addition, during strenuous activity, sympathetic nerves constrict the renal vasculature.

Exercise activates several different hormonal systems that affect cardiovascular function. Many of the hormonal systems are activated by sympathetic stimulation. The cardiovascular effects of hormone activation are generally slower than the direct effects of autonomic activation on the heart and circulation.

Sympathetic nerves innervating the adrenal medulla cause the secretion of epinephrine and lesser amounts of norepinephrine into the blood (see Chapter 6). Plasma norepinephrine concentrations increase more than ten-fold during exercise. A large fraction of this norepinephrine comes from sympathetic nerves. Normally, most of the norepinephrine released by sympathetic nerves is taken back up by the nerves (neuronal reuptake); however, some of the norepinephrine can diffuse into the capillary blood (i.e., spillover) and enter the systemic circulation. This spillover is greatly enhanced when the level of sympathetic activity is high in the body. The blood transports the epinephrine and norepinephrine to the heart and other organs, where they act upon alpha- and beta-adrenoceptors to enhance cardiac function and either constrict or dilate blood vessels. In Chapter 6, we learned that epinephrine (at low concentrations) binds to β_2-adrenoceptors in skeletal muscle, which causes vasodilation. At high concentrations, epinephrine also binds to postjunctional α_1 and α_2-adrenoceptors on blood vessels to cause vasoconstriction. Circulating norepinephrine constricts blood vessels by binding preferentially to α_1-adrenoceptors in most organs. During exercise, circulating levels of norepinephrine and epinephrine can become very high so that the net effect on the vasculature is α-adrenoceptor-mediated vasoconstriction, except in those organs (e.g., heart and active skeletal muscle) in which metabolic mechanisms produce vasodilation. It is important to note that vasoconstriction produced by sympathetic nerves and circulating catecholamines does not occur in the active skeletal muscle, coronary circulation, or brain. Blood flow in these organs is primarily controlled by local metabolic vasodilator mechanisms.

Increased sympathetic activity stimulates renal release of renin, which leads to the formation of angiotensin II. Increased angiotensin II increases renal sodium and water reabsorption by directly affecting renal function and by stimulating aldosterone secretion; in addition, angiotensin II augments sympathetic activity (see Chapter 6). Circulating arginine vasopressin (antidiuretic hormone) also increases during exercise, most likely resulting from increased plasma osmolarity. Although these hormonal changes promote renal retention of sodium and water, especially after prolonged periods of exercise, blood volume often decreases during exercise (particularly in hot environments) because of water loss through sweating and increased respiratory exchange.

Two mechanisms operate to activate the autonomic nervous system during exercise. One mechanism is referred to as **"central command."** When physical activity is anticipated or already underway, higher brain centers (e.g., the cortex) relay this information to hypothalamic centers to coordinate autonomic outflow to the cardiovascular system. By this central command mechanism, anticipation of exercise can lead to autonomic changes that increase cardiac output and arterial pressure before exercise begins. This serves to prime the cardiovascular system for exercise. A second mechanism involves muscle mechanoreceptors and chemoreceptors. Once physical activity is underway, these muscle receptors respond to changes in muscle mechanical activity and tissue chemical environment (e.g., increased lactic acid), and then relay that information to the central nervous system via afferent fibers. This information is processed by the hypothalamus and medullary cardiovascular centers to enhance the sympathetic outflow to the heart and systemic vasculature.

Arterial baroreceptor function is altered during physical activity. Exercise normally is associated with a rise in both arterial pressure and heart rate. If arterial baroreceptor function were not modified, the increase in arterial pressure would result in a reflex bradycardia. Instead, the baroreceptor reflex is modified (reset to a higher control point) by the central nervous system (see Chapter 6).

Steady-State Changes in Cardiovascular Function during Exercise

Changes in cardiovascular function during physical activity depend upon the level of physical exertion. If the level of physical exertion is expressed as workload, heart rate, cardiac output, and arterial pressure increase in nearly direct proportion to the increase in workload (Fig. 9-2, Panel A). In contrast, systemic vascular resistance falls as workload increases. Ventricular stroke volume increases at low to moderate workloads, then plateaus. Although not shown in Figure 9-2, the increase in stroke volume is responsible for an increase in arterial pulse pressure.

Stroke volume may decline at very high workloads because ventricular filling time is reduced as heart rate increases. Decreased filling time decreases ventricular filling (decreases preload), which decreases stroke volume by the Frank-Starling mechanism. This would prevent the heart from increasing cardiac output during physical activity if not for several mechanisms that work together to ensure that stroke volume is maintained and even increased as heart rate increases (Table 9-2). For example, during a physical activity such as running, enhanced venous return by the muscle pump and abdominothoracic pump systems helps to maintain preload despite the increase in heart rate (see Chapter 5). Furthermore, increased atrial and ventricular inotropy enhances ventricular stroke volume and ejection fraction, and increased lusitropy helps to augment ventricular filling. When the heart rate approaches its maximal rate, the effects of reduced filling time can predominate over these compensatory mechanisms, thereby causing ventricular filling and stroke volume to fall. The point at which increased heart rate begins to decrease stroke volume varies considerably among individuals because of age, health, and physical conditioning. Furthermore, this point can vary within an individual depending on the

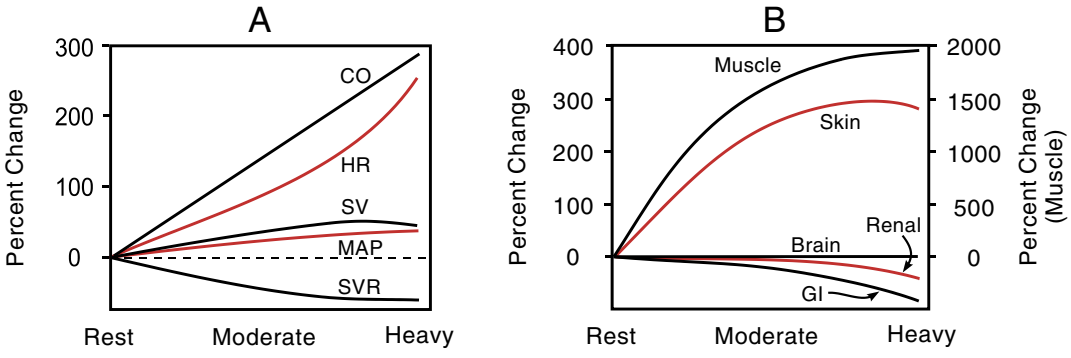

FIGURE 9-2 Systemic hemodynamic and organ blood flow responses at different levels of exercise intensity. Panel *A* shows systemic hemodynamic changes. Systemic vascular resistance (*SVR*) decreases because of vasodilation in active muscles; mean arterial pressure (*MAP*) increases because cardiac output (*CO*) increases more than SVR decreases. CO and heart rate (*HR*) increase almost proportionately to the increase in workload. Stroke volume (*SV*) plateaus at high heart rates. Panel *B* shows organ blood flow changes. Muscle blood flow increases to very high levels because of active hyperemia; skin blood flow increases because of the need to remove excess heat from the body. Sympathetic-mediated vasoconstriction decreases gastrointestinal (*GI*) blood flow and renal blood flow. Brain blood flow changes very little.

type of exercise and the environmental conditions.

Blood flow to major organs depends upon the level of physical activity (Fig. 9-2, Panel B). During whole-body exercise (e.g., running), the blood flow to the active working muscles may increase more than twenty-fold (see Chapter 7). At rest, muscle blood flow is about 20% of cardiac output; this value may increase to 90% during strenuous exercise. Coronary blood flow can increase several-fold as the metabolic demands of the myocardium increase and local regulatory mechanisms cause coronary vasodilation. The need for increased blood flow to active muscles and the coronary circulation would exceed the reserve capacity of the heart to increase its output if not for blood flow being reduced to other organs. During exercise, blood flow decreases to the splanchnic circulation (gastrointestinal, splenic, and hepatic circulations) and nonactive skeletal muscle as workload increases. This is brought about primarily by increased sympathetic nerve activity to these organs. With very strenuous exercise, renal blood flow is also decreased by sympathetic-mediated vasoconstriction.

Skin blood flow increases with increasing workloads, but it can then decrease at very high workloads, especially in hot environments. Increases in cutaneous blood flow are controlled by hypothalamic thermoregulatory centers (see Chapter 7). During physical activity, increased blood temperature is sensed

TABLE 9-2 MECHANISMS MAINTAINING STROKE VOLUME AT HIGH HEART RATES DURING EXERCISE

- Increased venous return promoted by the abdominothoracic and skeletal muscle pumps maintains central venous pressure and therefore ventricular preload.
- Venous constriction (decreased venous compliance) maintains central venous pressure.
- Increased atrial inotropy augments atrial filling of the ventricles.
- Increased ventricular inotropy decreases end-systolic volume, which increases stroke volume and ejection fraction.
- Enhanced rate of ventricular relaxation (lusitropy) aids in filling.

by thermoreceptors in the hypothalamus. To enhance heat loss through the skin, the hypothalamus decreases sympathetic nerve activity to cutaneous blood vessels, which increases skin blood flow. At the same time, activation of sympathetic cholinergic nerves to the skin causes sweating, which is mediated in part by bradykinin that acts as a vasodilator.

While cutaneous vasodilation is essential for thermoregulation during physical activity, this requirement must be balanced by the need to maintain arterial pressure. Cutaneous vasodilation contributes to the fall in systemic vascular resistance that is also brought about by the active muscles. If increased cardiac output is unable to maintain arterial pressure at very high workloads, baroreceptor mechanisms restore sympathetic tone to the skin and decrease its blood flow. Although this may help to preserve arterial pressure temporarily, reduced heat exchange through the skin can lead to dangerous elevations in core temperature, resulting in organ damage and loss of autonomic control. **Heat stroke** is a potentially lethal condition that occurs when core temperatures rise above 105°F.

Factors Influencing Cardiovascular Response to Exercise

The cardiovascular changes associated with physical activity are modified by many different factors. The level of activity, which is commonly expressed as work performed or whole body oxygen consumption, affects the cardiac and vascular responses. Several other important factors influence cardiovascular responses to physical activity.

The **type of exercise** significantly affects cardiovascular responses. The previous section described the cardiovascular responses to dynamic exercise such as running, walking, bicycling, or swimming. This type of activity results in joint movement as muscles contract rhythmically. In contrast, muscle contraction without joint movement (isometric or static contraction) elicits a different cardiovascular response. An example of this activity would be trying to lift a very heavy weight at maximal effort (e.g., bench or leg press). This type of activity does not incorporate rhythmic contraction of synergistic and antagonistic muscle groups; therefore, the muscle pump system

CASE 9-1

A 45-year-old male with type 2 diabetes is diagnosed with autonomic neuropathy, which impairs autonomic function. He complains of becoming weak and "light headed" when he performs physical work such as mowing the lawn. Explain how this patient's autonomic dysfunction may account for his inability to be engaged in normal physical activities.

Autonomic neuropathy affects the function of most organ systems of the body because autonomic nerves play a vital role in regulating normal function. In the cardiovascular system, autonomic nerves, particularly sympathetic adrenergic nerves, regulate arterial pressure through their actions on the heart and vasculature. Patients with type 2 diabetes who have impaired autonomic control of the cardiovascular system may have abnormal responses to exercise because heart rate and inotropy may not increase normally and sympathetic stimulation of the arterial and venous system may be impaired. This loss of sympathetic control may result in a fall in arterial pressure during exercise owing to a greater-than-normal reduction in systemic vascular resistance, a decrease in central venous pressure owing to loss of venous tone, and a reduction in cardiac output caused by smaller-than-normal increases in heart rate and stroke volume. Hypotension during exercise impairs muscle perfusion, causing fatigue. Decreased cerebral perfusion caused by hypotension can lead to dizziness, visual disturbances, and syncope.

cannot operate to promote venous return and so cardiac output increases relatively little. Furthermore, the abdominothoracic pump does not contribute to enhancing venous return, particularly if the subject holds his or her breath during the forceful contraction, effectively performing a Valsalva maneuver (see Valsalva in Chapter 5 on CD). Unlike dynamic exercise, static exercise leads to a large increase in systemic vascular resistance, particularly if a large muscle mass is being contracted at maximal effort. The increased systemic vascular resistance results from enhanced sympathetic adrenergic activity to the peripheral vasculature and from mechanical compression of the vasculature in the contracting muscles. As a result, systolic arterial pressure may increase to over 250 mm Hg during forceful isometric contractions, particularly those involving large muscle groups. This acute hypertensive state can produce vascular damage (e.g., hemorrhagic stroke) in susceptible individuals. In contrast, dynamic exercise leads to only modest increases in arterial pressure.

Body posture also influences how the cardiovascular system responds to exercise because of the effects of gravity on venous return and central venous pressure (see Chapter 5). When a person exercises in the supine position (e.g., swimming), central venous pressure is higher than when the person is exercising in the upright position (e.g., running). In the resting state before the physical activity begins, ventricular stroke volume is higher in the supine position than in the upright position owing to increased right ventricular preload. Furthermore, the resting heart rate is lower in the supine position. When exercise commences in the supine position, the stroke volume cannot be increased appreciably by the Frank-Starling mechanism because the high resting preload reduces the reserve capacity of the ventricle to increase its end-diastolic volume. Stroke volume still increases during exercise although not as much as when exercising while standing; however, the increased stroke volume is resulting primarily from increases in inotropy and ejection fraction with minimal contribution from the Frank-Starling mechanism. Because heart rate is initially lower in the supine position, the percent increase in heart rate is greater in the supine position, which compensates for the reduced ability to increase stroke volume. Overall, the change in cardiac output during exercise, which depends upon the fractional increases in both stroke volume and heart rate, is not appreciably different in the supine versus standing position.

The level of **physical conditioning** significantly influences maximal cardiac output and therefore maximal exercise capacity. A conditioned individual is able to achieve a higher cardiac output, whole-body oxygen consumption, and workload than a person who has a sedentary lifestyle. The increased cardiac output capacity is a consequence, in part, of increased ventricular and atrial responsiveness to inotropic stimulation by sympathetic nerves. Conditioned individuals also have hypertrophied hearts, much like what happens to skeletal muscle in response to weight training. Coupled with enhanced capacity for promoting venous return by the muscle pump system, these cardiac changes permit highly conditioned individuals to achieve ventricular ejection fractions that exceed 90% during exercise. In comparison, a sedentary individual may not be able to increase ejection fraction above 75%. Although the maximal heart rate of a conditioned individual is not necessarily any greater than that of a sedentary individual, the lower resting heart rates of a conditioned person allow for a greater percent increase in heart rate. Heart rate is lower in conditioned individuals because resting stroke volume is increased owing to the larger heart size and increased inotropy. Because resting cardiac output is not necessarily increased in a conditioned person, the heart rate is reduced by increased vagal tone to offset the increase in resting stroke volume, thereby maintaining a normal cardiac output at rest. The enhanced reserve capacity for increasing heart rate and stroke volume enables conditioned individuals to achieve maximal cardiac outputs (and workloads) that can be 50% higher than those found in sedentary people. Another important distinction between a sedentary and conditioned person is that for a given workload, the

conditioned person has a lower heart rate. Furthermore, a conditioned person is able to sustain higher workloads for a longer duration and recover from the exercise much more rapidly.

Environmental factors affect cardiovascular responses to exercise. High altitudes, for example, decrease maximal stroke volume and cardiac output. The reason for this is that the pO_2 in arterial blood is reduced at higher elevations because of decreased atmospheric pressure. This decreases oxygen delivery to tissues, particularly to contracting muscle (both skeletal and cardiac), thereby resulting in insufficient oxygenation at lower workloads. Myocardial hypoxia decreases inotropy, which results in reduced stroke volume. Reduced oxygen delivery to exercising muscle reduces exercise capacity in the muscle and results in increased production of lactic acid as the muscle switches over to more anaerobic metabolism in the absence of adequate oxygen; i.e., the anaerobic threshold is reached at a lower workload.

Increased temperature and humidity affect cardiovascular responses during exercise by diverting a greater fraction of cardiac output to the skin to enhance heat removal from the body. This decreases the availability of blood flow for the contracting muscles. With elevated temperature and humidity, maximal cardiac output and oxygen consumption are reached at lower workloads, thereby reducing exercise capacity as well as endurance. Furthermore, dehydration can accompany high temperatures. Dehydration reduces blood volume and central venous pressure, and it attenuates the normal increase in cardiac output associated with exercise. This can lead to a fall in arterial pressure and heat exhaustion. Signs of **heat exhaustion** include general fatigue, muscle weakness, nausea, and mental confusion; it usually results from dehydration and loss of sodium chloride associated with physical activity in a hot environment—core temperature is not necessarily elevated.

Increased age reduces maximal exercise capacity. Maximal oxygen consumption decreases about 40% between 20 and 70 years of age. Many reasons exist for this decline. With increasing age, maximal heart rate decreases. Maximal heart rate is approximately 220 beats/minute minus the age of a person. Therefore, the maximal heart rate of a 70-year-old person is about 25% lower than the maximal heart rate of a 20-year-old person. Increasing age also reduces maximal stroke volume because of impaired ventricular filling (decreased ventricular compliance) and reduced inotropic responsiveness to sympathetic stimulation. Together, these changes reduce maximal cardiac output substantially. Older individuals have reduced skeletal muscle mass as well as decreased maximal muscle blood flow per unit weight of muscle. Recent research indicates a reduction in vasodilatory capacity of resistance vessels in skeletal muscle in older persons may be related to reduced endothelial production or bioavailability of nitric oxide and altered vascular smooth muscle responsiveness to metabolic vasodilators. Although increasing age inevitably limits exercise capacity, exercise habits and general health can significantly influence the decline in maximal cardiac output with age.

Finally, **gender** influences cardiovascular responses to exercise. Generally, males can reach and sustain significantly higher workloads and maximal oxygen consumptions than can females. Maximal cardiac outputs are about 25% less in females, although the maximal heart rates are similar. This difference is partly owing to increased skeletal muscle mass and to increased cardiac mass in males.

MATERNAL CHANGES IN CARDIOVASCULAR FUNCTION DURING PREGNANCY

Pregnancy causes significant changes in the cardiovascular system (Fig. 9-3). Increased uterine mass and the developing fetus require large amounts of blood flow. To supply this flow, cardiac output increases by 30% to 50% during the first and second trimesters and then plateaus during the third trimester. In the first half of the pregnancy, the cardiac output is primarily increased through increases in stroke volume. By the third trimester, however, stroke volume may be

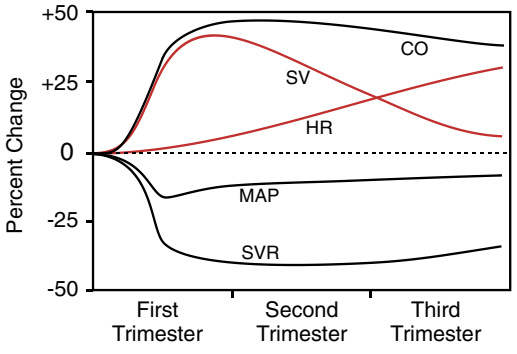

FIGURE 9-3 Changes in maternal hemodynamics during pregnancy. Early in the course of pregnancy, cardiac output (*CO*) increases because stroke volume (*SV*) increases owing to an increase in blood volume; systemic vascular resistance (*SVR*) and mean arterial pressure (*MAP*) decrease. Heart rate (*HR*) gradually increases throughout pregnancy; SV declines as HR increases.

only slightly elevated. At this stage of pregnancy, the increased cardiac output is sustained by an elevated heart rate, which may increase by 10–20 beats/minute.

Cardiac output increases because blood volume increases dramatically during pregnancy. By week 6, blood volume may be increased by 10%. By the end of the third trimester, blood volume may be increased by 50%. The increase in blood volume is brought about by estrogen-mediated activation of the renin-angiotensin-aldosterone system, which increases sodium and water retention by the kidneys.

Although cardiac output is elevated, mean arterial pressure generally falls owing to a disproportionate decrease in systemic vascular resistance. The fall in systemic vascular resistance may be caused in part by hormonal changes that dilate resistance vessels; however, the major factor contributing to the reduced resistance is the development of low-resistance uterine circulation, particularly in the later stages of pregnancy. Diastolic pressure falls more than systolic pressure because of reduced systemic vascular resistance, so there is an increase in pulse pressure. Increased pulse pressure results from the increase in stroke volume during the first and second trimesters.

Pregnancy significantly alters the cardiovascular responses to exercise. Because cardiac output at rest is substantially elevated, there is less capacity for it to increase during exercise. In addition, compression of the inferior vena cava caused by an elevated intra-abdominal pressure, particularly during the third trimester, limits venous return and thereby prevents stroke volume from increasing as it normally would during exercise. Compression of the inferior vena cava, especially in the supine position, can also diminish venous return at rest, thereby reducing cardiac output and arterial pressure (supine hypotensive syndrome).

HYPOTENSION

Causes of Hypotension

Hypotension is often defined clinically as a systolic arterial pressure less than 90 mm Hg, or a diastolic pressure less than 60 mm Hg. There are many causes of hypotension as summarized in Figure 9-4. Because arterial pressure is the product of cardiac output and systemic vascular resistance, a decrease in either will reduce arterial pressure (see Chapter 5).

A reduction in systemic vascular tone or impaired vasoconstrictor responsiveness to baroreceptor reflexes can lead to hypotension. For example, septic shock (or Systemic Inflammatory Response Syndrome, SIRS), which usually results from a bacterial infection in the blood, causes a loss of vascular tone and hypotension. Septic shock is caused by the release of bacterial endotoxins (e.g., lipopolysaccharide) that activate the inflammatory cascade. This leads to the production of cytokines (e.g., tumor necrosis factor, interleukins) and excessive amounts of nitric oxide, causing systemic vasodilation. Systemic vascular resistance can also be decreased if autonomic dysfunction occurs. For example, in diabetic individuals having autonomic neuropathy, baroreceptor-mediated reflex vasoconstriction may be depressed, which can result in a fall in arterial pressure when the person stands up (orthostatic hypotension) and when the person exercises. Injury to the

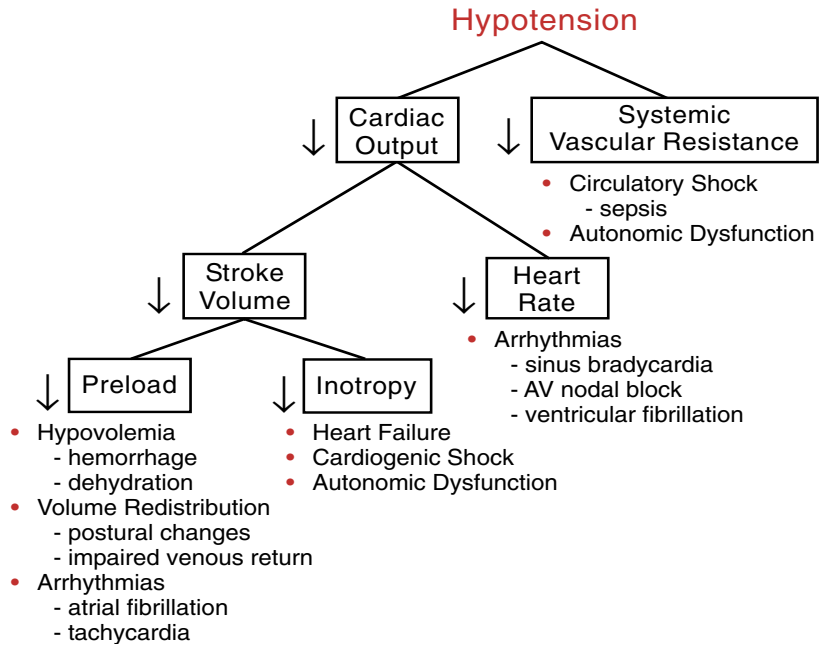

FIGURE 9-4 Mechanisms and causes of hypotension. Ultimately, hypotension occurs because there is a reduction in cardiac output, systemic vascular resistance, or both.

spinal cord can remove sympathetic tone in major organs, leading to hypotension.

Hypotension, however, more commonly occurs because cardiac output is reduced by a decrease in either heart rate or stroke volume. Ventricular rate can be reduced by sinus bradycardia, which may be caused by excessive vagal activation of the SA node. Second- and third-degree AV nodal blockade (see Chapter 2) reduce ventricular rate. A vasovagal reflex can lower heart rate and arterial pressure sufficiently to cause syncope (see Chapter 6).

Stroke volume can be reduced by decreases in either inotropy or ventricular filling (preload) (see Chapter 4). Reduced inotropy occurs during heart failure (systolic failure) and when autonomic dysfunction decreases sympathetic outflow or cardiac responsiveness to sympathetic stimulation. Decreased preload can be caused by several conditions: (1) hypovolemia, which results from blood loss (hemorrhage) or dehydration; (2) a redistribution of blood volume, as occurs when a person stands up (see Chapter 5); (3) reduced venous return, which can result from compression of the vena cava (e.g., during pregnancy); and (4) some types of cardiac arrhythmias (e.g., atrial fibrillation, ventricular tachycardia).

Compensatory Mechanisms during Hypotension

When hypotension occurs, the body attempts to restore arterial pressure by activating neurohumoral compensatory mechanisms (see Chapter 6). Initial, short-term mechanisms involve the baroreceptor reflex, which constricts systemic vascular beds and stimulates the heart. This increases arterial pressure and helps to maintain normal cerebral and coronary perfusion at the expense of reduced blood flow to less essential organs. The baroreceptor compensatory mechanism for hypotension that results from blood loss (**hemorrhagic hypotension**) is summarized in Figure 9-5. More slowly activated, long-term compensatory mechanisms include the renin-angiotensin-aldosterone system and vasopressin. These hormone systems, summarized in Figure 9-6, serve to increase blood volume and reinforce the vasoconstriction caused by increased sympathetic activity.

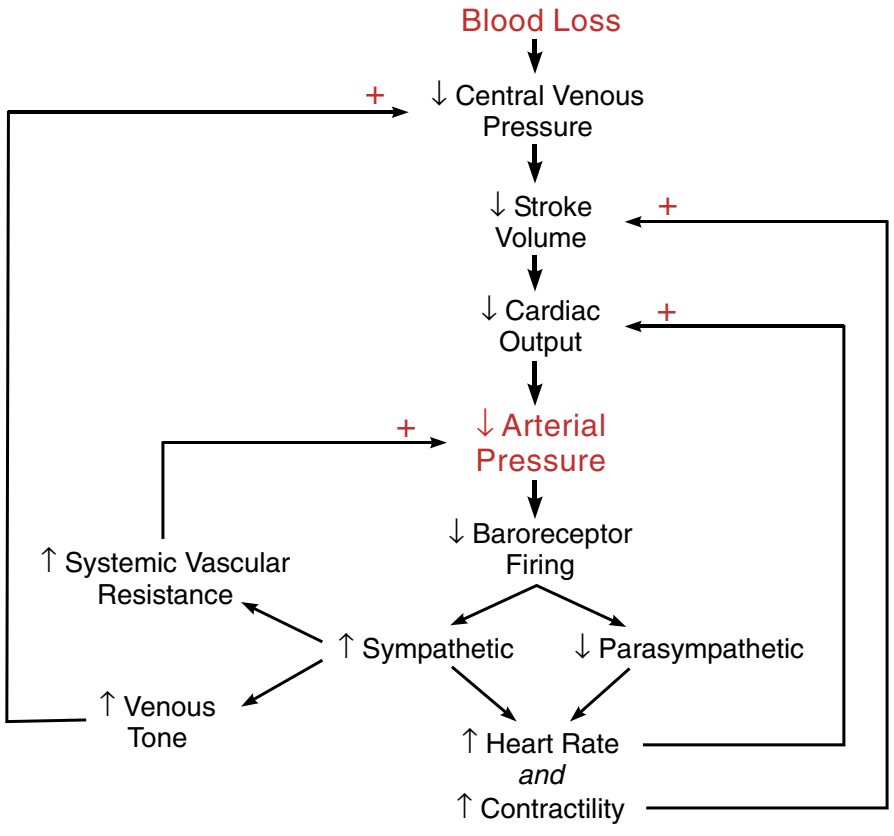

FIGURE 9-5 Activation of baroreceptor mechanisms following acute blood loss (hemorrhage). Blood loss reduces cardiac preload, which decreases cardiac output and arterial pressure. Reduced firing of arterial baroreceptors activates the sympathetic nervous system, which stimulates cardiac function, and constricts resistance and capacitance vessels. These actions increase systemic vascular resistance, central venous pressure, and cardiac output, thereby partially restoring arterial pressure.

Most of the compensatory responses occur regardless of the cause of hypotension; however, the ability of the heart and vasculature to respond to a specific compensatory mechanism may differ depending upon the cause of the hypotension. For example, if hypotension is caused by cardiogenic shock (a form of acute heart failure) secondary to a myocardial infarction, the heart will not be able to respond to sympathetic stimulation in the same manner as would a normal heart. As another example, vascular responsiveness to sympathetic-mediated vasoconstriction is significantly impaired in a person in septic shock. The following discussion specifically addresses compensatory mechanisms in hypotension caused by hemorrhage-induced hypovolemia.

The baroreceptor reflex is the first compensatory mechanism to become activated in response to hypotension caused by blood loss (see Fig. 9-5). This reflex occurs within seconds of a fall in arterial pressure. As described in Chapter 6, a reduction in mean arterial pressure or arterial pulse pressure decreases the firing of arterial baroreceptors. This activates the sympathetic nervous system and inhibits vagal influences to the heart. These changes in autonomic activity increase heart rate and inotropy. It is important to note that cardiac stimulation alone does not lead to a significant increase in cardiac output. For cardiac output to increase, some mechanism must increase central venous pressure and therefore filling pressure for the ventricles. This is accomplished, at least initially follow-

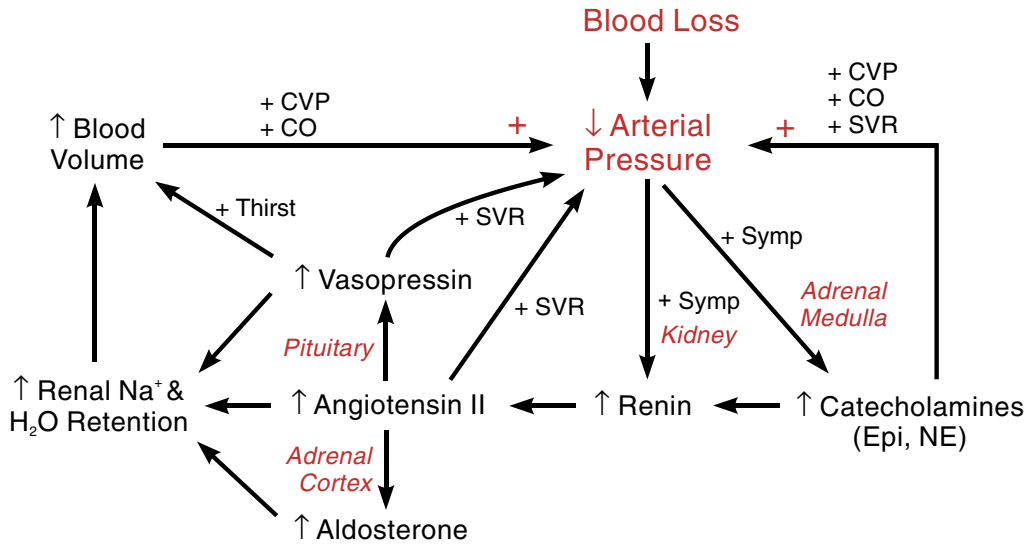

FIGURE 9-6 Activation of humoral mechanisms following acute blood loss (hemorrhage). Decreased arterial pressure activates the sympathetic nervous system (*+Symp*) (baroreceptor reflex). Renin release is stimulated by the enhanced sympathetic activity, increased circulating catecholamines, and hypotension, which leads to the formation of angiotensin II and aldosterone. Vasopressin release from the posterior pituitary is stimulated by angiotensin II, reduced atrial pressure (not shown), and increased sympathetic activity (not shown). These hormones act together to increase blood volume through their renal actions (sodium and water retention), which increases central venous pressure (*+CVP*) and cardiac output (*+CO*). Angiotensin II and vasopressin also increase systemic vascular resistance (*+SVR*). Increased circulating catecholamines (*Epi,* epinephrine; *NE,* norepinephrine) reinforce the effects of sympathetic activation on the heart and vasculature. These changes in systemic vascular resistance, central venous pressure, and cardiac output partially restore the arterial pressure.

ing hemorrhage, by an increase in venous tone produced by sympathetic stimulation of the venous capacitance vessels. The partially restored central venous pressure increases stroke volume through the Frank-Starling mechanism. The increased preload, coupled with cardiac stimulation, causes cardiac output and arterial pressure to increase toward their normal values.

Although the baroreceptor reflex can respond quickly to a fall in arterial pressure and provide initial compensation, the long-term recovery of cardiovascular homeostasis requires activation of hormonal compensatory mechanisms to restore blood volume through renal mechanisms (see Fig. 9-6). Some of these humoral systems also reinforce the baroreceptor reflex by causing cardiac stimulation and vasoconstriction.

The renin-angiotensin-aldosterone system is activated by increased renal sympathetic nerve activity and renal artery hypotension via decreased sodium delivery to the macula densa. Increased circulating angiotensin II constricts the systemic vasculature directly by binding to AT_1 receptors and indirectly by enhancing sympathetic effects. Angiotensin II stimulates aldosterone secretion. Vasopressin secretion is stimulated by reduced atrial stretch, sympathetic stimulation, and angiotensin II. Working together, angiotensin II, aldosterone, and vasopressin cause the kidneys to retain sodium and water, thereby increasing blood volume, cardiac preload, and cardiac output. Increased vasopressin also stimulates thirst so that more fluid is ingested. The renal and vascular responses to these hormones are further enhanced by decreased secretion of atrial natriuretic peptide by the atria, owing to decreased atrial stretch associated with the hypovolemic state.

The vascular responses to angiotensin II and vasopressin occur rapidly in response to increased plasma concentrations of these

vasoconstrictors. The renal effects of angiotensin II, aldosterone, and vasopressin, in contrast, occur more slowly as decreased sodium and water excretion gradually increases blood volume over several hours and days.

Enhanced sympathetic activity stimulates the adrenal medulla to release catecholamines (epinephrine and norepinephrine). This causes cardiac stimulation (β_1-adrenoceptor mediated) and peripheral vasoconstriction (α-adrenoceptor mediated), and contributes to the release of renin by the kidneys through renal β-adrenoceptors.

Other mechanisms besides the baroreceptor reflex and hormones have a compensatory role in hemorrhagic hypotension. Severe hypotension can lead to activation of chemoreceptors (see Chapter 6). Low perfusion pressures and reduced organ blood flow causes increased production of lactic acid as organs are required to switch over to anaerobic glycolysis for the production of ATP. Acidosis stimulates peripheral and central chemoreceptors, leading to increased sympathetic activity to the systemic vasculature. Stagnant hypoxia in the carotid body chemoreceptors, which results from reduced carotid body blood flow, stimulates chemoreceptor firing. If cerebral perfusion becomes impaired and the brain becomes ischemic, intense sympathetic-mediated vasoconstriction of the systemic vasculature will result.

Reduced arterial and venous pressures, coupled with a decrease in the post-to-precapillary resistance ratio, decreases capillary hydrostatic pressures (see Chapter 8). This leads to enhanced capillary fluid reabsorption. This mechanism can result in up to 1 liter/hour of fluid being reabsorbed back into the intravascular compartment, which can lead to a significant increase in blood volume and arterial pressure after a few hours. Although capillary fluid reabsorption increases intravascular volume and serves to increase arterial pressure, it also leads to a reduction in hematocrit and dilution of plasma proteins until new blood cells and plasma proteins are synthesized. The reduced hematocrit decreases the oxygen-carrying capacity of the blood. Dilution of plasma proteins decreases plasma oncotic pressure, which limits the amount of fluid reabsorption.

CASE 9-2

A patient who is being aggressively treated for severe hypertension with a diuretic, an angiotensin-converting enzyme inhibitor, and a calcium-channel blocker is in a serious automobile accident that causes significant intra-abdominal bleeding. How might these drugs affect the compensatory mechanisms that are activated following hemorrhage? How might this alter the course of this patient's recovery?

Recovery from hemorrhage partly involves arterial and venous constriction, cardiac stimulation, and renal retention of sodium and water. The diuretic would counter the normal renal compensatory mechanisms of sodium and water retention. The angiotensin-converting enzyme inhibitor would reduce the formation of circulating angiotensin II that normally plays an important compensatory role through constricting blood vessels and increasing blood volume by enhancing renal reabsorption of sodium and water. The calcium-channel blocker, depending upon its class, would depress cardiac function and cause systemic vasodilation, both of which would counteract normal compensatory responses to hemorrhage. These drugs, therefore, would impair and prolong the recovery process following hemorrhage. Fortunately, many of these drugs have relatively short half-lives so that their effects diminish within several hours.

Decompensatory Mechanisms Following Severe and Prolonged Hypotension

Severe, prolonged hypotension can lead to irreversible shock and death. This occurs when normal compensatory mechanisms (and additional medical resuscitation) are unable to restore arterial pressure to adequate levels in a timely manner. For example, if 40% of a person's blood volume is lost by hemorrhage, arterial pressure may begin to recover as compensatory mechanisms are activated; however, the recovery may last only an hour or two before arterial pressure once again falls, causing death despite heroic interventions.

This secondary fall in arterial pressure results from the activation of decompensatory mechanisms. These decompensatory mechanisms are **positive feedback** cycles, in contrast to the negative feedback control offered by compensatory mechanisms. A negative feedback mechanism attempts to restore a controlled variable (in this case arterial pressure) to its normal value, whereas a positive feedback mechanism causes the controlled variable to move even farther away from its control point.

In the case of severe hemorrhagic shock and some other forms of hypotensive shock (e.g., cardiogenic and septic shock), several potential positive feedback mechanisms can lead to irreversible shock and death. These mechanisms include cardiac depression, sympathetic escape, metabolic acidosis, cerebral ischemia, rheological factors, and systemic inflammatory responses.

Figure 9-7 illustrates how cardiac depression and sympathetic escape can lead to decompensation. A large decrease in blood volume decreases cardiac output and arterial pressure. If mean arterial pressure falls below 60 mm Hg, coronary perfusion becomes reduced, because this pressure is below the coronary autoregulatory range (see Chapter 7). Reduced coronary blood flow causes myocardial hypoxia, which impairs cardiac contractions (reduces inotropy). When this occurs, stroke volume and cardiac output decrease, causing additional decreases in arterial pressure and coronary perfusion—a positive feedback cycle. Also shown in Figure 9-7 is the effect of hypotension on organ blood flow. Hypotension decreases organ blood flow by decreasing perfusion pressure and through baroreceptor-mediated sympathetic activation

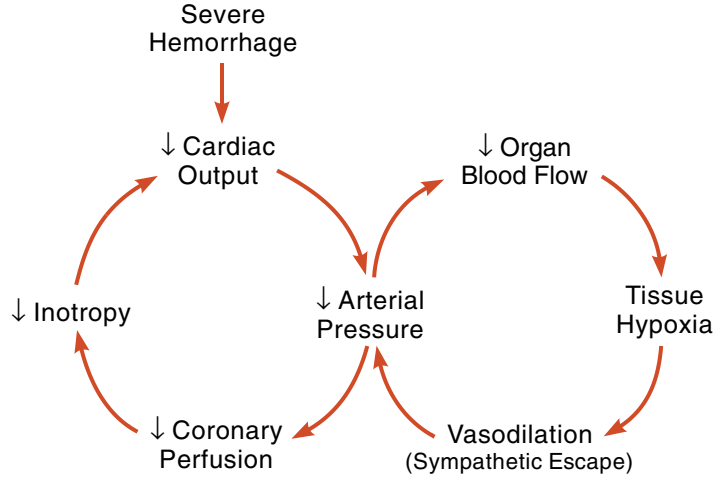

FIGURE 9-7 Positive feedback decompensatory mechanisms triggered by severe hypotension. Impairment of coronary perfusion leads to a loss in cardiac inotropy and an additional decrease in cardiac output and pressure. Prolonged tissue ischemia caused by hypotension (and sympathetic activation) leads to vasodilation (sympathetic escape), which reduces systemic vascular resistance and arterial pressure.

that constricts resistance vessels. This reduced flow causes tissue hypoxia. The more hypoxic a tissue becomes and the longer it remains hypoxic (especially under low flow conditions), the greater the buildup of vasodilator metabolites. These metabolites eventually override the sympathetic-mediated vasoconstriction (sympathetic escape), and blood flow begins to increase within the organ. When this sympathetic escape occurs within major organs of the body (e.g., skeletal muscle and gastrointestinal tract), systemic vascular resistance falls. This reduces arterial pressure and further reduces organ perfusion, which leads to further vasodilation and hypotension—a positive feedback cycle.

Several other positive feedback cycles can contribute to irreversible shock:

- Prolonged hypotension with accompanying tissue hypoxia results in metabolic acidosis as organs begin to generate ATP by anaerobic pathways. Acidosis impairs cardiac contraction and vascular smooth muscle contraction, which decreases cardiac output and systemic vascular resistance, thereby lowering arterial pressure even more.
- Cerebral ischemia and hypoxia during severe hypotension, although initially causing strong sympathetic activation, eventually results in depression of all autonomic outflow as the cardiovascular regulatory centers cease to function because of the lack of oxygen. This withdrawal of sympathetic tone causes arterial pressure to fall, which further reduces cerebral perfusion.
- Reduced organ perfusion during hypotension and intense sympathetic vasoconstriction causes increased blood viscosity within the microcirculation, microvascular plugging by leukocytes and platelets, and disseminated intravascular coagulation. Low-flow states within the microcirculation cause red blood cells to adhere to each other, which increases the viscosity of the blood. Furthermore, low-flow states enhance leukocyte-endothelial adhesion and platelet-platelet adhesion. This reduces organ perfusion even more and can lead to ischemic damage and stimulation of inflammatory processes, which can further enhance metabolic acidosis and impair cardiac and vascular function.

In summary, the body responds to hypotension by activating neurohumoral mechanisms that serve as negative feedback—compensatory mechanisms to restore arterial pressure. With severe hypotension, positive feedback control mechanisms may become operative. These mechanisms counteract the compensatory mechanisms and eventually lead to an additional reduction in arterial pressure.

Physiologic Basis for Therapeutic Intervention

Treatment for hypotension depends upon the underlying cause of the hypotension. If hypotension is caused by hypovolemia owing to hemorrhage or excessive fluid loss (e.g., dehydration), increasing blood volume by administration of blood or fluids becomes a treatment priority. Restoring blood volume increases preload on the heart and thereby increases cardiac output, which is reduced in hypovolemic states. Administration of fluids is occasionally accompanied by the administration of pressor agents. These drugs increase arterial pressure by increasing systemic vascular resistance (e.g., α-adrenoceptor agonists such as norepinephrine and phenylephrine) or by stimulating cardiac function (e.g., β-adrenoceptor agonists such as dobutamine). Treatment of hypotension caused by cardiogenic shock often includes drugs that stimulate the heart (e.g., β-adrenoceptor agonists such as dobutamine or dopamine, or cAMP-dependent phosphodiesterase inhibitors such as milrinone that inhibit the degradation of cAMP); however, depending upon the magnitude of the hypotension, either pressor or depressor agents may be used. Because the primary cause of hypotension in cardiogenic shock is impaired cardiac function, drugs such as phosphodiesterase inhibitors that stimulate the heart and dilate arterial vessels can improve cardiac function by enhancing inotropy and decreasing afterload on the heart. Systemic vasodilators, however, cannot be

used alone if the hypotension is severe, because arterial pressure may fall further. Hypotension associated with septic shock results from systemic vasodilation and, in its later stages, cardiac depression. Therefore, pressor agents are commonly used with this form of shock in addition to administration of fluid and antibiotics.

HYPERTENSION

High blood pressure (hypertension) is a condition that afflicts more than 50 million Americans and is a leading cause of morbidity and mortality. Hypertension is much more than a "cardiovascular disease" because it can damage other organs such as kidney, brain, and eye. One-third of hypertensive people are not aware of being hypertensive because it is usually asymptomatic until the damaging effects of hypertension (such as stroke, myocardial infarction, renal dysfunction, visual disturbances, etc.) are observed.

The term "hypertension" can apply to elevations in mean arterial pressure, diastolic pressure, or systolic pressure above normal values. Normal arterial pressure is defined as a systolic pressure less than 120 mm Hg (but greater than 90 mm Hg) and diastolic pressure less than 80 mm Hg (but greater than 60 mm Hg). Diastolic pressures of 80–89 mm Hg and systolic pressures of 120–139 mm Hg are considered prehypertension. Hypertension is defined as diastolic or systolic pressures equal to or greater than 90 mm Hg or 140 mm Hg, respectively. Both diastolic and systolic hypertension have been shown to be significant risk factors for causing other cardiovascular disorders such as stroke and myocardial infarction. Mean arterial pressure is usually not discussed in the context of hypertension because it is not normally measured in a patient.

Hypertension is caused by either an increase in systemic vascular resistance or an increase in cardiac output, and both are usually increased in chronic hypertension. For example, administration of a vasoconstrictor drug (e.g., an α_1-adrenoceptor agonist such as phenylephrine) increases arterial pressure acutely by increasing systemic vascular resistance. Cardiac stimulation with a β-adrenoceptor agonist (e.g., isoproterenol) causes a small increase in cardiac output and arterial pressure by increasing heart rate and inotropy.

To sustain a hypertensive state (i.e., chronic hypertension), it is necessary to increase blood volume through renal retention of sodium and water. Evidence for this comes from studies showing that acute elevations in arterial pressure (e.g., by infusing a vasoconstrictor) cause **pressure natriuresis** in the kidneys (see Pressure Natriuresis on CD. Briefly, an elevation in renal artery pressure increases glomerular filtration and excretion of sodium and water. The loss of sodium and water decreases blood volume and restores pressure. Therefore, with normal renal function, an acute elevation in arterial pressure caused by increasing systemic vascular resistance or stimulating the heart is compensated by a reduction in blood volume, which restores the arterial pressure to normal. Considerable evidence shows that in chronic hypertension, the pressure natriuresis curve is shifted to the right so that a higher arterial pressure is required to maintain sodium balance. The elevated pressure is sustained by an increase in blood volume. These changes in renal handling of sodium and water can be brought about by changes in sympathetic activity and hormones that affect renal function (e.g., angiotensin II, aldosterone, vasopressin). In addition, changes in renal function associated with renal disease alter kidney filtration and sodium balance, which can shift the pressure natriuresis curve to the right, leading to sustained hypertension.

Essential (Primary) Hypertension

Essential (or primary) hypertension accounts for approximately 90% to 95% of patients diagnosed with hypertension (Table 9-3). Despite many years of active research, no unifying hypothesis accounts for the pathogenesis of essential hypertension. However, a natural progression of this disease suggests that early elevations in blood volume and cardiac output might precede and then initiate subsequent increases in systemic vascular resistance. This

TABLE 9-3 CAUSES OF HYPERTENSION

Essential hypertension (90% to 95%)

- Unknown causes
- Involves:
  - increased blood volume
  - increased systemic vascular resistance (vascular disease)
- Associated with:
  - heredity
  - abnormal response to stress
  - diabetes and obesity
  - age, race, and socioeconomic status

Secondary hypertension (5% to10%)

- Renal artery stenosis
- Renal disease
- Hyperaldosteronism (primary)
- Pheochromocytoma (catecholamine-secreting tumor)
- Aortic coarctation
- Pregnancy (preeclampsia)
- Hyperthyroidism
- Cushing's syndrome (excessive glucocorticoid secretion)

has led some investigators to suggest that the basic underlying defect in hypertensive patients is an inability of the kidneys to adequately handle sodium. Increased sodium retention could account for the increase in blood volume. Indeed, many excellent experimental studies as well as clinical observations have shown that impaired renal natriuresis (sodium excretion) can lead to chronic hypertension.

Besides the renal involvement in hypertension, it is well known that vascular changes can contribute to hypertensive states, especially in the presence of impaired renal function. For example, essential hypertension is usually associated with increased systemic vascular resistance caused by a thickening of the walls of resistance vessels and by a reduction in lumen diameters. In some forms of hypertension, this is mediated by enhanced sympathetic activity or by increased circulating levels of angiotensin II, causing smooth muscle contraction and vascular hypertrophy. In recent years, experimental studies have suggested that changes in vascular endothelial function may cause these vascular changes. For example, in hypertensive patients, the vascular endothelium produces less nitric oxide. Nitric oxide, besides being a powerful vasodilator, inhibits vascular hypertrophy. Increased endothelin-1 production may enhance vascular tone and induce hypertrophy. Evidence suggests that hyperinsulinemia and hyperglycemia in type 2 diabetes (non–insulin-dependent diabetes) cause endothelial dysfunction through increased formation of reactive oxygen species and decreased nitric oxide bioavailability, both of which may contribute to the abnormal vascular function and hypertension often associated with diabetes.

Essential hypertension is related to heredity, age, race, and socioeconomic status. The strong hereditary correlation may be related to genetic abnormalities in renal function and

neurohumoral control mechanisms. The incidence of essential hypertension increases with age, and people of African descent are more likely to develop hypertension than are Caucasians. Hypertension is more prevalent among lower socioeconomic groups.

Some patients with essential hypertension are more strongly influenced by stressful conditions than are normotensive individuals. Stress not only leads to acute elevations in arterial pressure, but it can also lead to chronic elevations in pressure. Stress activates the sympathetic nervous system, which increases cardiac output and systemic vascular resistance. Furthermore, stress causes the adrenal medulla to secrete more catecholamines (epinephrine and norepinephrine) than normal. Sympathetic activation increases circulating angiotensin II, aldosterone, and vasopressin, which together can increase systemic vascular resistance and, through their renal effects, increase sodium and water retention. In addition, prolonged elevation of angiotensin II and catecholamines leads to vascular and cardiac hypertrophy.

Secondary Hypertension

Secondary hypertension accounts for 5% to 10% of hypertensive cases. This form of hypertension has identifiable causes that often can be remedied. Regardless of the underlying cause, arterial pressure becomes elevated owing to an increase in cardiac output, an increase in systemic vascular resistance, or both. When cardiac output is elevated, it is often related to increased blood volume and neurohumoral activation of the heart. Several causes of secondary hypertension are summarized in Table 9-3 and discussed below.

Renal artery stenosis occurs when the renal artery becomes narrowed (stenotic) owing to atherosclerotic or fibromuscular lesions. This reduces the pressure at the afferent arteriole, which stimulates the release of renin by the kidney (see Chapter 6). Increased plasma renin activity increases circulating angiotensin II and aldosterone. Angiotensin II causes vasoconstriction by binding to vascular AT_1 receptors and by augmenting sympathetic influences. Furthermore, angiotensin II along with aldosterone increases renal sodium and water reabsorption. The net effect of the renal actions is an increase in blood volume that augments cardiac output by the Frank-Starling mechanism. In addition, chronic elevation of angiotensin II promotes cardiac and vascular hypertrophy. Therefore, hypertension caused by renal artery stenosis is associated with increases in cardiac output and systemic vascular resistance.

Renal disease (e.g., diabetic nephropathy, glomerulonephritis) damages nephrons in the kidney. When this occurs, the kidney cannot excrete normal amounts of sodium, which leads to sodium and water retention, increased blood volume, and increased cardiac output. Renal disease may increase the release of renin, leading to a renin-dependent form of hypertension. The elevation in arterial pressure secondary to renal disease can be viewed as an attempt by the kidney to increase renal perfusion, thereby restoring normal glomerular filtration and sodium excretion.

Primary hyperaldosteronism is increased secretion of aldosterone by an adrenal adenoma or adrenal hyperplasia. This condition causes renal retention of sodium and water, thereby increasing blood volume and arterial pressure. Aldosterone acts upon the distal convoluted tubule and cortical collecting duct of the kidney to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are excreted in the urine. Plasma renin levels generally are decreased as the body attempts to suppress the renin-angiotensin system. In addition, hypokalemia is associated with the high levels of aldosterone.

A **pheochromocytoma** (a catecholamine-secreting tumor, usually in the adrenal medulla) can cause high levels of circulating catecholamines (both epinephrine and norepinephrine). A pheochromocytoma is diagnosed by measuring plasma or urine catecholamine levels and their metabolites (vanillylmandelic acid and metanephrine). This condition leads to α-adrenoceptor-mediated systemic vasoconstriction and β_1-adrenoceptor-mediated cardiac stimulation that can cause substantial elevations in arterial pres-

sure. Although arterial pressure rises to very high levels, tachycardia still occurs because of the direct effects of the catecholamines on the heart and vasculature. Excessive β_1-adrenoceptor stimulation in the heart often leads to arrhythmias in addition to the hypertension.

Aortic coarctation is a narrowing of the aortic arch usually just distal to the left subclavian artery. It is a congenital defect that obstructs aortic outflow, leading to elevated pressures proximal to the coarctation (i.e., elevated arterial pressures in the head and arms). Distal pressures, however, are not necessarily reduced as would be expected from the hemodynamics associated with a stenosis. The reason for this is that reduced systemic blood flow, and in particular reduced renal blood flow, leads to an increase in the release of renin and an activation of the renin-angiotensin-aldosterone system. This in turn elevates blood volume and arterial pressure. Although the aortic arch and carotid sinus baroreceptors are exposed to higher-than-normal pressures, the baroreceptor reflex is blunted owing to structural changes in the walls of vessels where the baroreceptors are located. Furthermore, baroreceptors become desensitized to chronic elevation in pressure and become "reset" to the higher pressure.

Preeclampsia is a type of hypertension that occurs in about 5% of pregnancies during the third trimester. Preeclampsia differs from less severe forms of pregnancy-induced hypertension in that preeclampsia causes a loss of albumin in the urine because of renal damage, and it is accompanied by significant systemic edema. Preeclampsia results from increased blood volume and tachycardia, as well as increased vascular responsiveness to vasoconstrictors, which can lead to vasospasm. It is unclear why some women develop this condition during pregnancy; however, it usually disappears after parturition unless an underlying hypertensive condition exists.

Hyperthyroidism induces systemic vasoconstriction, an increase in blood volume, and increased cardiac activity, all of which can lead to hypertension. It is less clear why some patients with hypothyroidism also develop hypertension, but it may be related to decreased tissue metabolism reducing the release of vasodilator metabolites, thereby producing vasoconstriction and increased systemic vascular resistance.

Cushing's syndrome, which results from excessive glucocorticoid secretion, can lead to hypertension. Glucocorticoids such as cortisol, which are secreted by the adrenal cortex, share some of the same physiologic properties as aldosterone, a mineralocorticoid also secreted by the adrenal cortex. Therefore, excessive glucocorticoids can lead to volume expansion and hypertension.

Physiologic Basis for Therapeutic Intervention

If a person has secondary hypertension, it is sometimes possible to correct the underlying cause. For example, renal artery stenosis can be corrected by placing a wire stent within the renal artery to maintain vessel patency; aortic coarctation can be surgically corrected; a pheochromocytoma can be removed. However, for the majority of people who have essential hypertension, the cause is unknown so it cannot be targeted for correction. Therefore, the therapeutic approach for these patients involves modifying the factors that determine arterial pressure by using drugs.

Because hypertension results from an increase in cardiac output and increased systemic vascular resistance, these are the two physiologic mechanisms that are targeted in drug therapy. In most hypertensive patients, altered renal function causes sodium and water retention. This increases blood volume, cardiac output, and arterial pressure. Therefore, the most common treatment for hypertension is the use of a diuretic to stimulate renal excretion of sodium and water. This reduces blood volume and arterial pressure very effectively in most patients. In addition to a diuretic, most hypertensive patients are given at least one other drug. This is because decreasing blood volume with a diuretic leads to activation of the renin-angiotensin-aldosterone system, which counteracts the effects of the diuretic. Therefore, many patients are given an angiotensin-converting enzyme

(ACE) inhibitor or angiotensin receptor blocker (ARB) as well.

In addition to using diuretics, cardiac output can be reduced using β-blockers and the more cardiac-selective calcium-channel blockers (e.g., verapamil). Beta-blockers are particularly useful in patients who may have excessive sympathetic stimulation owing to emotional stress, and these drugs also inhibit sympathetic-mediated release of renin.

In combination with a diuretic, some hypertensive patients can be effectively treated with an α-adrenoceptor antagonist, which dilates resistance vessels and reduces systemic vascular resistance. Other drugs that reduce systemic vascular resistance include ACE inhibitors, angiotensin receptor blockers, calcium-channel blockers (especially dihydropyridines), and direct-acting arterial dilators such as hydralazine.

Although pharmacologic intervention is an important therapeutic modality in treating hypertension, improved diet and exercise have been shown to be effective in reducing arterial pressure in many patients. A proper, balanced diet that includes sodium restriction can prevent the progressive of, and in some cases reverse, cardiovascular changes associated with hypertension. Regular exercise, especially aerobic exercise, reduces arterial pressure and has beneficial effects on vascular function.

HEART FAILURE

Heart failure occurs when the heart is unable to supply adequate blood flow and therefore oxygen delivery to peripheral tissues and organs, or to do so only at elevated filling pressures. Heart failure most commonly involves the left ventricle. Right ventricular failure, although sometimes found alone or in association with pulmonary disease, more often occurs secondary to left ventricular failure. Mild heart failure is manifested as reduced exercise capacity and the development of shortness of breath during physical activity (**exertional dyspnea**). In more severe forms of heart failure, a patient may have virtually no capacity for physical exertion and will experience dyspnea even while at rest. Furthermore, the patient will likely have significant pulmonary or systemic edema.

More than 400,000 new cases of heart failure are diagnosed each year in the United States. It is estimated that 15 million new cases of heart failure occur each year worldwide. The numbers are rapidly increasing owing to the aging population. Despite many new advances in drug therapy, the prognosis for chronic heart failure remains poor. One-year mortality figures are 50% to 60% for patients diagnosed with severe failure, 15% to 30% for patients in mild to moderate failure, and about 10% for patients in mild or asymptomatic failure.

Causes of Heart Failure

Heart failure can be caused by factors originating from the heart (i.e., intrinsic disease or pathology) or from external factors that place excessive demands upon the heart. The number-one cause of heart failure is coronary artery disease, which reduces coronary blood flow and oxygen delivery to the myocardium, thereby causing myocardial hypoxia and impaired function. Another common cause of heart failure is myocardial infarction. Infarcted tissue does not contribute to the generation of mechanical activity, and noninfarcted regions must compensate for the loss of function. Over time, the additional demands placed upon the noninfarcted tissue can cause functional changes leading to failure. Valvular disease and congenital defects place increased demands upon the heart that can precipitate failure. Cardiomyopathies (intrinsic diseases of the myocardium that result in a loss of inotropy) of known origin (e.g., bacterial or viral; alcohol-induced) or idiopathic can lead to failure. Infective or noninfective myocarditis (inflammation of the myocardium) can have a similar effect. Chronic arrhythmias also can precipitate ventricular failure.

External factors precipitating heart failure include increased afterload (pressure load; e.g., uncontrolled hypertension), increased stroke volume (volume load; e.g., arterial-

venous shunts), and increased body demands (high output failure; e.g., thyrotoxicosis, pregnancy).

Systolic versus Diastolic Dysfunction

Heart failure can result from impaired ability of the heart muscle to contract (**systolic failure**) or impaired filling of the heart (**diastolic failure**). Systolic failure is caused by changes in cellular signal transduction mechanisms and excitation-contraction coupling that lead to a loss in inotropy (see Chapter 3). Functionally, this causes a downward shift in the Frank-Starling curve (Fig. 9-8). This decreases stroke volume and causes a compensatory rise in preload (clinically measured as increased ventricular end-diastolic pressure or volume, or increased pulmonary capillary wedge pressure [see Pulmonary Wedge Pressure on CD). The rise in preload is an important compensatory mechanism because it activates the Frank-Starling mechanism to help maintain stroke volume despite the loss of inotropy. If preload did not undergo a compensatory increase, the decline in stroke volume would be even greater for a given loss of inotropy. As systolic failure progresses, the ability of the heart to compensate by the Frank-Starling mechanism becomes exhausted.

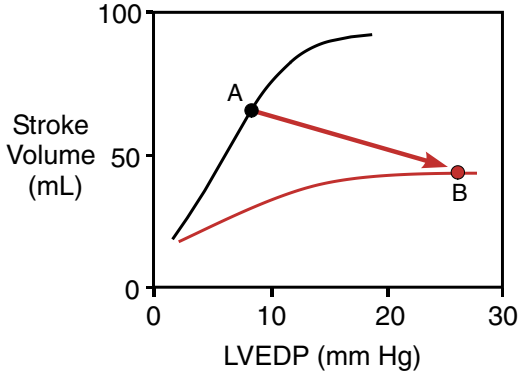

FIGURE 9-8 Effects of systolic failure on left ventricular Frank-Starling curves. Systolic failure decreases stroke volume and leads to an increase in ventricular preload (left ventricular end-diastolic pressure, *LVEDP*). Point *A*, control point; point *B*, systolic failure.

The effects of a loss of inotropy on stroke volume, end-diastolic volume, and end-systolic volume can be depicted using ventricular pressure-volume loops (Fig. 9-9, panel A) (the concept of pressure-volume loops was developed in Chapter 4). Systolic failure decreases the slope of the end-systolic pressure-volume relationship, which occurs because of reduced inotropy. Because of this change, at any given ventricular volume, less pressure can be generated during systole and therefore less volume can be ejected. This leads to an increase in end-systolic volume. The pressure-volume loop also shows that the end-diastolic increases (compensatory increase in preload). Ventricular preload increases because as the heart loses its ability to eject blood, more blood remains in the ventricle at the end of ejection. This results in the ventricle filling to a larger end-diastolic volume as venous return enters the ventricle. The increase in end-diastolic volume, however, is not as great as the increase in end-systolic volume. Therefore, the net effect is a decrease in stroke volume (decreased width of the pressure-volume loop). Because stroke volume decreases and end-diastolic volume increases, a substantial reduction in ejection fraction occurs. Ejection fraction is normally greater than 55%, but it can fall below 20% in severe systolic failure.

The second type of heart failure is diastolic failure, which is caused by impaired ventricular filling. Diastolic failure can be caused by either decreased ventricular compliance (e.g., as occurs with ventricular hypertrophy; see Chapter 4) or impaired relaxation (decreased lusitropy; see Chapter 3). Reduced ventricular compliance, whether of anatomic or physiologic origin, shifts the ventricular end-diastolic pressure-volume relationship (i.e., passive filling curve) up and to the left (Fig. 9-9, panel B). This results in less ventricular filling (decreased end-diastolic volume) and a greater end-diastolic pressure. Stroke volume, therefore, decreases. Depending upon the relative change in stroke volume and end-diastolic volume, ejection fraction may or may not change. For this reason, reduced ejection fraction is useful only as an indicator of systolic failure.

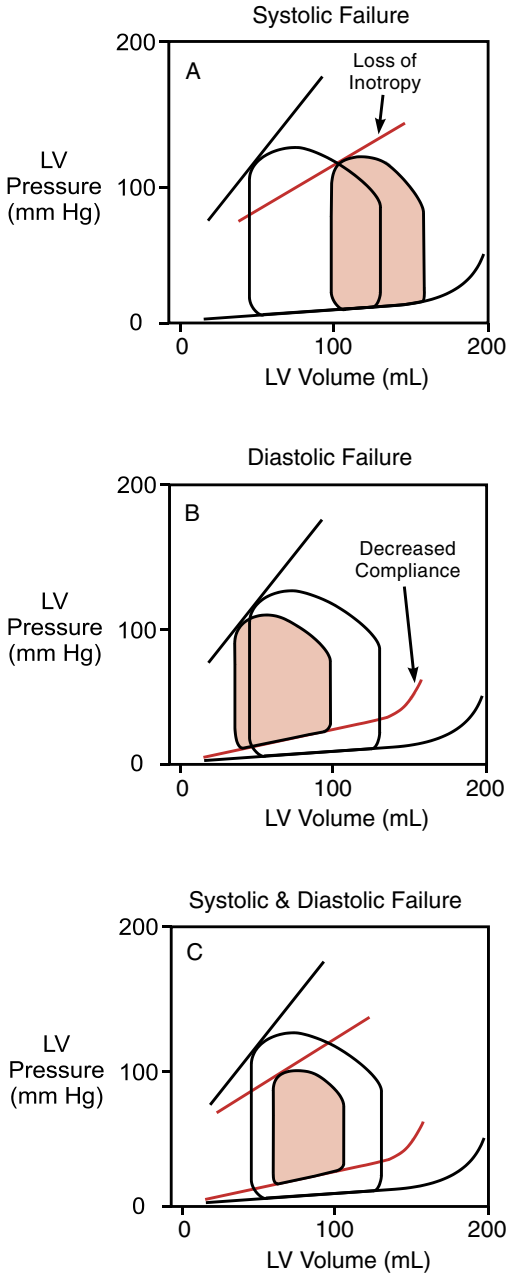

FIGURE 9-9 Effects of systolic, diastolic, and combined failures on left ventricular pressure-volume loops. Panel *A* shows that systolic failure decreases the slope of the end-systolic pressure-volume relationship and increases end-systolic volume. This causes a secondary increase in end-diastolic volume. The net effect is that stroke volume and ejection fraction decrease. Panel *B* shows that diastolic failure increases the slope of the end-diastolic pressure-volume relationship (passive filling curve) because of reduced ventricular compliance caused either by hypertrophy or decreased lusitropy. This reduces the end-diastolic volume and increases end-diastolic pressure. End-systolic volume may decrease slightly as a result of reduced afterload. The net effect is reduced stroke volume; ejection fraction may or may not change. Panel *C* shows that combined systolic and diastolic failure reduces end-diastolic volume and increases end-systolic volume so that stroke volume is greatly reduced; end-diastolic pressure may become very high.

Increased ventricular end-diastolic pressure (which can exceed 30 mm Hg in left ventricular failure—normally less than 10 mm Hg) can have serious clinical consequences because left atrial and pulmonary capillary pressures rise. This can lead to pulmonary edema when the pulmonary capillary wedge pressure exceeds 20 mm Hg. If the right ventricle is in diastolic failure, the increase in end-diastolic pressure is reflected back into the right atrium and systemic venous vasculature. This can lead to peripheral edema and abdominal ascites.

It is not uncommon in chronic heart failure to have a combination of both systolic and diastolic dysfunction to varying degrees (Fig. 9-9, panel C). With both systolic and diastolic dysfunction, the slope of the end-systolic pressure-volume relationship is decreased and the slope of the passive filling curve is increased. This causes a dramatic reduction in stroke volume because end-systolic volume is increased and end-diastolic volume is decreased. This combination of systolic and diastolic dysfunction can lead to high end-diastolic pressures that can cause pulmonary congestion and edema.

Systemic Compensatory Mechanisms in Heart Failure

Heart failure, whether systolic or diastolic in nature, leads to a reduction in cardiac output. In the absence of compensatory mechanisms, a fall in cardiac output has two effects: decreased arterial pressure and increased central venous pressure (see Fig. 5-14). These changes activate neurohumoral mechanisms that attempt to restore cardiac output and arterial pressure (Fig. 9-10).

In response to an acute reduction in cardiac output and arterial pressure, decreased firing of arterial baroreceptors activates the sympathetic adrenergic nerves to the heart and vasculature. The baroreceptor reflex responds only to acute changes in arterial pres-

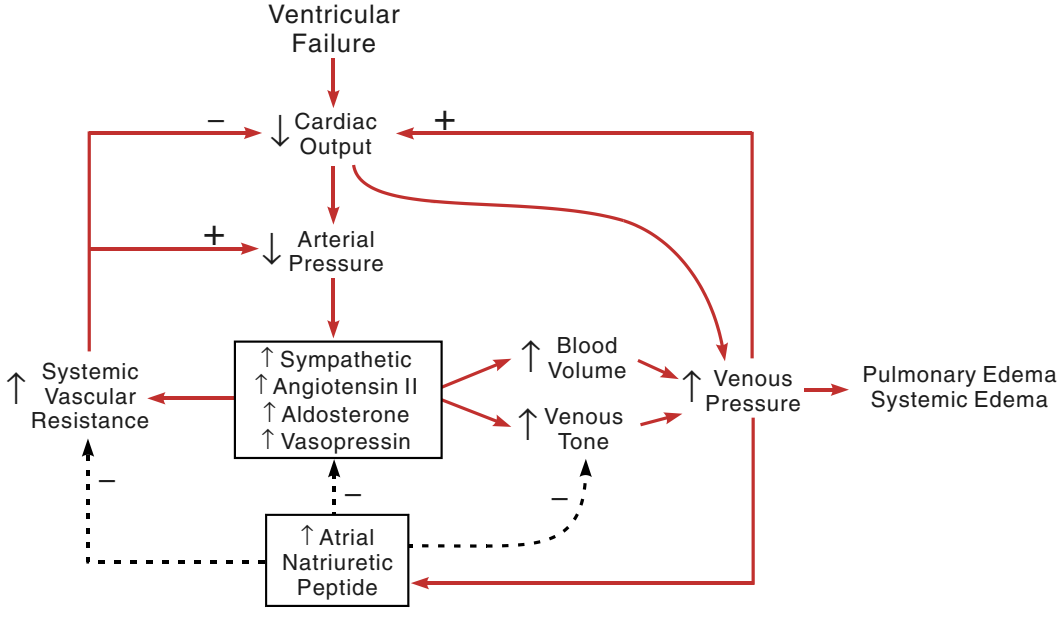

FIGURE 9-10 Summary of neurohumoral changes associated with heart failure. Activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and vasopressin cause an increase in systemic vascular resistance, blood volume, and central venous pressure. Although increased central venous pressure helps to enhance cardiac output by the Frank-Starling mechanism, it can also lead to pulmonary and systemic edema. The increased systemic vascular resistance, although helping to maintain arterial pressure, can impair cardiac output because of increased afterload. Increased atrial natriuretic peptide counter-regulates the other hormonal systems.

sure and therefore cannot be responsible for the increased sympathetic drive when hypotension accompanies chronic heart failure. In addition, not all patients in chronic heart failure are hypotensive; therefore, it is not clear what drives the characteristic increase in sympathetic activity in heart failure.

Important humoral changes occur during heart failure to help compensate for the reduction in cardiac output. Arterial hypotension, along with sympathetic activation, stimulates renin release, leading to the formation of angiotensin II and aldosterone. Vasopressin (antidiuretic hormone) release from the posterior pituitary is also stimulated. Increased vasopressin release seems paradoxical because right atrial pressure is often elevated in heart failure, which should inhibit the release of vasopressin (see Chapter 6). It may be that vasopressin release is stimulated in heart failure by sympathetic activation and increased angiotensin II.

These changes in neurohumoral status constrict resistance vessels, which causes an increase in systemic vascular resistance to help maintain arterial pressure. Venous capacitance vessels constrict as well. This increased venous tone further increases venous pressure. Angiotensin II and aldosterone, along with vasopressin, increase blood volume by increasing renal reabsorption of sodium and water. This contributes to a further increase in venous pressure, which increases cardiac preload and helps to maintain stroke volume through the Frank-Starling mechanism. Increased right atrial pressure stimulates the synthesis and release of atrial natriuretic peptide to counter-regulate the renin-angiotensin-aldosterone system. These neurohumoral responses function as compensatory mechanisms, but they can aggravate heart failure by increasing ventricular afterload (which depresses stroke volume) and increasing preload to the point at which pulmonary or systemic congestion and edema occur.

Exercise Limitations Imposed by Heart Failure

Heart failure can severely limit exercise capacity. In early or mild stages of heart failure, cardiac output and arterial pressure may be normal at rest because of compensatory mechanisms. When the person in heart failure begins to perform physical work, however, the maximal workload is reduced and he or she experiences fatigue and dyspnea at less than normal maximal workloads.

A comparison of exercise responses in a normal person and in a heart failure patient is shown in Table 9-4. In this example, the degree of heart failure is moderate to severe. At rest, the person with congestive heart failure (CHF) has reduced cardiac output (decreased 29%) caused by a 38% decrease in stroke volume. Mean arterial pressure is slightly

TABLE 9-4 COMPARISON OF CARDIOVASCULAR FUNCTION IN A NORMAL PERSON AND A PATIENT WITH MODERATE-TO-SEVERE CONGESTIVE HEART FAILURE (CHF) AT REST AND AT MAXIMAL (MAX) EXERCISE

	CO (LITERS/MIN)	HR (BEATS/MIN)	SV (ML)	MAP (MM HG)	VO_2 (ML O_2/MIN)	A–VO_2 (ML O_2/100 ML)
Normal (Rest)	5.6	70	80	95	220	4.0
Normal (Max)	18.0	170	106	120	2500	13.9
CHF (Rest)	4.0	80	50	90	220	5.5
CHF (Max)	6.0	120	50	85	780	13.0

CO, cardiac output; HR, heart rate; SV, stroke volume; MAP, mean arterial pressure; VO_2, whole-body oxygen consumption; A–VO_2, arterial–venous oxygen difference. VO_2 is calculated from the product of CO and A–VO_2, after the units for CO are converted to mL/min and the units for A–VO_2 are converted to mL O_2/mL blood.

decreased, and resting heart rate is elevated. Whole-body oxygen consumption is normal at rest, but the reduced cardiac output results in an increase in the arterial-venous oxygen difference as more oxygen is extracted from the blood because organ blood flow is reduced. At a maximally tolerated exercise workload, the CHF patient can increase cardiac output by only 50%, compared to a 221% increase in the normal person. The reduced cardiac output is a consequence of the inability of the left ventricle to augment stroke volume as well as a lower maximal heart rate. The CHF patient has a significant reduction in arterial pressure during exercise in contrast to the normal person's increase in arterial pressure. Arterial pressure falls because the increase in cardiac output is not sufficient to maintain arterial pressure as the systemic vascular resistance falls during exercise. The maximal whole-body oxygen consumption is greatly reduced in the CHF patient because reduced perfusion of the active muscles limits oxygen delivery and therefore the oxygen consumption of the muscles. The CHF patient experiences substantial fatigue and dyspnea during exertion, which limits the patient's ability to sustain the physical activity.

Some of the neurohumoral compensatory mechanisms that operate to maintain resting cardiac output in heart failure contribute to limiting exercise capacity. The chronic increase in sympathetic activity to the heart down-regulates β_1-adrenoceptors, which reduces the heart's chronotropic and inotropic responses to acute sympathetic activation during exercise. Increased sympathetic activity (and possibly circulating vasoconstrictors) to the skeletal muscle vasculature limits the degree of vasodilation during muscle contraction. This limits oxygen delivery to the working muscle and leads to increased oxygen extraction (increased arterial-venous oxygen difference), enhanced lactic acid production (and a lower anaerobic threshold), and muscle fatigue at lower workloads. The increase in blood volume, although helping to maintain stroke volume at rest through the Frank-Starling mechanism, decreases the reserve capacity of the heart to increase preload during exercise.

Physiologic Basis for Therapeutic Intervention

Therapeutic goals in the pharmacologic treatment of heart failure include (1) reducing the clinical symptoms of edema and dyspnea; (2) improving cardiovascular function to enhance organ perfusion and increase exercise capacity; and (3) reducing mortality.

Four pharmacologic approaches are taken to achieve these goals. The first approach is to reduce venous pressure to decrease edema and help relieve the patient of dyspnea. Diuretics are routinely used to reduce blood volume by increasing renal excretion of sodium and water. Drugs that dilate the venous vasculature (e.g., angiotensin-converting enzyme inhibitors) also can reduce venous pressure. Judicious use of these drugs to decrease blood volume and venous pressure does not significantly reduce stroke volume because the Frank-Starling curve associated with systolic failure is relatively flat at left ventricular end-diastolic pressures above 15 mm Hg (see Fig. 9-8).

The second approach is to use drugs that reduce afterload on the ventricle by dilating the systemic vasculature. Drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have proven to be useful in this regard for patients with chronic heart failure. Decreasing the afterload on the ventricle can significantly enhance stroke volume and ejection fraction, which also reduces ventricular end-diastolic volume (preload). Because arterial vasodilators enhance cardiac output in heart failure patients, the reduction in systemic vascular resistance does not usually lead to an unacceptable fall in arterial pressure.

The third approach is to use drugs that stimulate ventricular inotropy. A commonly used drug is digitalis, which inhibits the Na^+/K^+- ATPase and thereby increases intracellular calcium (see Chapter 2). This drug, however, has not been shown to reduce mortality associated with heart failure. Drugs that

CASE 9-3

A patient is diagnosed with dilated cardiomyopathy. The echocardiogram shows substantial left ventricular dilation (end-diastolic volume is 240 mL) and an ejection fraction of 20%; the arterial pressure is 115/70 mm Hg. Calculate the stroke volume and end-systolic volume. How would combined therapy with an angiotensin-converting enzyme (ACE) inhibitor and diuretic alter ventricular volumes, ejection fraction, and arterial pressure?

Given that the ejection fraction is 20% and the end-diastolic volume is 240 mL, the stroke volume is 48 mL/beat using the following relationship: stroke volume = ejection fraction x end-diastolic volume. The end-systolic volume is the end-diastolic volume minus the stroke volume, which equals 192 mL. The administration of a diuretic would decrease the end-diastolic volume by decreasing blood volume. The ACE inhibitor would reinforce the effects of the diuretic on the kidney and also cause dilation of resistance and capacitance vessels. These actions would further decrease end-diastolic pressure by decreasing venous pressure, and would reduce the afterload. This latter effect enhances stroke volume by decreasing the end-systolic volume and increasing the cardiac output. The increased stroke volume and decreased end-diastolic volume would cause the ejection fraction to increase. Although the ACE inhibitor would decrease systemic vascular resistance, the increased cardiac output might prevent arterial pressure from falling, or at least partially offset the pressure-lowering effect of systemic vasodilation.

stimulate β_1-adrenoceptors (e.g., dobutamine) or inhibit cAMP-dependent phosphodiesterase (e.g., milrinone) are sometimes used as inotropic agents (see Chapter 3). With the exception of digitalis, inotropic drugs are used only in acute heart failure and end-stage chronic failure because their long-term use has been shown to be deleterious to the heart.

The fourth therapeutic approach involves using β-blockers. Although this might seem counterintuitive, many recent clinical trials have clearly demonstrated the efficacy of newer generation β-blockers (e.g., carvedilol). The mechanism of their efficacy is not clear, but it is known that long-term sympathetic activation of the heart is deleterious. Therefore, β-blockers probably work by reducing the deleterious actions of long-term sympathetic activation. Beta-blockers (as well as angiotensin-converting enzyme inhibitors) provide long-term benefit through ventricular remodeling (e.g., reducing ventricular hypertrophy or dilation). Furthermore, β-blockers such as carvedilol significantly reduce mortality in heart failure.

It should be noted that the therapeutic approaches described above are nearly always used in combination with a diuretic.

SUMMARY OF IMPORTANT CONCEPTS

- Dynamic exercise such as running is associated with a large fall in systemic vascular resistance owing to metabolic vasodilation in active skeletal muscle (i.e., active hyperemia). To maintain (and elevate) arterial pressure, sympathetic activation increases cardiac output and constricts blood vessels in the gastrointestinal tract, nonactive muscles, and kidneys. Skin blood flow increases to facilitate heat loss.
- Adrenal release of catecholamines and activation of the renin-angiotensin-aldosterone system contribute directly or indirectly to the cardiac stimulation and

changes in vascular resistance that occur during exercise.

- Cardiovascular responses to exercise are significantly influenced by the type of exercise (dynamic versus static), body posture, physical conditioning, altitude, temperature, age, and gender.
- The skeletal muscle and abdominothoracic pump systems, along with increased venous tone, facilitate venous return during exercise and prevent preload from falling as heart rate and inotropy increase, thereby enabling cardiac output to increase.
- Pregnancy is associated with an increase in blood volume and cardiac output and a decrease in systemic vascular resistance and mean arterial pressure; heart rate gradually increases during pregnancy.
- Hypotension is most commonly caused by a reduction in cardiac output, which can result from heart failure, cardiac arrhythmias, hemorrhage, dehydration, or changing from supine to standing position. Impaired baroreceptor reflexes (e.g., autonomic dysfunction associated with diabetes) or reduced systemic vascular resistance as occurs in circulatory shock (e.g., septic shock) can also cause hypotension.
- Negative feedback compensatory mechanisms are triggered by hypotension, and they help to restore arterial pressure. These mechanisms include baroreceptor reflexes, renin-angiotensin-aldosterone system activation, increased circulating vasopressin (antidiuretic hormone), adrenal release of catecholamines, and enhanced capillary fluid reabsorption.
- Severe hypotension activates positive feedback mechanisms that can lead to irreversible shock and death. These mechanisms include cardiac depression caused by myocardial ischemia and acidosis, vascular escape from sympathetic vasoconstriction, autonomic depression resulting from cerebral ischemia, rheological factors that impair organ perfusion, and systemic inflammatory responses that damage tissues and impair perfusion.
- Hypertension can result from increases in cardiac output or systemic vascular resistance. Impaired sodium and water excretion by the kidneys, leading to increases in blood volume and cardiac output, appears to be a major factor in the development of essential hypertension, although increases in systemic vascular resistance occur as the disease progresses. Conditions causing secondary hypertension include renal artery stenosis, renal disease, primary hyperaldosteronism, pheochromocytoma, aortic coarctation, pregnancy, hyperthyroidism, and Cushing's syndrome.
- Hypertension can be controlled by drugs that (1) reduce cardiac output (e.g., β-blockers, calcium-channel blockers); (2) decrease systemic vascular resistance (e.g., α-adrenoceptor antagonists, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers); and (3) reduce blood volume (e.g., diuretics).
- Heart failure occurs when the heart is unable to supply adequate blood flow and thus oxygen delivery to peripheral tissues and organs, or when it is able to do so only at elevated filling pressures. It may involve systolic dysfunction (depressed ventricular inotropy) or diastolic dysfunction. The latter is associated with reduced ventricular compliance, often caused by hypertrophy or impaired relaxation; this leads to impaired filling.
- Heart failure is associated with the following cardiovascular changes and clinical symptoms: reduced stroke volume, reduced ejection fraction (systolic dysfunction), increased ventricular and atrial filling pressures, increased blood volume, venous congestion, pulmonary or systemic edema, increased systemic vascular resistance, hypotension (depending upon severity), shortness of breath, fatigue, and reduced exercise capacity.
- The following compensatory mechanisms are activated during heart failure: sympathetic nervous system, renin-angiotensin-aldosterone system, atrial natriuretic peptide, and vasopressin. The overall effect of these mechanisms is an increase in blood volume and systemic vascular resistance to help maintain arterial pressure.

- Pharmacologic management of heart failure is directed toward the following: (1) reducing blood volume, venous congestion, and edema by using diuretics; (2) dilating the systemic vasculature to reduce afterload on the ventricle and thereby improve stroke volume and reduce preload; (3) stimulating the heart with positive inotropic drugs to increase stroke volume and reduce preload (particularly in acute heart failure); and (4) reducing the deleterious effects of chronic sympathetic activation by using β-blockers.

Review Questions

Please refer to appendix for the answers to the review questions.

For each question, choose the one best answer:

1. During a moderate level of whole-body exercise (e.g., running),
   a. Arterial pulse pressure decreases owing to the elevated heart rate.
   b. Sympathetic-mediated vasoconstriction occurs in the skin.
   c. Systemic vascular resistance increases owing to sympathetic activation.
   d. Vagal influences on the sinoatrial node are inhibited.

2. One important reason why stroke volume is able to increase during running exercise is that
   a. Central venous pressure decreases.
   b. Heart rate increases.
   c. The rate of ventricular relaxation decreases.
   d. Venous return is enhanced by the muscle pump system.

3. Maximal cardiac output during exercise
   a. Decreases with age because of decreased maximal heart rate and stroke volume.
   b. Increases by exercise training owing to increased maximal heart rates.
   c. Is higher when exercising in a standing than in a supine position.
   d. Is higher with static than dynamic exercise.

4. In an exercise study, the subject's resting heart rate and left ventricular stroke volume were 70 beats/min and 80 mL/beat, respectively. While the subject was walking rapidly on a treadmill, the heart rate and stroke volume increased to 140 beats/min and 100 mL/beat, respectively; ejection fraction increased from 60% to 75%. The subject's mean arterial pressure increased from 90 mm Hg at rest to 110 mm Hg during exercise. One can conclude that
   a. Cardiac output doubled.
   b. Compared to rest, the cardiac output increased proportionately more during exercise than systemic vascular resistance decreased.
   c. Ventricular end-diastolic volume increased.
   d. The increase in mean arterial pressure during exercise indicates that systemic vascular resistance increased.

5. During pregnancy,
   a. Systemic vascular resistance is increased.
   b. Heart rate is decreased.
   c. Cardiac output is decreased.
   d. Blood volume is increased.

6. The baroreceptor reflex in hemorrhagic shock
   a. Decreases venous compliance.
   b. Decreases systemic vascular resistance.
   c. Increases vagal tone on the SA node.
   d. Stimulates angiotensin II release from the kidneys.

7. Long-term recovery of cardiovascular homeostasis following moderate hemorrhage involves
   a. Aldosterone inhibition of renin release.
   b. Enhanced renal loss (excretion) of sodium.
   c. Increased capillary fluid filtration.

d. Vasopressin-mediated water reabsorption by the kidneys.

8. A mechanism that may contribute to irreversible, decompensated hemorrhagic shock is
   a. Diminished sympathetic-mediated vasoconstriction.
   b. Increased capillary fluid reabsorption.
   c. Myocardial depression by metabolic alkalosis.
   d. Increased renin release by kidneys.

9. Hypertension may result from
   a. Excessive nitric oxide production by vascular endothelium.
   b. Low plasma concentrations of catecholamines.
   c. Low plasma renin activity.
   d. Decreased renal sodium excretion.

10. One mechanism by which a β-blocker lowers blood pressure in a patient with essential hypertension is by
    a. Dilating the systemic vasculature.
    b. Increasing plasma renin activity.
    c. Increasing ventricular preload.
    d. Reducing heart rate.

11. Left ventricular systolic failure is usually associated with
    a. Decreased systemic vascular resistance.
    b. Increased ejection fraction.
    c. Increased left ventricular end-diastolic volume.
    d. Reduced pulmonary capillary pressures.

12. Compared to the maximal exercise responses of a normal subject, a patient with moderate-to-severe heart failure during maximal exercise will have a
    a. Lower arterial pressure.
    b. Lower arterial-venous oxygen extraction.
    c. Higher ejection fraction.
    d. Similar maximal oxygen consumption.

13. Reducing afterload with an arterial vasodilator in a patient diagnosed with heart failure
    a. Improves ventricular ejection fraction.
    b. Increases stroke volume by increasing preload.
    c. Reduces organ perfusion.
    d. Reduces preload and cardiac output.

SUGGESTED READINGS

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Answers to Review Questions

CHAPTER 1

1. The correct answer is "a" because blood flow carries heat from the deep organs within the body to the skin where the heat energy can be given off to the environment. Choice "b" is incorrect because the pulmonary and systemic circulations are in series. Choice "c" is incorrect because carbon dioxide is transported from the tissues to the lungs. Choice "d" is incorrect because blood transports oxygen from the lungs to the tissues.
2. The correct answer is "d" because when the volume per beat (stroke volume) is multiplied by the number of beats per minute (heart rate), the units become volume per minute, which is the flow out of the heart (cardiac output). Choice "a" is incorrect because the pulmonary veins empty into the left atrium. Choice "b" is incorrect because the left ventricle generates much higher pressures than the right ventricle during contraction. Choice "c" is incorrect because the right and left ventricles are in series.
3. The correct answer is "a" because when a person stands up, blood pools in the legs, reducing the filling of the heart, which leads to a fall in cardiac output and arterial pressure. Choice "b" is incorrect because increased blood volume leads to an increase in cardiac output and arterial pressure. Choice "c" is incorrect because increased cardiac output increases arterial pressure. Choice "d" is incorrect because increases in circulating angiotensin II and aldosterone increase arterial pressure by constricting systemic blood vessels (angiotensin II) and by acting on the kidneys to increase blood volume (angiotensin II and aldosterone).

CHAPTER 2

1. The correct answer is "d" because the sarcolemmal Na^+/K^+-ATPase is an electrogenic pump that generates hyperpolarizing currents; inhibition of this pump results in depolarization. Furthermore, inhibition of the pump leads to an increase in intracellular sodium and a decrease in intracellular potassium, both of which cause depolarization. Choices "a" and "b" are incorrect because decreased calcium and sodium conductance reduces the inward movement of positive charges that normally depolarize the membrane. Choice "c" is incorrect because increased potassium conductance hyperpolarizes the membrane (see Equations 2-4 and 2-5).
2. The correct answer is "c" because slow depolarization leads to closure of the h-gates, which inactivates the fast sodium channels. Choice "a" is incorrect because the m-gates open at the onset of phase 0, which activates the fast sodium channels. Choice "b" is incorrect because it is the closure of the h-gates that inactivates the channel. Choice "d" is incorrect because L-type (long-lasting) calcium channels have a prolonged phase of activation before they become inactivated.
3. The correct answer is "d" because the membrane potential during phase 4 is primarily determined by the high potassium conductance. Choices "a," "b," and "c" are incorrect because the overall potassium conductance is reduced during phases 0

through 2, and it begins to recover only during early phase 3.

4. The correct answer is "a" because one effect of β_1-adrenoceptor activation is to increase I_f, which enhances the rate of spontaneous depolarization. Choice "b" is incorrect because fast sodium channels are inactivated in SA nodal cells; inward calcium currents are responsible for phase 0. Choice "c" is incorrect because potassium conductance is lowest during phase 0. Choice "d" is incorrect because vagal stimulation reduces pacemaker firing rate, in part, by decreasing the slope of phase 4.
5. The correct sequence of activation and conduction within the heart is choice "a".
6. The correct answer is "b" because acetylcholine released by the vagus nerve binds to M_2 receptors, which decreases conduction velocity. Removal of vagal tone through the use of a muscarinic receptor antagonist (e.g., atropine) leads to an increase in conduction velocity. Choice "a" is incorrect because blocking β_1-adrenoceptors would decrease the influence of sympathetic nerves on the AV node and lead to a decrease in conduction velocity. Choice "c" is incorrect because depolarization of the AV node, which occurs during hypoxic conditions, decreases conduction velocity. Choice "d" is incorrect because L-type calcium channel blockers (e.g., verapamil) reduce conduction velocity by decreasing the rate of calcium entry into the cells during depolarization, which decreases the slope of phase 0 in AV nodal cells.
7. The correct answer is "c" because the T wave represents repolarization of the ventricular muscle. Choice "a" is incorrect because the normal P-R interval is between 0.12 and 0.20 seconds. Choice "b" is incorrect because the duration of the ventricular action potential is most closely associated with the Q-T interval. Choice "d" is incorrect because the duration of the QRS complex is normally less than 0.1 seconds.
8. The correct answer is "a" because the positive electrode is on the left arm and the negative electrode in on the right arm for lead I. Choices "b" and "d" are incorrect because lead II and aV_F have the positive electrode on the left leg. Choice "c" is incorrect because the positive electrode is on the right arm for aV_R.
9. The correct answer is "a" because when lead II is biphasic, the mean electrical axis must be perpendicular to that lead, and therefore it is either –30° or +150°. Because aV_L is positive, the mean electrical axis must be –30° because that is the axis for aV_L. All the other choices are therefore incorrect.
10. The correct answer is "c" because a complete dissociation between P waves and QRS complexes indicates a complete (third-degree) AV nodal block. Furthermore, the rate of ventricular depolarizations and the normal shape and duration of the QRS complexes suggest that the pacemaker driving ventricular depolarization lies within the AV node or bundle of His so that conduction follows normal ventricular pathways. Choice "a" is incorrect because a first-degree AV nodal block increases only the P-R interval. Choice "b" is incorrect because some of the QRS complexes would still be preceded by a P wave in a second-degree block. Choice "d" is incorrect because premature ventricular complexes normally have an irregular discharge rhythm and the QRS is abnormally shaped and has a longer-than-normal duration.

CHAPTER 3

1. The correct answer is "b" because myosin light chain kinase is involved in myosin phosphorylation in both types of muscle. Choice "a" is incorrect because dense bodies are specialized regions found only within vascular smooth muscle cells where bands of actin filaments are joined together. Choices "c" and "d" are incorrect because these structures are found in

cardiac muscle cells, not smooth muscle cells.

2. The correct answer is "b" because myosin is the major component of the thick filament. Choices "a," "c," and "d" are incorrect because they are all components of the thin filament.
3. The correct answer is "c" because a myosin binding site is exposed on the actin after calcium binds to TN-C. Choices "a" and "b" are incorrect because calcium binds to TN-C, not myosin or TN-I. Choice "d" is incorrect because SERCA pumps calcium back into the sarcoplasmic reticulum.
4. The correct answer is "d" because phosphorylation of the L-type calcium channels by protein kinase A increases the permeability of the channel to calcium, thereby permitting more calcium to enter the cell during depolarization, which triggers the release of calcium by the sarcoplasmic reticulum. Choice "a" is incorrect because Gi-protein activation decreases cAMP formation, thereby decreasing inotropy. Choice "b" is incorrect because calcium binding to TN-C enhances inotropy. Choice "c" is incorrect because it is the calcium that is released by the terminal cisternae of the sarcoplasmic reticulum that binds to TN-C leading to contraction.
5. The correct answer is "d" because β_2-adrenoceptor activation in vascular smooth muscle increases cAMP, which inhibits phosphorylation of myosin light chains by myosin light chain kinase. Choice "a" is incorrect because activation of myosin light chain kinase leads to myosin phosphorylation and contraction. Choice "b" is incorrect because β_2-adrenoceptor activation causes smooth muscle relaxation. Choice "c" is incorrect because β_2-adrenoceptor activation increases cAMP.
6. The correct answer is "c" because angiotensin II receptors (AT_1) are coupled to the Gq-protein and phospholipase C, which increases IP_3 when activated. Choice "a" is incorrect because angiotensin II activates the Gq-protein. Choice "b" is incorrect because the Gq-protein stimulates IP_3 formation, not cAMP. Choice "d" is incorrect because the increase in IP_3 stimulates calcium release from the sarcoplasmic reticulum.
7. The correct answer is "b" because endothelin-1 (ET-1) acts through the Gq-protein pathway to increase IP_3, which leads to contraction. Choices "a" and "c" are incorrect because increased nitric oxide stimulates the formation of cGMP, which leads to relaxation. Choice "d" is incorrect because prostacyclin (PGI_2) causes smooth muscle relaxation by acting through the Gs-protein and stimulating the formation of cAMP.

CHAPTER 4

1. The correct answer is "c" because the mitral valve is open throughout ventricular filling. Choice "a" is incorrect because S_4, when heard, is associated with atrial contraction and frequently is heard in hypertrophied hearts. Choice "b" is incorrect because the aortic valve is open only during ventricular ejection. Choice "d" is incorrect because the ventricular pressure is higher than aortic pressure only during the phase of rapid ejection.
2. The correct answer is "c" because more time is available for filling at reduced heart rates (diastole is lengthened); therefore, preload is increased at reduced heart rates. Choices "a," "b," and "d" are incorrect because decreased atrial contractility, blood volume, and ventricular compliance lead to reduced ventricular filling and therefore reduced preload.
3. The correct answer is "a" because increased preload causes length-dependent activation of actin and myosin, which increases active tension development. This is the basis for the Frank-Starling mechanism. Choice "b" is incorrect because changes in inotropy are independent of sarcomere length. Choice "c" is incorrect because an increase in preload, by

definition, is an increase in sarcomere length. Choice "d" is incorrect because an increase in preload increases the velocity of shortening by shifting the force-velocity curve to the right.

4. The correct answer is "d" because ventricular hypertrophy reduces ventricular compliance, which results in elevated end-diastolic pressures when the ventricle fills. Choice "a" is incorrect because decreased afterload leads to a reduction in end-systolic volume, which results in a secondary fall in end-diastolic volume and pressure. Choice "b" is incorrect because decreased venous return decreases ventricular filling, which decreases ventricular end-diastolic volume and pressure. Choice "c" is incorrect because increased inotropy reduces end-systolic volume, which results in a secondary fall in end-diastolic volume and pressure.
5. The correct answer is "a" because decreased inotropy diminishes the ability of the ventricle to develop pressure and eject blood. Choice "b" is incorrect because increased venous return increases stroke volume by the Frank-Starling mechanism. Choice "c" is incorrect because reduced afterload enhances the ability of the ventricle to eject blood and therefore increases stroke volume. Choice "d" is incorrect because a reduced heart rate provides more time for filling, which increases preload and stroke volume by the Frank-Starling mechanism.
6. The correct answer is "c" because a decrease in inotropy causes a reduction in stroke volume, which increases the end-systolic volume. Choice "a" is incorrect because a sudden increase in aortic pressure increases the afterload on the ventricle, which reduces stroke volume and increases end-systolic volume. Choice "b" is incorrect because end-diastolic volume, by definition, is the ventricular volume at the end of filling, whereas the end-systolic volume is that which is left in the ventricle after ejection. Choice "d" is incorrect because increasing preload alone does not change end-systolic volume.
7. The correct answer is "a" because β_1-adrenoceptors are coupled to the Gs-protein, which increases cAMP (see Chapter 3). Choice "b" is incorrect because an increase in heart rate leads to an increase in inotropy (Bowditch effect), probably owing to an increase in intracellular calcium. Choice "c" is incorrect because calcium movement into the cell during the action potential triggers the release of calcium from the sarcoplasmic reticulum, which leads to contraction (see Chapter 3). Therefore, decreased calcium entry into the cell results in less calcium release by the sarcoplasmic reticulum and decreased inotropy. Choice "d" is incorrect because vagal activation decreases inotropy.
8. The correct answer is "b" because an increase in inotropy increases stroke volume, which is the width of the pressure-volume loop. Choice "a" is incorrect because increased inotropy increases stroke volume and reduces the end-systolic volume. Choice "c" is incorrect because increased inotropy causes a secondary reduction in end-diastolic volume because of the reduced end-systolic volume. Choice "d" is incorrect because increased inotropy shifts the force-velocity curve to the right so that for any given afterload, an increase in muscle fiber shortening velocity occurs.
9. The correct answer is "b". Choices "a" and "c" are incorrect because increasing afterload decreases ejection velocity and stroke volume, which leads to an increase in end-systolic volume. Choice "d" is incorrect because V_{max}, which is the y-intercept of the force-velocity relationship, changes only when there are changes in inotropy.
10. The correct answer is "b" because an increase in end-diastolic volume will increase stroke volume; however, stroke volume changes are about one-fourth as effective in changing myocardial oxygen consumption as are changes in heart rate, mean arterial pressure, or ventricular radius because of the relationships between oxygen consumption, wall stress, ventric-

ular pressure, and ventricular radius. For this reason, choices "a," "c," and "d" are incorrect.

CHAPTER 5

1. The correct answer is "c" because these vessels are the most permeable to fluid. Choice "a" is incorrect because capillaries, not arterioles, have the highest individual resistance because of their small diameter. Choice "b" is incorrect because the large number of parallel capillaries reduces their overall resistance as a group of vessels. Choice "d" is incorrect because the small arteries and arterioles are the primary sites for pressure and flow regulation.
2. The correct answer is "a" because any factor that reduces stroke volume will decrease pulse pressure. Choice "b" is incorrect because increased inotropy increases stroke volume, which increases pulse pressure. Choice "c" is incorrect because aortic compliance decreases with age. Choice "d" is incorrect because the perfusion pressure for the systemic circulation is aortic pressure minus right atrial pressure.
3. The correct answer is "c;" "a" and "b" are incorrect because reducing heart rate by 10% without changing stroke volume decreases cardiac output by 10%. Because mean arterial pressure is also reduced by 10% and mean arterial pressure equals cardiac output times systemic vascular resistance (when central venous pressure is zero), systemic vascular resistance is not changed. Choice "d" is incorrect because systemic vascular resistance changes if the systemic vasculature dilates.
4. The correct answer is "d" because a 50% increase in diameter will increase flow by about five-fold because flow is proportional to radius (or diameter) to the fourth power in a single vessel segment (assuming that the pressure gradient does not change appreciably). Choice "a" is incorrect because decreasing temperature increases blood viscosity, which decreases flow. Choice "b" is incorrect because increasing perfusion pressure by 100% increases flow by about 100%. Choice "c" is incorrect because flow is inversely related to blood viscosity.
5. The correct answer is "a" because systemic vascular resistance equals arterial minus venous pressure (mm Hg) divided by cardiac output (mL/min).
6. The correct answer is "b" because the renal artery is the distributing artery to the kidney, which is in series with the renal artery. Although decreasing the diameter by 50% increases the resistance of the renal artery sixteen-fold, the total renal resistance increases only about 15% because the renal artery resistance is about 1% of total renal resistance. Therefore, flow will decrease about 13%.
7. The correct answer is "a" because a forced expiration against a closed glottis (Valsalva maneuver) increases intrapleural pressure, which compresses the vena cava and increases central venous pressure. Choice "b" is incorrect because increasing cardiac output decreases venous blood volume, which decreases central venous pressure. Choice "c" is incorrect because increasing venous compliance decreases venous pressure. Choice "d" is incorrect because gravitational forces associated with standing causes blood to pool in the legs, which decreases central venous volume and pressure.
8. Choice "d" is correct because inspiration reduces intrapleural pressure, which expands the right atrium, lowers its pressure, and thereby enhances venous return. Choice "a" is incorrect because an increase in cardiac output must increase venous return because the circulatory system is closed. Choice "b" is incorrect because decreased sympathetic activation of the veins causes them to relax, which increases their compliance. This reduces preload on the heart, which leads to a reduction in cardiac output and venous return. Choice "c" is incorrect because a Valsalva maneuver increases intrapleural

pressure, compresses the vena cava, and reduces venous return.

9. Choice "a" is correct because decreased venous compliance shifts the systemic function curve to the right, which increases the mean circulatory filling pressure (value of the x-intercept). Choice "b" is incorrect because changes in systemic vascular resistance alter the slope of the systemic function curve, but not its x-intercept. Choice "c" is incorrect because a decrease in blood volume causes a parallel shift in the systemic function curve to the left, which decreases mean circulatory filling pressure. Choice "d" is incorrect because mean circulatory filling pressure, by definition, is the intravascular pressure when cardiac output is zero, and therefore it is independent of cardiac output.
10. The correct answer is "b" because a decrease in systemic vascular resistance increases the slope of the systemic function curve. Choices "a" and "d" are incorrect because decreased blood volume and increased venous compliance decrease right atrial pressure and cardiac output by causing a leftward parallel shift in the systemic function curve. Choice "c" is incorrect because increased heart rate increases cardiac output a small amount and decreases right atrial pressure.

CHAPTER 6

1. The correct answer is "c" because this region of the brainstem contains cell bodies for both sympathetic and parasympathetic neurons; choices "a" and "b" are therefore incorrect. Choice "d" is incorrect because the nucleus tractus solitarius is the region in the medulla that receives afferent fibers from peripheral sensors (e.g., baroreceptors) and then sends excitatory or inhibitory fibers to sympathetic and parasympathetic neurons within the medulla.
2. The correct answer is "b" because norepinephrine binds to α_1-adrenoceptors located on vascular smooth muscle to stimulate vasoconstriction. Choice "a" is incorrect because norepinephrine preferentially binds to β_1-adrenoceptors in the heart. Choice "c" is incorrect because prejunctional β_2-adrenoceptors facilitate norepinephrine release (prejunctional α_2-adrenoceptors inhibit release). Choice "d" is incorrect because norepinephrine stimulates renin release through β_1-adrenoceptors.
3. The correct answer is "d" because the vagus nerve is parasympathetic cholinergic and therefore releases acetylcholine. Choice "a" is incorrect because efferent right vagal stimulation primarily affects the sinoatrial node and has no significant direct effects on the systemic vasculature. Choice "b" is incorrect because vagal stimulation decreases atrial inotropy. Choice "c" is incorrect because right vagal stimulation reduces heart rate by decreasing the slope of phase 4 of the pacemaker action potential.
4. The correct answer is "c" because increased carotid artery pressure stimulates the firing of carotid sinus baroreceptors (therefore, choice "a" is incorrect), which leads to a reflex activation of vagal efferents to slow the heart rate (therefore, choice "d" is incorrect). Choice "b" is incorrect because the baroreceptor reflex would attempt to reduce arterial pressure by withdrawing sympathetic tone on the systemic vasculature.
5. The correct answer is "b" because increased blood pCO_2 stimulates chemoreceptors, which activate the sympathetic nervous system to constrict the systemic vasculature and raise arterial pressure. Choice "a" is incorrect because submerging the face in cold water elicits the "diving reflex," which causes bradycardia. Choice "c" is incorrect because increased carotid sinus firing (usually caused by elevated arterial pressure) causes a reflex decrease in heart rate brought about by vagal activation and sympathetic withdrawal. Choice "d" is incorrect because the vasovagal reflex causes vagal activation and bradycardia.
6. The correct answer is "d" because this dose of epinephrine binds to both β_2 and α_1-adrenoceptors on blood vessels. Therefore, if the β_2-adrenoceptors (which

produce vasodilation) are blocked, the α_1-adrenoceptors can produce vasoconstriction unopposed by the β_2-adrenoceptors. Choice "a" is incorrect because the unopposed α-adrenoceptor activation increases arterial pressure. Choice "b" is incorrect because epinephrine binds to both α and β-adrenoceptors. Choice "c" is incorrect because the increase in arterial pressure will cause a reflex bradycardia.

7. The correct answer is "c" because acetylcholine dilates blood vessels, which lowers arterial pressure and causes a baroreceptor-mediated increase in heart rate brought about by sympathetic activation. Choice "a" is incorrect because stimulation of muscarinic receptors on the sinoatrial node induces bradycardia. Choice "b" is incorrect because the hypotension causes decreased carotid sinus firing. Choice "d" is incorrect because reflex systemic vasodilation can occur only if arterial pressure is elevated and baroreceptor firing increases.
8. The correct answer is "b" because increased angiotensin II acts directly on the kidney and indirectly by increasing aldosterone secretion (therefore, choice "c" is incorrect) to increase sodium reabsorption, which leads to an increase in blood volume. Choice "a" is incorrect because angiotensin II enhances sympathetic activity by facilitating the release of norepinephrine from sympathetic nerves and decreasing norepinephrine re-uptake. Choice "d" is incorrect because angiotensin II stimulates the release of atrial natriuretic peptide.
9. The correct answer is "c" because atrial natriuretic peptide is counter-regulatory to the renin-angiotensin-aldosterone system (therefore, choices "a" and "b" are incorrect). Choice "d" is incorrect because depression of the renin-angiotensin-aldosterone system leads to enhanced sodium loss, hypovolemia, and a subsequent reduction in cardiac output.

CHAPTER 7

1. The correct answer is "c." Choice "a" is incorrect because elevated pCO_2 causes vasodilation in most organs; therefore decreased pCO_2 would cause vasoconstriction. Choice "b" is incorrect because increased tissue pO_2 causes vasoconstriction. Choice "d" is incorrect because endothelin-1 is a vasoconstrictor.
2. The correct answer is "a" because in response to a reduction in perfusion pressure and blood flow, the kidney undergoes autoregulation through dilation of the afferent arterioles. Choice "b" is incorrect. When the pressure is first reduced, blood flow will fall by about 30%, but after 2 minutes the blood flow will be near normal owing to the autoregulation. Choice "c" is incorrect because afferent arteriolar vasodilation reduces renal vascular resistance. Choice "d" is incorrect because autoregulation, by maintaining blood flow, protects the kidney against ischemia and hypoxia.
3. The correct answer is "c" because the increase in flow (reactive hyperemia) following release of the occlusion causes a flow-dependent release of nitric oxide by the vascular endothelium, which further contributes to the increase in blood flow. Choice "a" is incorrect because active hyperemia is associated with increased tissue metabolic activity and not with postischemic hyperemia. Choice "b" is incorrect because vasodilation occurs during ischemia. Choice "d" is incorrect because increased interstitial adenosine dilates coronary arterioles.
4. The correct answer is "c." Choice "a" is incorrect because the brain responds little to sympathetic activation. Although the coronary vasculature in the heart (choice "b") is capable of responding to sympathetic activation, concurrent stimulation of heart rate and inotropy lead to metabolic vasodilation. Choice "d" is incorrect because sympathetic control of the skin circulation is primarily related to thermoregulation; therefore, the baroreceptor reflex associated with standing has little influence on cutaneous blood flow.
5. The correct answers are "f" and "i".
6. The correct answers are "b" and "d".
7. The correct answer is "e".

8. The correct answer is “c”.
9. The correct answer is “a”.
10. The correct answer is “g”.

CHAPTER 8

1. The correct answer is “a” because this is the mechanism by which fluid and accompanying electrolytes move through capillary intercellular junctions. Choice “b” is incorrect because diffusion, although an important mechanism of exchange, is quantitatively less important than bulk flow. Choice “c” is incorrect because osmosis concerns the movement of water. Choice “d” is incorrect because vesicular transport is primarily for the transport of large macromolecules.
2. The correct answer is “c” because decreased tissue pO_2 increases the concentration gradient for oxygen diffusion from the blood into the tissue. Choice “a” is incorrect because decreased arteriolar flow reduces capillary pO_2, which lowers the concentration gradient for diffusion out of the blood. Choice “b” is incorrect because decreased arteriolar pO_2 decreases capillary pO_2 and therefore the oxygen gradient between the blood and tissue. Choice “d” is incorrect because a decrease in the number of flowing capillaries decreases the surface area available for oxygen exchange.
3. The correct answer is “a” because capillary plasma oncotic pressure opposes filtration, therefore decreasing this pressure enhances filtration. Choice “b” is incorrect because decreasing venous pressure reduces capillary hydrostatic pressure, thereby decreasing filtration. Choice “c” is incorrect because increased precapillary resistance decreases capillary hydrostatic pressure and reduces filtration. Choice “d” is incorrect because increased tissue hydrostatic pressure opposes filtration.
4. The correct answer is “b” because the net driving force, calculated from the given values, is –2 mm Hg, which causes reabsorption. Choices “a” and “c” are incorrect because the net driving force is a negative value.
5. The correct answer is “a” because increased filtration results in more fluid being taken up by the lymphatics and removed from the tissue. Choice “b” is incorrect because increased capillary filtration increases filtration fraction. Choice “c” is incorrect because histamine increases the capillary filtration constant, thereby increasing filtration. Choice “d” is incorrect because increased filtration increases interstitial fluid volume, which increases interstitial fluid pressure.
6. The correct answer is “d” because lymphatic obstruction prevents the normal removal of excess filtration from the tissue. Choice “a” is incorrect because increased arteriolar resistance decreases capillary hydrostatic pressure, which decreases filtration. Choice “b” is incorrect because increased plasma protein concentration enhances reabsorption. Choice “c” is incorrect because reduced venous pressure decreases capillary pressure and filtration.

CHAPTER 9

1. The correct answer is “d” because heart rate is increased during exercise through activation of sympathetic adrenergic nerves and inhibition of vagal (parasympathetic) nerves on the sinoatrial node. Choice “a” is incorrect because arterial pulse pressure increases during moderate exercise because of the increase in stroke volume. Choice “b” is incorrect because cutaneous vasodilation occurs during exercise to facilitate heat loss from the body. Choice “c” is incorrect because systemic vascular resistance falls owing to vasodilation in the active skeletal muscle.
2. The correct answer is “d” because the muscle pump system facilitates venous return, which maintains or elevates ventricular filling pressures. Choice “a” is incorrect because a decrease in central venous pressure would decrease stroke volume. Choice “b” is incorrect because an in-

crease in heart rate, with no other compensatory changes, decreases stroke volume. Choice "c" is incorrect because the rate of ventricular relaxation (lusitropy) increases during exercise owing to sympathetic influences, which aids ventricular filling and enhances stroke volume.

3. The correct answer is "a" because the maximal rate of sinoatrial node firing decreases with age, and stroke volume decreases because of a decline in inotropic responsiveness and decreased ventricular compliance. Choice "b" is incorrect because exercise training does not significantly change maximal heart rate, although it improves inotropic responses. Choice "c" is incorrect because body posture does not significantly affect maximal cardiac output, although it influences the relative changes in heart rate and stroke volume. Choice "d" is incorrect because static exercise, unlike dynamic exercise, does not enhance venous return by the muscle pump.
4. The correct answer is "b" because arterial pressure increased; therefore, cardiac output must have increased more than systemic vascular resistance decreased. Choice "a" is incorrect because cardiac output (the product of heart rate and stroke volume) increased from 5.6 to 14.0 liters/min (i.e., it more than doubled). Choice "c" is incorrect because stroke volume increased by 25% (from 80 to 100 mL/beat), and the ejection fraction increased by 25% (from 60% to 75%). Therefore, end-diastolic volume could not have changed because ejection fraction equals stroke volume divided by end-diastolic volume. Choice "d" is incorrect because the percent change in cardiac output is much greater than the percent change in arterial pressure; the systemic vascular resistance can be approximated from the arterial pressure divided by the cardiac output.
5. The correct answer is "d" because activation of the renin-angiotensin-aldosterone system during pregnancy increases blood volume. Choice "a" is incorrect because systemic vascular resistance decreases during pregnancy owing to the developing uterine circulation. Choices "b" and "c" are incorrect because heart rate and cardiac output increase during pregnancy.
6. The correct answer is "a" because the baroreceptor reflex activates sympathetic adrenergic nerves that constrict arterial and venous vessels. Choice "b" is incorrect because sympathetic activation increases systemic vascular resistance. Choice "c" is incorrect because sympathetic activation is accompanied by withdrawal of vagal tone on the heart. Choice "d" is incorrect because renin, not angiotensin II, is released from the kidneys.
7. The correct answer is "d" because long-term recovery from hypovolemia requires renal retention of water, which is partially regulated by vasopressin. Choice "a" is incorrect because increased renin release and subsequent formation of angiotensin II and aldosterone contribute to renal reabsorption of sodium and water. Choice "b" is incorrect because sodium reabsorption, not loss, is enhanced following hemorrhage. Choice "c" is incorrect because increased capillary fluid filtration would decrease blood volume and not serve as a compensatory mechanism following hemorrhage.
8. The correct answer is "a" because organs become ischemic and hypoxic following intense sympathetic activation, and their vasculature eventually escape the sympathetic-mediated vasoconstriction. Choice "b" is incorrect because capillary fluid reabsorption functions as a compensatory mechanism. Choice "c" is incorrect because myocardial depression in hemorrhagic shock occurs in response to metabolic acidosis, not alkalosis. Choice "d" is incorrect because increased renin release and subsequent angiotensin II and aldosterone formation is a compensatory mechanism.
9. The correct answer is "d" because decreased sodium excretion leads to an increase in blood volume, which increases pressure. Choice "a" is incorrect because

nitric oxide is a vasodilator; therefore, excessive production causes hypotension, not hypertension. Choice "b" is incorrect because high levels of circulating catecholamines produce hypertension. Choice "c" is incorrect because high renin levels cause hypertension through the actions of angiotensin II and aldosterone on the vasculature and kidneys.

10. The correct answer is "d" because β-blockers antagonize sympathetic effects on the sinoatrial node, which decreases heart rate and cardiac output. Choice "a" is incorrect because blocking β_2-adrenoceptors on blood vessels increases sympathetic vascular tone owing to unopposed α-adrenoceptor stimulation. Choice "b" is incorrect because β-blockers antagonize sympathetic-stimulated release of renin by the kidneys. Although depressing cardiac function increases ventricular preload, choice "c" is incorrect because increased preload does not contribute to lowering arterial pressure.
11. The correct answer is "c" because loss of inotropy in systolic failure decreases stroke volume and increases end-systolic volume, which leads to a compensatory increase in end-diastolic volume. Choice "a" is incorrect because neurohumoral activation in heart failure increases systemic vascular resistance. Choice "b" is incorrect because ejection fraction decreases because of the decrease in stroke volume and increase in end-diastolic volume. Choice "d" is incorrect because systolic failure increases end-diastolic pressure, which is transmitted back into the pulmonary circulation.
12. The correct answer is "a" because cardiac output is unable to increase sufficiently to maintain arterial pressure as systemic vascular resistance falls during exercise. Choice "b" is incorrect because reduced organ perfusion increases oxygen extraction from the arterial blood. Choice "c" is incorrect because impaired inotropic responses during exercise reduces ejection fraction. Choice "d" is incorrect because the heart failure patient achieves lower maximal oxygen consumption because maximal cardiac output is reduced.
13. The correct answer is "a" because reducing afterload increases stroke volume and reduces ventricular end-diastolic volume; these changes enhance ejection fraction. Choice "b" is incorrect because the arterial vasodilator, by reducing afterload and enhancing stroke volume, decreases ventricular preload in the failing heart. Choice "c" is incorrect because the arterial dilator decreases systemic vascular resistance and increases cardiac output; these changes increase organ perfusion. Choice "d" is incorrect for the reasons given above.

Cardiovascular Physiology Concepts
Supplemental Content

ION PERMEABILITY AND CONDUCTANCE

Permeability and conductance both refer to the ease of movement of solutes across membranes. These terms are often used interchangeably, although they refer to different, but related, concepts.

Permeability (P) is the rate of movement (J) of a solute (i) per unit time (e.g., moles/hour) in response to a standard driving force, such as a 1 molar concentration difference (ΔC); therefore, $P_i = J_i/\Delta C_i$. Permeability can be thought of as a chemical phenomenon, and is used to describe the diffusion of charged solutes (e.g., ions such as sodium) and uncharged solutes (e.g., glucose) across a membrane.

Conductance (g) is an electrical measurement, applicable only to charged solutes (i.e., ions). It is the amount of transmembrane current (I; amps or coul/sec) carried by ions, or by a given ion (i), per unit of applied electrical driving force (i.e., voltage, V); therefore, $g_i = I_i/V$.

Permeability and conductance are related in a practical sense because when the membrane permeability increases to an ion such as sodium, the membrane conductance to sodium also increases. Changes in membrane permeability to ions (and therefore conductance) is controlled by specific membrane channels (see Chapter 2) that open and close to permit the ion, driven by either concentration or electrical differences, to move across the membrane.

REENTRY MECHANISMS

Reentry is an important mechanism in the generation of tachycardias. There are three fundamental requirements for reentry. First, reentry requires the presence of a unidirectional block within a conducting pathway (usually caused by partial depolarization resulting from tissue hypoxia). Second, the timing between action potentials is critical. Third, duration of the effective refractory period of involved action potentials determine whether or not a reentry circuit can become established.

A model for reentry is shown in Figure 1. If a single Purkinje fiber forms two branches (1 and 2), the action potential will divide and

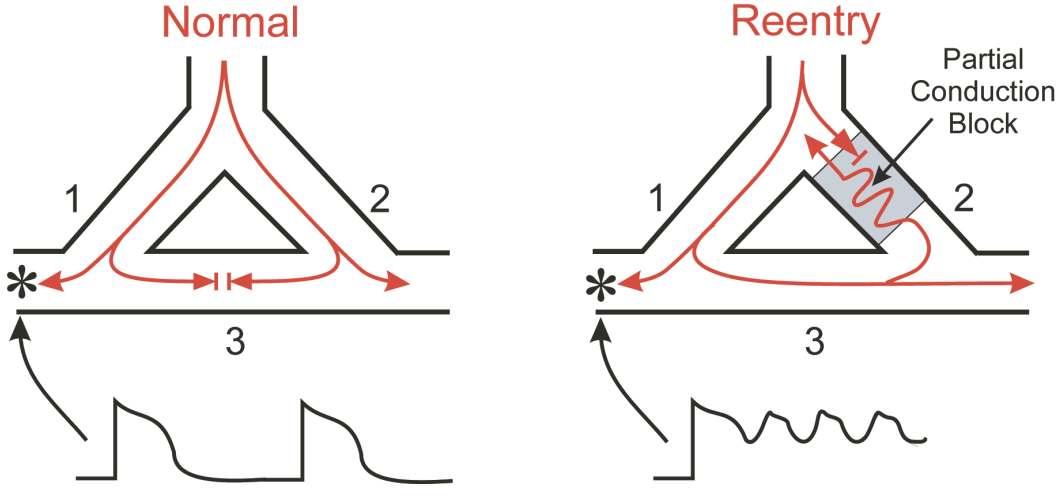

FIGURE 1 Mechanism of reentry. The *left panel* shows normal conduction of action potentials, in which impulses traveling down branches 1 and 2 cancel out each other in branch 3. A recording electrode placed at the asterisk (*) will record a single action potential each time one is conducted in these pathways. The *right panel* shows that reentry can occur if branch 2 has impaired conduction that blocks orthograde impulses, but slowly conducts retrograde impulses. If a retrograde impulse emerging from branch 2 reaches excitable tissue (after the effective refractory period, but before the next normal impulse), an additional, early impulse can be conducted down branch 1. If this occurs repetitively, increased action potential frequency (tachycardia) will be recorded.

travel down each branch (left panel). If these branches then come together into a common branch (3), the action potentials will cancel each other out. An electrode (*) recording from branch 3 would record single, normal action potentials as they are conducted in this branch. This is what occurs in normal conduction.

To model what occurs during reentry, suppose that branch 2 (right panel) has a unidirectional block (impulses can travel retrograde but not orthograde) caused by partial depolarization. An action potential traveling down branch 1, after entering the common distal path (branch 3), travels in retrograde fashion through the unidirectional block in branch 2. Within the block, the conduction velocity is reduced because the tissue is depolarized. As the action potential exits the block, if it finds the tissue excitable, then the action potential will once again be conducted down branch 1 (i.e., reenter branch 1). If the action potential exits the block and finds the tissue unexcitable, then the action potential will cease to propagate. Therefore, timing is critical because the action potential exiting the block must find the tissue excitable for continued propagation and the establishment of a reentry circuit.

Reentry can occur either globally (e.g., between the atria and ventricles) or locally (e.g., within a small region of the ventricle or atrium) as shown in Figure 2. Global reentry between the atria and ventricles often involves accessory conduction pathways such as the bundle of Kent. Accessory pathways allow impulses to be conducted by one or more routes in addition to the normal AV nodal pathway. In the example shown in Figure 2, the impulse travels through the accessory pathway, depolarizes the ventricular tissue, then travels backward (retrograde) through the AV node to re-excite the atrial tissue and thereby establish a counter-clockwise global reentry circuit. (The reentry circuit can also occur clockwise in direction.) Global reentry between the atria and ventricles results in supraventricular tachyarrhythmias (e.g., Wolf-Parkinson-White syndrome, WPW). Local sites of reentry within a small region of the ventricle or atrium

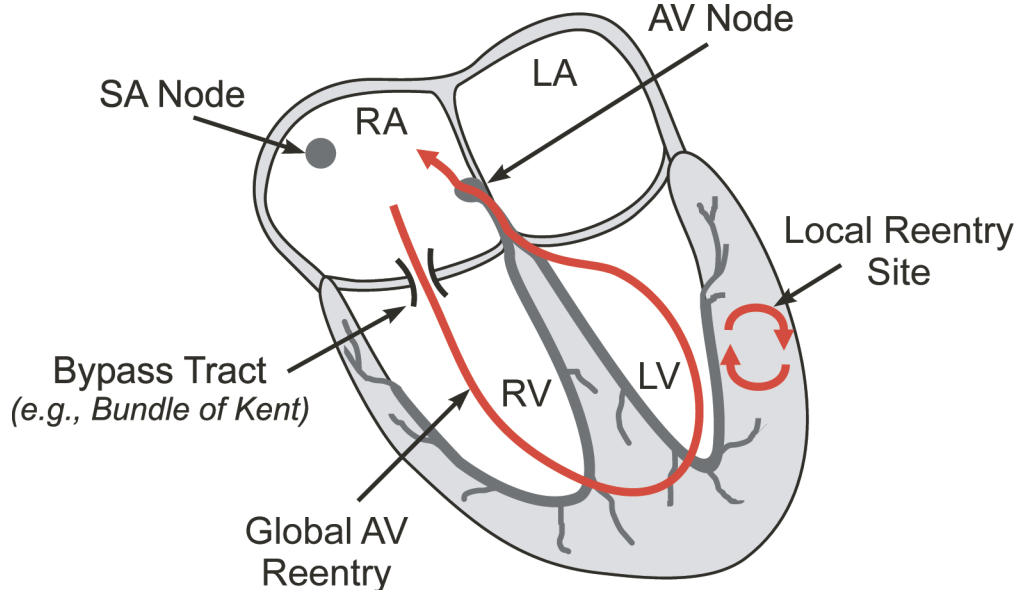

FIGURE 2 Global and local reentry. Global reentry can occur between the atria and ventricles utilizing an accessory pathway in addition to the atrioventricular (*AV*) node. One such pathway is the Bundle of Kent between the right atrium (*RA*) and right ventricle (*RV*), which can lead to retrograde action potential conduction (in this illustration) through the AV node and cause early excitation of atrial muscle and a supraventricular tachycardia. Local reentry circuits can occur within either the ventricles or atria. *LA* = left atrium; *LV* = left ventricle; *SA* = sinoatrial.

can precipitate ventricular or atrial tachyarrhythmias, respectively.

Because both timing and refractory state of the tissue are important for reentry to occur, alterations in timing (related to conduction velocity) and refractoriness (related to effective refractory period) can either precipitate or abolish reentry circuits. Arrhythmias caused by reentry are often paroxysmal in nature (sudden onset and disappearance) because the conditions necessary to establish and maintain reentry are altered by normal variations in conduction velocity and refractoriness brought about by autonomic and other influences. Changes in autonomic nerve function, therefore, can significantly affect reentry mechanisms, either precipitating in susceptible individuals or terminating reentry circuits. Many anti-arrhythmic drugs alter the effective refractory period or conduction velocity, and thereby affect (hopefully abolish) reentry mechanisms. Surgical ablation of accessory pathways can effectively abolish reentry in some patients.

FORMATION AND PHYSIOLOGICAL ACTIONS OF NITRIC OXIDE

Nitric oxide (NO) is produced by vascular endothelium and smooth muscle, cardiac muscle, and many other cell types. The substrate for NO formation is L-arginine, which is acted upon by nitric oxide synthase (NOS) to form NO and citrulline (Figure 1).

There are two general forms of NOS: constitutive (cNOS) and inducible (iNOS). NO is

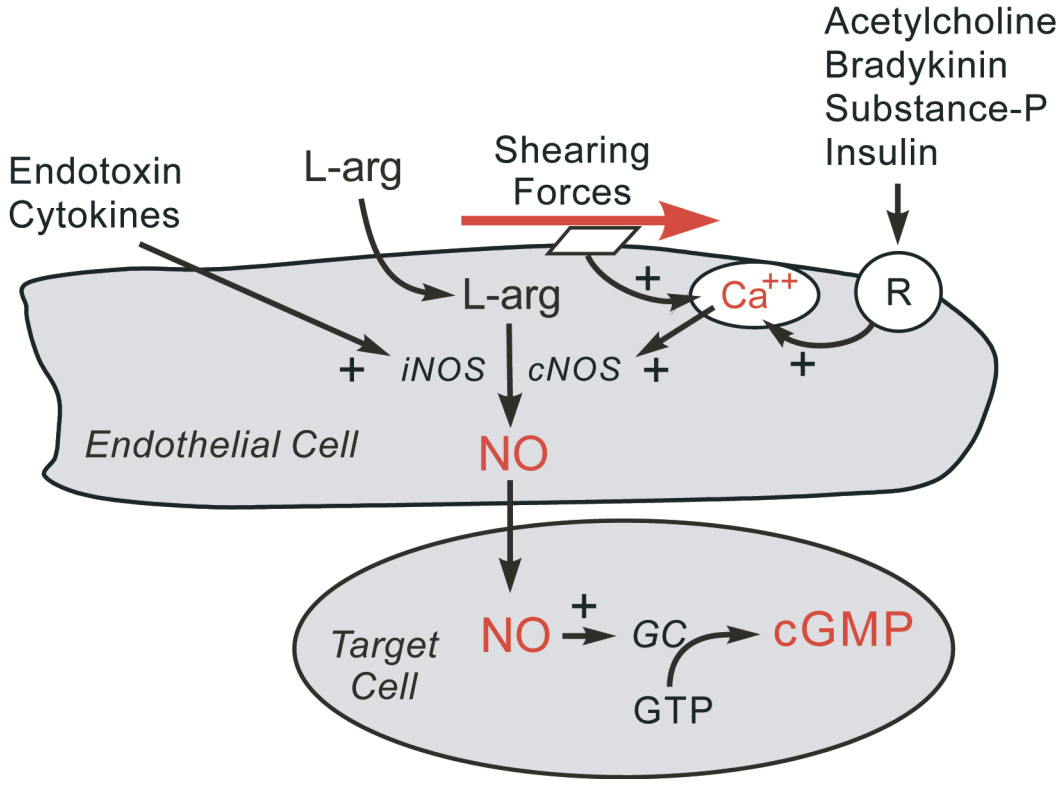

FIGURE 1 Endothelial formation and vascular actions of nitric oxide (*NO*). NO forms from nitric oxide synthase (*NOS*) acting on intracellular L-arginine (L-arg). Constitutive NOS (*cNOS*) is activated by calcium, which can be released in response to increased shearing forces acting on the endothelium or by various compounds that release calcium through receptor-operated mechanisms (*R*). Inducible NOS (*iNOS*) is stimulated by bacterial endotoxins and by cytokines. Once formed, NO diffuses from the endothelial cell to adjacent smooth muscle cells where it activates guanylyl cyclase (*GC*), which leads to the formation of cyclic guanosine monophosphate (*cGMP*) and relaxation of the vascular smooth muscle.

continuously produced by constitutive cNOS, which is found in vascular endothelial cells (other terms for this NOS isoform are eNOS, ecNOS, or Type III NOS). The activity of cNOS is modulated by calcium that is released from subsarcolemmal storage sites in response to the binding of certain ligands (e.g., acetylcholine, bradykinin, insulin, substance P) to their respective receptors. Another important mechanism regulating the release of NO is shearing forces acting on the luminal surface of the vascular endothelium. Increased flow velocity, which increases the shearing forces, stimulates calcium release and increased cNOS activity.

The inducible form of NOS (iNOS, or Type II NOS) is not calcium-dependent, but instead is stimulated by the actions of cytokines (e.g., tumor necrosis factor, interleukins) and bacterial endotoxins (e.g., lipopolysaccharide). Induction of this enzyme occurs over several hours and results in NO production that can be more than a 1,000-fold greater than that produced by cNOS. This is an important mechanism in the pathogenesis of inflammation.

A third type of NOS, neural NOS (nNOS, bNOS, or Type I NOS), is formed in specialized nerves and is involved with central and peripheral neural regulation. Like ecNOS, it is constitutive and activated by calcium release. NO formed by this isoform of NOS is involved in vasodilation caused by activation of specialized non-adrenergic, non-cholinergic (NANC) autonomic nerves that innervate penile erectile tissues.

Nitric oxide serves many important functions in the cardiovascular system as summarized below:

- Vasodilation
- Inhibition of vasoconstrictor influences (e.g., inhibits angiotensin II and sympathetic-mediated vasoconstriction)
- Inhibition of platelet adhesion to the vascular endothelium (i.e., anti-thrombotic)
- Inhibition of leukocyte adhesion to vascular endothelium (i.e., anti-inflammatory)
- Inhibition of smooth muscle hyperplasia following vascular injury (i.e., antiproliferative)
- Scavenging superoxide anion (i.e., anti-inflammatory)

The mechanism of many of these actions of NO involves the formation of cGMP. When NO is formed by an endothelial cell, it readily diffuses out of the cell and into adjacent smooth muscle cells where is binds to a heme moiety on guanylyl cyclase and activates this enzyme to produce cGMP from GTP. Increased cGMP activates a kinase that subsequently inhibits calcium influx into the smooth muscle cell, and decreases calcium-calmodulin stimulation of myosin light chain kinase (see Chapter 3). This in turn decreases the phosphorylation of myosin light chains, thereby decreasing smooth muscle tension development and causing vasodilation. There is also evidence that increased cGMP can de-phosphorylate myosin light chains by activating the myosin light chain phosphatase. The anti-platelet (anti-aggregatory) effects of NO are also signaled by the increase in cGMP. Drugs that inhibit the breakdown of cGMP by inhibiting cGMP-dependent phosphodiesterase (e.g., sildenafil [Viagra®]) potentiate the effects of NO-mediated actions on the target cell.

Nitric oxide is very labile, and has a half-life of only a few seconds. It avidly binds to the heme moiety not only on guanylyl cyclase, but also on hemoglobin. Nitric oxide is subsequently broken down to nitrites and nitrates, incorporated into other nitroso compounds, or scavenged by superoxide anion.

When NO production is impaired, as occurs when the vascular endothelium becomes damaged or dysfunctional, the following can result:

- Vasoconstriction (e.g., coronary vasospasm, elevated systemic vascular resistance, hypertension)
- Platelet aggregation and adhesion leading to thrombosis
- Upregulation of leukocyte and endothelial adhesion molecules leading to enhanced inflammation and leukocyte plugging of microcirculation
- Vascular stenosis, or restenosis such as often occurs following balloon angioplasty and vascular stent placement

- Excessive inflammation and tissue damage mediated by reactive oxygen species such as superoxide anion and hydroxyl radical because of reduced scavenging of superoxide anion by NO

There is considerable evidence that the following diseases/conditions are associated with endothelial dysfunction and reduced NO production and/or bioavailability:

- Hypertension
- Coronary vasospasm (Printzmetal's variant angina)
- Obesity
- Dyslipidemias (particularly hypercholesterolemia and hypertriglyceridemia)
- Diabetes (both type I and II)
- Heart failure
- Atherosclerosis, cigarette smoking, aging, and vascular injury

FORMATION AND PHYSIOLOGICAL ACTIONS OF ENDOTHELIN-1

Endothelin-1 (ET-1) is synthesized from an endothelin precursor (big ET-1 or pro-ET-1) and cleaved to ET-1 by **endothelin converting enzyme (ECE)** found on the endothelial cell membrane (Figure 1). ET-1 binds to ET_A receptors by diffusing to adjacent smooth muscle cells and by circulating in the blood to distant receptor sites. Stimulation of ET_A receptors causes calcium mobilization and smooth muscle contraction. The ET_A receptor is coupled to a Gq-protein linked to phospho-

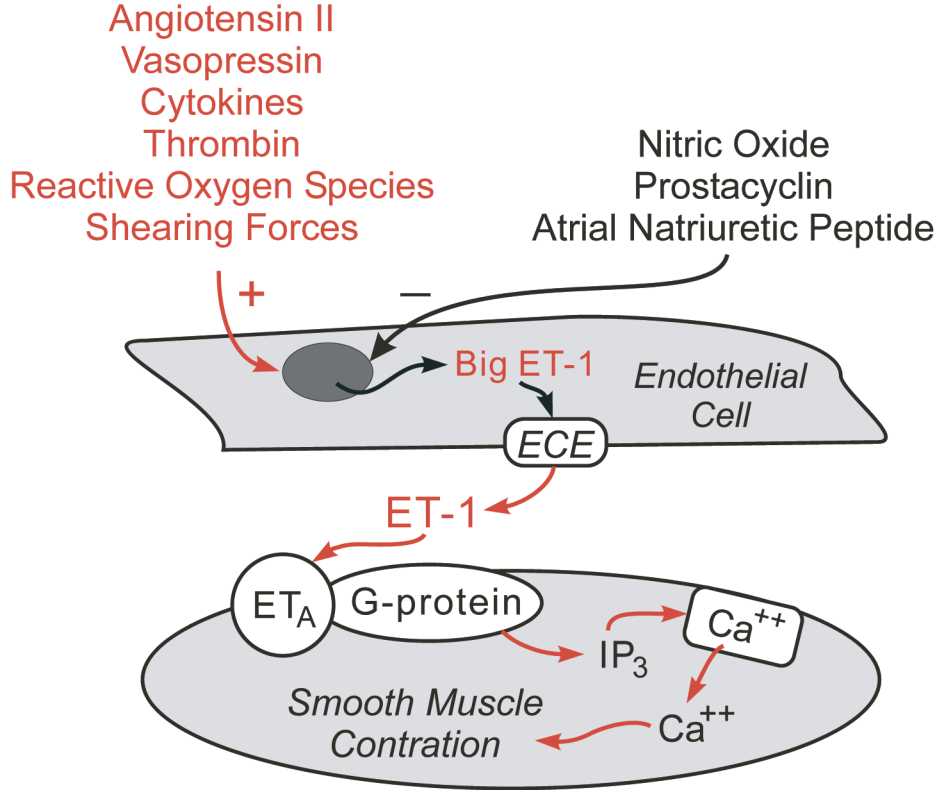

FIGURE 1 Formation and vascular action of endothelin-1 (*ET-1*). Endothelial production of ET-1 is stimulated (+) and inhibited (-) by many different circulating and paracrine factors. Big ET-1, a precursor of ET-1, is acted upon by endothelin converting enzyme (*ECE*) to form ET-1. ET-1 diffuses to the vascular smooth muscle where it binds to ET_A receptors, which stimulate Gq-proteins and the inositol triphosphate (IP_3) pathway to cause vasoconstriction by enhancing intracellular release of calcium.

lipase-C and the formation of IP_3 (see Chapter 3). ET-1 can also bind to a second type of receptor (ET_B) located on the vascular endothelium that stimulates nitric oxide (see CD3 – nitric oxide) and prostacyclin synthesis and release (see CD3 – prostaglandins), which act as negative feedback mechanisms to counteract the vascular effects of ET-1.

ET-1 formation and release by endothelial cells is stimulated by angiotensin II, vasopressin (antidiuretic hormone, ADH), thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by nitric oxide, as well as by prostacyclin and atrial natriuretic peptide.

ET-1 has several cardiovascular actions including:

- Vasoconstriction
- Positive inotropy and chronotropy in the heart
- Cardiac and vascular myocyte hypertrophy
- Decreases renal blood flow and glomerular filtration
- Stimulates aldosterone secretion
- Stimulates release of atrial natriuretic peptide

ET-1 has been implicated in the pathogenesis of hypertension, vasospasm, and heart failure. In the latter condition, ET-1 is released by the failing myocardium where it can contribute to calcium overload and hypertrophy. Experimentally, ET_A receptor antagonists have been shown to decrease mortality and improve hemodynamics in heart failure.

FORMATION AND PHYSIOLOGICAL ACTIONS OF METABOLITES OF ARACHIDONIC ACID

Endothelium, smooth muscle, leukocytes, platelets and parenchymal cells are capable of producing a variety of vasoactive substances, collectively referred to as eicosanoids, which are products of arachidonic acid metabolism. The most important eicosanoids are prostaglandins, prostacyclin, leukotrienes, and thromboxanes. These substances are either vasodilators or vasoconstrictors, among their many biological activities.

Membrane phospholipids, acted upon by phospholipase A_2, release **arachidonic acid,** which serves as the precursor for prostaglandins, prostacyclin, and thromboxanes (Figure 1). **Cyclooxygenase** (COX) is the key

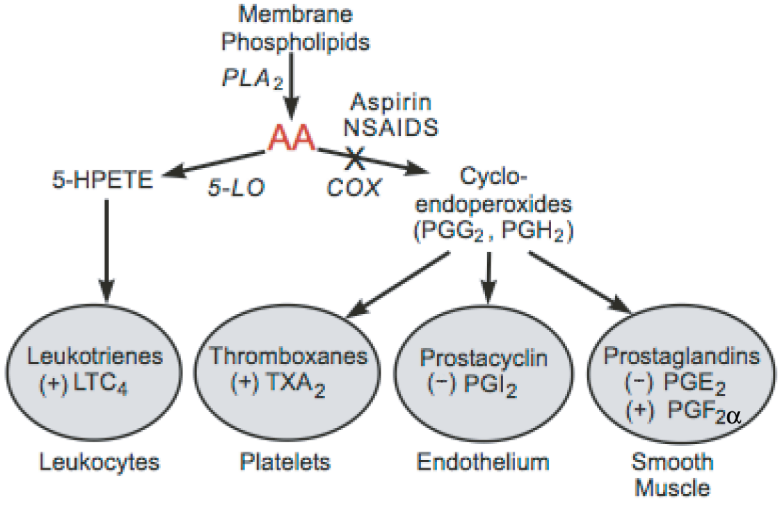

FIGURE 1 Eicosanoid formation from arachidonic acid. Stimulation of phospholipase A_2 (PLA_2) forms arachidonic acid (AA) from membrane phospholipids. Cyclooxygenase (COX) acts upon AA to form intermediates (cyclo-endoperoxides, PGG_2 and PGH_2), which are acted upon by other enzymes to form prostacyclin (PGI_2) in vascular endothelium, prostaglandins (e.g., PGE_2 and $PGF_{2\alpha}$) in vascular smooth muscle, and thromboxanes (e.g., TXA_2) in platelets. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDS; e.g., ibuprofen) inhibit COX. Leukocytes form leukotrienes (e.g., LTC_4) from AA through the 5-lipoxygenase (5-LO) enzyme pathway. Eicosanoids produce vasoconstriction (+) or vasodilation (-).

enzyme responsible for the formation of these eicosanoids. COX is inhibited by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin®) and acetaminophen (Tylenol®). There are two important isoforms of COX: COX-1 and COX-2. Newer anti-inflammatory drugs target COX-2 and have fewer gastrointestinal side effects than the non-selective COX inhibitors such as aspirin and ibuprofen. Cyclo-endoperoxide products of COX (PGG_2 and PGH_2) are acted upon by thromboxane synthase (in platelets) or prostacyclin synthase (in endothelium) to form thromboxanes or prostacyclin, respectively. The cyclo-endoperoxides can also form prostaglandins such as PGE_2 and $PGF_{2\alpha}$. Arachidonic acid can also serve as a substrate for 5-lipoxygenase to form leukotrienes (primarily in leukocytes).

Prostacyclin plays an important role in vascular function because, like nitric oxide, it inhibits platelet adhesion to the vascular endothelium and is a potent vasodilator. Damaged endothelial cells do not produce prostacyclin, thereby making the vessel more susceptible to thrombosis and vasospasm. **Thromboxanes** (e.g., TXA_2) and **leukotrienes** (e.g., LTC_4) constrict blood vessel and are important modulators of vascular function during tissue injury and inflammation.

Prostaglandins affect the blood vessels during inflammation, and play a subtle role in normal flow regulation, most notably as modulators of other control mechanisms. Prostaglandins have both vasoconstrictor (e.g., $PGF_{2\alpha}$) and vasodilator activities (e.g., PGE_2). Leukotrienes and prostaglandins can make the vascular endothelium more "leaky" by increasing the capillary filtration constant (see Chapter 8), thereby promoting edema formation during inflammation.

COMPLIANCE

The ability of a blood vessel or a cardiac chamber to change its volume in response to changes in pressure has important physiological implications. In physical terms, the relationship between a change in volume (ΔV) and a change in pressure (ΔP) is the compliance (C) (Equation 1).

$$C = \Delta V / \Delta P \qquad \text{Equation 1}$$

Compliance, therefore, is related to the ease by which a given change in pressure causes a change in volume.

In biological tissues, the relationship between ΔV and ΔP is not linear. As shown in Figure 1, compliance (which is the slope of the line relating volume and pressure) de-

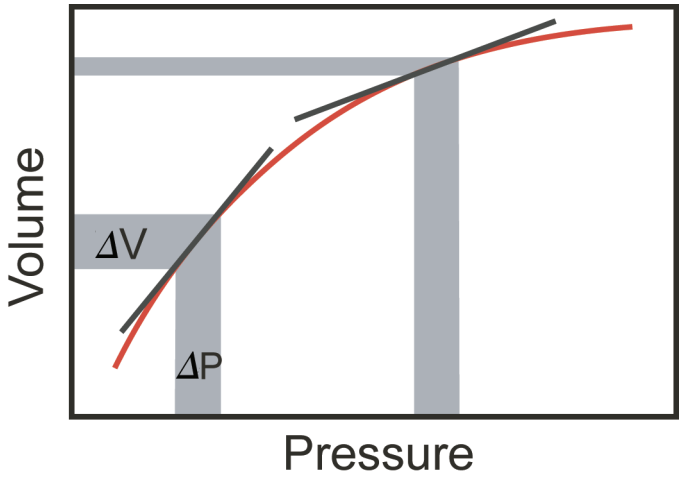

FIGURE 1 Compliance curve for a biological tissue such as an artery. At low pressures and volumes, compliance (slope of tangent) is much greater than at high pressures and volumes. The change in volume (*ΔV*) for a given change in pressure (*ΔP*) is greater at higher compliance (C) because $C = \Delta V/\Delta P$.

creases at higher volumes and pressures. Another way to view this is that the "stiffness" of a cardiac chamber or vessel wall increases at higher volumes and pressures.

ENERGETICS OF FLOWING BLOOD

The total energy of flowing blood can be described by the **Bernoulli principle,** in which the total energy (E) of flowing blood is equal to the kinetic energy (KE) plus potential energy (PE) in the absence of gravitational (Equation 1).

$$E = KE + PE \qquad \text{Equation 1}$$

The PE is the pressure exerted against the wall of the blood vessel (i.e., lateral pressure). The kinetic energy (KE) of flowing blood is proportional to the velocity squared (Equation 3) (derived from $KE = \frac{1}{2} \rho V^2$; in which ρ = density and V = mean velocity).

$$KE \propto V^2 \qquad \text{Equation 2}$$

Therefore, total energy is proportional to the velocity squared plus potential (pressure) energy (Equation 3).

$$E \propto V^2 + PE \qquad \text{Equation 3}$$

Equations 2 and 3 show that as the velocity of blood flow increases, there is a disproportionate increase in KE and total energy (E).

Although we usually think of blood flowing through a vessel as being driven by a pressure gradient along the length of the vessel, it is actually the difference in the total energy of the flowing blood along the length of a vessel that determines the flow at any given resistance. As blood flows through a vessel, there is a loss of total energy due to friction. This is illustrated in the top panel of Figure 1 in which a hypothetical length of blood vessel of constant radius shows a 2 mm Hg decrease in potential and total energy between its two ends. The KE is constant along the length of the vessel because the velocity is the same at every point along the vessel. Because the total energy must decline along the length of vessel due to frictional energy losses, the pressure energy decreases.

From Equation 1 we see that for a given total energy, if kinetic energy increases, pressure energy must decrease, and visa versa. In other words, there is an interconversion between kinetic energy and pressure energy. This is illustrated in the bottom panel of Figure 1 in which a blood vessel has a region of stenosis (narrowing). In this example, the radius of the mid-section of the vessel is reduced by 50%. This results in a 4-fold increase in velocity (from 10 to 40) in that section of the vessel because at constant flow, velocity is inversely related to radius squared ($V \propto 1/r^2$). This latter relationship is derived from flow equals mean velocity times cross-sectional area ($F = V \cdot A$); therefore, the velocity is inversely proportional to the area ($V \propto 1/A$), and since area is proportional to the radius square ($A = \pi r^2$), velocity is inversely proportional to one over radius squared.

A 4-fold increase in velocity causes a 16-fold increase in KE because $KE \propto V^2$ (see Equation 2). If KE is the equivalent of 2 mm Hg at the entrance of the vessel, the KE will be 32 mm Hg in the stenotic region, a 16-fold increase. Total energy decreases in the stenotic region despite the increase in KE because there is a disproportionate loss of PE due to increased resistance (frictional forces).

In the post-stenotic segment, the velocity returns to the pre-stenotic value (because radius and velocity are the same in the pre- and post-stenotic segments). Therefore, KE is the same in the post- and pre-stenotic segments. There is, however, an additional loss of PE due to turbulence, thereby further decreasing total energy. It might seem paradoxical that the lateral pressure (PE) is lower in the stenotic segment than in the post-stenotic segment. Volume flow, however, stills goes from left to right in this illustration because it is the total energy that actually drives the flow through the vessel.

The above considerations illustrate the following important principle: *blood flowing at higher velocities will have a higher ratio of kinetic energy to potential (pressure) energy.* High kinetic energies are found in the aortic arch because of the high ejection velocities achieved by the left ventricle during systole. When stroke volume is augmented as during exercise, the moving blood has an even higher kinetic energy relative to pressure energy.

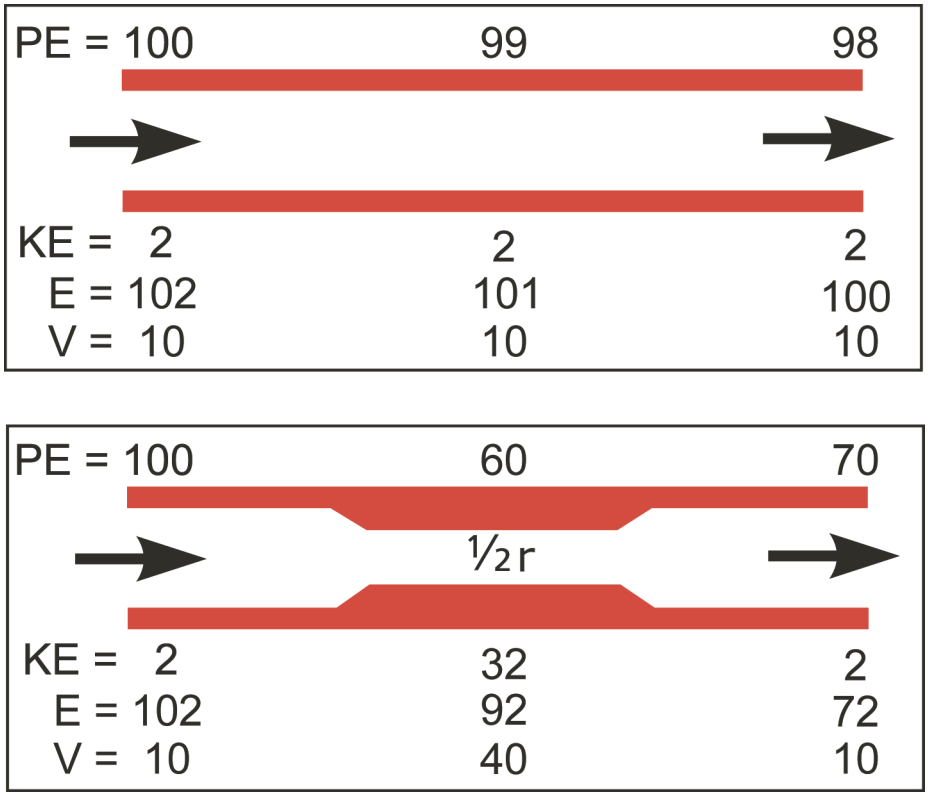

FIGURE 1 Effects of vessel narrowing (stenosis) on energetics of flow. Vessel narrowing (stenosis) increases velocity (*V*) and kinetic energy (*KE*), and decreases pressure (potential) energy (*PE*) and total energy (*E*). The following relationships are illustrated in this figure: $E = KE + PE$; $KE \propto V^2$; $V \propto 1/r^2$.

ABNORMAL CARDIAC PRESSURES AND VOLUMES CAUSED BY VALVE DISEASE

Normal valve function is characterized as having (1) low pressure gradients across the valve as blood flows through the orifice, and (2) unidirectional flow. These normal features are altered when heart valves function abnormally.

There are two general categories of valve defects: stenosis and insufficiency. **Valvular stenosis** results from a narrowing of the valve orifice. Fibrosis, often accompanied by calcification, causes the valve leaflets to thicken so that they cannot open fully, which decreases cross-sectional area of the open orifice. Furthermore, the valve cusps can fuse together, which prevents them from fully opening. **Valvular insufficiency** occurs when the valve leaflets do not completely seal when the valve is closed; this causes blood to flow backward (regurgitate) into the proximal chamber. Both of these valve defects alter intracardiac pressures and volumes during the cardiac cycle.

Valve defects produce murmurs that can be heard with a stethoscope. A murmur is a rumbling or rasping sound caused by vibrations generated by the abnormal movement of blood within or between cardiac chambers, or by turbulent flow (see CD – turbulence) within the pulmonary artery or aorta just distal to the outflow valve. If a murmur is heard during systole between the first (S_1) and second (S_2) heart sounds, it is termed a "**systolic murmur.**" If it is heard during diastole (between S_2 and S_1), it is termed a "**diastolic murmur.**" The sound intensifies with increasing flow and turbulence across the valve.

The following sections describe pressure and volume changes that occur during mitral

and aortic valve stenosis, and mitral and aortic valve insufficiency. The descriptions are for acute changes that directly alter cardiac dynamics, and therefore do not include cardiac and systemic compensatory mechanisms that attempt to maintain cardiac output and arterial pressure. These compensatory responses include systemic vasoconstriction, increased blood volume, and increased heart rate and inotropy. Cardiac adaptations, such as hypertrophy or dilation, would also alter the passive ventricular filling and thereby affect the cardiac dynamics. Furthermore, severe valve disease usually leads to heart failure, which further modifies intracardiac pressures and volumes.

Valve Stenosis

Stenosis can occur at either an outflow valve (aortic or pulmonic valve) or inflow valve (mitral or tricuspid valve). Stenosis increases the resistance to flow across the valve, which causes a high pressure gradient as blood flows across the valve. The pressure gradient across a valve is the pressure difference on either side of the leaflets. For the aortic valve, the pressure gradient is the intraventricular pressure minus the aortic pressure; for the mitral valve, the pressure gradient is the left atrial pressure minus the left ventricular pressure. In normal valves, the pressure gradient is only a few mm Hg when the valve is open. The following equation is the general hemodynamic expression that relates pressure gradient (ΔP), flow (F) and resistance (R) under laminar, non-turbulent flow conditions:

$$\Delta P = F \cdot R$$

A reduced valve orifice increases the resistance to flow across the valve because resistance is inversely related to the radius (r) of the valve orifice to fourth power (equivalent to valve orifice area [A] to the second power because $A = \pi r^2$) (see Chapter 5). If the average valve radius is reduced by 50% (equivalent to a 75% reduction in area), the valve resistance is increased 16-fold, which increases the pressure gradient 16-fold if flow remains unchanged. In reality, the formation of turbulence increases the pressure gradient across the valve even further (see CD – turbulence). In summary, at a given flow across the valve, the greater the resistance, the greater the pressure gradient across the valve that is required to drive the flow.

Aortic valve stenosis

In Aortic valve stenosis, intraventricular pressure is increased during systole to eject blood across the narrowed valve (Figure 1, left panel). This leads to a large pressure gradient across the valve during systolic ejection. Increased flow velocity through the stenotic valve (velocity is inversely related to valve cross-sectional area at a given flow) causes turbulence and a systolic murmur. In moderate-to-severe aortic stenosis, the aortic pressure may be reduced because ventricular stroke volume (and cardiac output) is reduced. Because ejection is impeded by the increase in ventricular afterload caused by the increased valve resistance, more blood remains in the heart after ejection, which leads to an increase in left atrial volume and pressure.

Changes in left ventricular pressure-volume loops (described in Chapter 4) with moderate aortic stenosis are shown in Figure 1 (right panel). Left ventricular emptying is impaired (increased end-systolic volume) because of the high outflow resistance (increased afterload). Stroke volume decreases because the velocity of fiber shortening is decreased by the increased afterload (see Chapter 4, force-velocity relationship). Because end-systolic volume is elevated, the excess residual volume added to the incoming venous return causes the end-diastolic volume to increase. This increases preload and activates the Frank-Starling mechanism to increase the force of contraction and pressure development during systole to help the ventricle overcome, in part, the increased outflow resistance. In mild aortic stenosis, this can be adequate to maintain normal stroke volume, but in moderate and severe stenosis, the stroke volume falls as shown in Figure 1 (decreased width of pressure-volume loop) because the end-systolic volume increases more than the end-diastolic volume increases.

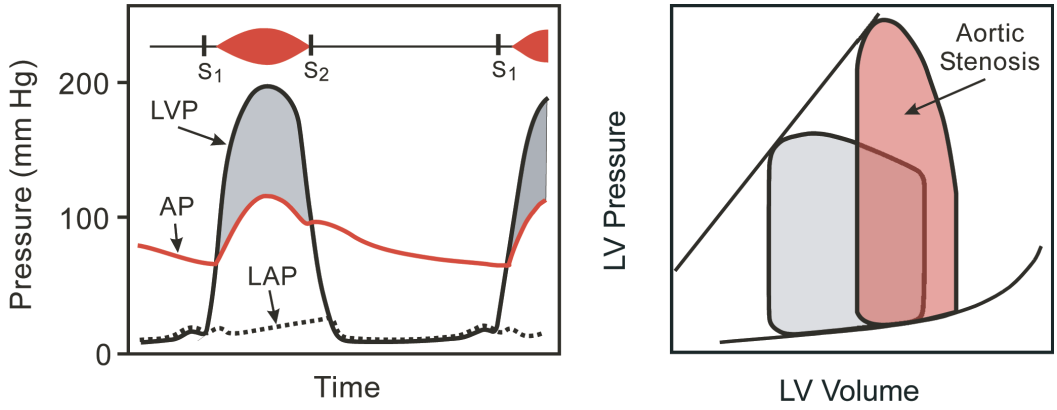

FIGURE 1 Changes in cardiac pressures and volumes associated with acute aortic valve stenosis. The *left panel* shows that during ventricular ejection, left ventricular pressure (*LVP*) exceeds aortic pressure (*AP*) (the gray area represents the pressure gradient generated by the stenosis); left atrial pressure (*LAP*) is elevated and a systolic murmur is present between the first (S_1) and second (S_2) heart sounds. The *right panel* shows the effects of acute aortic valve stenosis (*red loop*) on left ventricular (*LV*) pressure-volume loops. The end-systolic volume is increased, and there is a compensatory increase in end-diastolic volume; stroke volume is decreased, particularly in severe stenosis. These loops represent acute responses with no change in heart rate, inotropy, blood volume, or systemic vascular resistance.

Summary: ↑↑ESV + ↑EDV → ↓SV

Mitral valve stenosis

Mitral valve stenosis increases the pressure gradient across the mitral valve during ventricular filling, which leads to an increase in left atrial pressure and a small reduction in left ventricular pressure (Figure 2, left panel). In moderate-to-severe mitral stenosis, reduced ventricular filling causes a reduction in ventricular preload (both end-diastolic volume and pressure decrease). This leads to a decrease in stroke volume (width of pressure-volume loop; Figure 2, right panel) through the Frank-Starling mechanism, and a fall in cardiac output and aortic pressure. Reduced

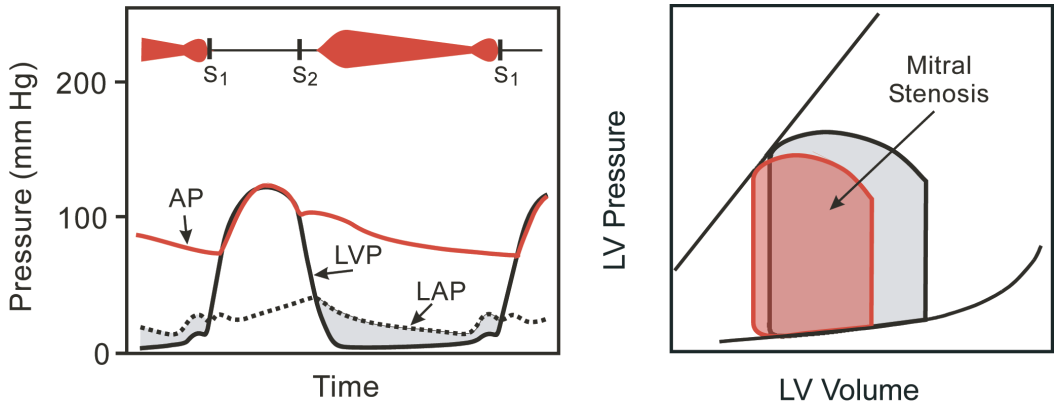

FIGURE 2 Changes in cardiac pressures and volumes associated with acute mitral valve stenosis. The *left panel* shows that during ventricular filling, left atrial pressure (*LAP*) exceeds left ventricular pressure (*LVP*) (the gray area represents the pressure gradient generated by the stenosis). Aortic pressure (*AP*) is reduced by severe mitral stenosis because of decreased cardiac output; a diastolic murmur is present between the second (S_2) and first (S_1) heart sounds. The *right panel* shows the effects of mitral valve stenosis (*red loop*) on left ventricular (*LV*) pressure-volume loops. End-diastolic volume is reduced, and end-systolic volume may be slightly reduced; therefore, stroke volume is reduced. These loops represent acute responses with no change in heart rate, inotropy, blood volume, or systemic vascular resistance.

afterload (particularly aortic diastolic pressure) enables the end-systolic volume to decrease slightly, but not enough to overcome the decline in end-diastolic volume. Therefore, the net effect is a decrease in stroke volume. A diastolic murmur is heard as blood flows at higher velocities across the narrowed valve during ventricular filling.

Summary: ↓↓EDV + ↓ESV → ↓SV

Valve Insufficiency

Valvular insufficiency can occur with either outflow valves (aortic and pulmonic) or inflow valves (mitral and tricuspid). In this condition, the valve does not close completely, which permits blood to flow backward (regurgitate) across the valve. Mitral and tricuspid valve insufficiency can occur following rupture of the chordae tendineae, following ischemic damage to the papillary muscles, or when the ventricles are pathologically dilated (e.g., as occurs in dilated cardiomyopathy).

Aortic valve regurgitation

Aortic valve regurgitation (Figure 3) causes blood to enter the left ventricle from the aorta (backward flow) during the time that the valve would normally be closed. Because blood leaves the aorta by two pathways (back into the ventricle as well as down the aorta), the aortic pressure falls more rapidly than usual during diastole, thereby reducing aortic diastolic pressure (see Figure 3, left panel). Ventricular (and aortic) peak systolic pressures are increased because the extra volume of blood that enters the ventricle from the aorta during diastole leads to an increase in end-diastolic volume (and pressure), which augments the force of contraction through the Frank-Starling mechanism. The increased systolic pressure and decreased diastolic pressure increase the aortic pulse pressure. The regurgitation, which takes place as the ventricle relaxes and fills, causes a diastolic murmur.

Because of the backward flow of blood from the aorta into the left ventricle, there is no true phase of isovolumetric relaxation (see Figure 3, right panel). Instead, the left ventricle begins to fill with blood from the aorta before the mitral valve opens. Once the mitral valve opens, ventricular filling occurs from the left atrium; however, blood continues to flow from the aorta into the ventricle throughout

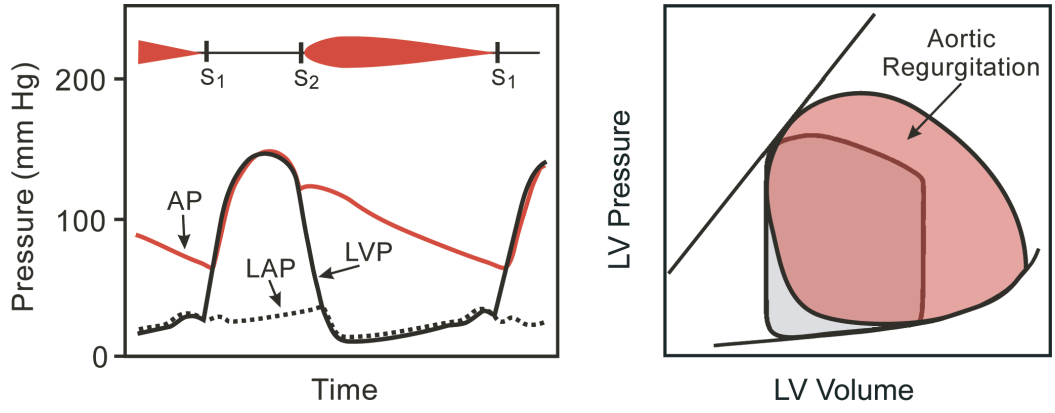

FIGURE 3 Changes in cardiac pressures and volumes associated with acute aortic valve regurgitation. The *left panel* shows that during ventricular relaxation, blood flows backwards from the aorta into the ventricle, causing a more rapid fall in aortic pressure (*AP*), which decreases diastolic pressure and increases aortic pulse pressure; left atrial pressure (*LAP*) increases because of blood backing up into atrium as left ventricular end-diastolic volume and pressure increase. An increase in ventricular stroke volume (because of increased filling) leads to an increase in peak ventricular and aortic pressures; a diastolic murmur is present between the second (S_2) and first (S_1) heart sounds. The *right panel* shows the effects of aortic valve regurgitation (*red loop*) on left ventricular (*LV*) pressure-volume loops. End-diastolic volume and stroke volume are greatly increased, and there are no true isovolumetric phases. These loops represent acute responses with no change in heart rate, inotropy, blood volume, or systemic vascular resistance.

diastole because aortic pressure is higher than ventricular pressure during diastole. This greatly enhances ventricular filling (end-diastolic volume), which activates the Frank-Starling mechanism to increase the force of contraction and stroke volume as shown by the increased width of the pressure-volume loop. Left ventricular peak pressure and systolic aortic pressure are also increased because of the large stroke volume ejected into the aorta. As long as the ventricle is not in failure, normal end-systolic volumes can be sustained; however, the end-systolic volume increases when the ventricle goes into systolic failure (see Chapter 9).

Summary: ↑↑EDV + →ESV → ↑↑SV
(although net SV into
aorta may be decreased)

Mitral valve regurgitation

In mitral valve regurgitation, blood flows backward into the left atrium as the left ventricle contracts. This leads to a large increase in the v-wave of the left atrial pressure tracing (Figure 4, left panel) and the generation of a systolic murmur. Ventricular systolic and aortic pressures decrease if the net ejection of blood into the aorta is significantly reduced.

There are several important changes in the left ventricular pressure-volume loop during mitral insufficiency (see Figure 4, right panel). One important change to note is that there is no true isovolumetric contraction phase. The reason for this is that blood begins to flow across the mitral valve and back into the atrium before the aortic valve opens. Mitral regurgitation reduces the afterload on the left ventricle (total outflow resistance is reduced), which causes stroke volume to be larger and end-systolic volume to be smaller than normal; however, end-systolic volume increases if the heart goes into systolic failure in response to chronic mitral regurgitation. Another change observed in the pressure-volume loop is that there is no true isovolumetric relaxation because as the ventricle begins to relax, the mitral valve is never completely closed; this permits blood to flow back into the left atrium as long as intraventricular pressure is greater than left atrial pressure. During diastole, the elevated pressure within the left atrium is transmitted to the left ventricle during filling so that left ventricular end-diastolic volume

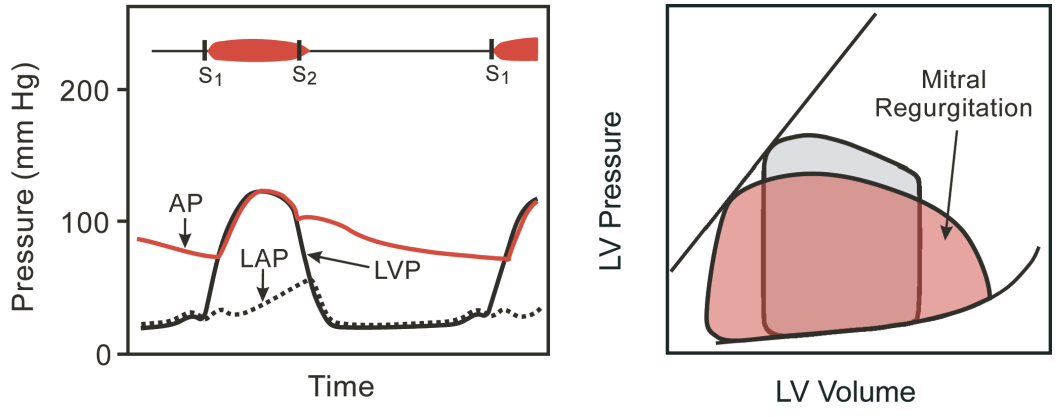

FIGURE 4 Changes in cardiac pressures and volumes associated with acute mitral valve regurgitation. The *left panel* shows that during ventricular contraction, the left ventricle ejects blood back into the left atrium as well as into the aorta, thereby increasing left atrial pressure (*LAP*), particularly the v-wave. The aortic pressure (*AP*) and left ventricular pressure (*LAP*) may fall in response to a reduction in the net volume of blood ejected into the aorta; a systolic murmur is present between the first (S_1) and second (S_2) heart sounds. The *right panel* shows the effects of mitral valve regurgitation (*red loop*) on left ventricular (*LV*) pressure-volume loops. End-systolic volume is reduced because of decreased outflow resistance (afterload); end-diastolic volume is increased because increased left atrial pressures increases ventricular filling; stroke volume is greatly enhanced. These loops represent acute responses with no change in heart rate, inotropy, blood volume, or systemic vascular resistance.

increases. This would cause wall stress (afterload) to increase if it were not for the reduced outflow resistance that tends to decrease afterload during ejection. The net effect of these changes is that the width of the pressure-volume loop is increased; however, ejection into the aorta is reduced. The increased ventricular stroke volume in this case includes the volume of blood ejected into the aorta as well as the volume ejected back into the left atrium.

Summary: ↑EDV + ↓ESV → ↑↑SV (although net SV into aorta may be decreased)

VENTRICULAR HYPERTROPHY

Ventricular hypertrophy (i.e., increased ventricular mass) occurs as the ventricle adapts to increased stress, such as chronically increased volume load (preload) or increased pressure load (afterload). Although hypertrophy is a physiological response to increased stress, the response can become pathological and ultimately lead to a deterioration in function. For example, hypertrophy is a normal physiological adaptation to exercise training that enables the ventricle to enhance its pumping capacity. This type of physiologic hypertrophy is reversible and non-pathological. In contrast, chronic hypertension causes pathologic ventricular hypertrophy. This response enables the heart to develop greater pressure and to maintain a normal stroke volume despite the increase in afterload. However, over time, pathologic changes occur in the heart that can lead to heart failure.

In the case of chronic pressure overload, the inside radius of the chamber may not change; however, the wall thickness greatly increases as new sarcomeres are added in parallel to existing sarcomeres. This is termed **concentric hypertrophy** (Figure 1). This type of ventricle is capable of generating greater forces and higher pressures, while the increased wall thickness maintains normal wall stress. A hypertrophied ventricle, however, becomes "stiff" (i.e., compliance is reduced – see CD9 – compliance), which impairs filling, reduces stroke volume and leads to a large increase in end-diastolic pressure (Figure 2). Changes in end-systolic volume depend upon changes in afterload and inotropy. Concentric hypertrophy, which is one cause of diastolic dysfunction (see Chapter 9), can lead to pulmonary congestion and edema.

If the precipitating stress is volume overload, the ventricle responds by adding new sarcomeres in series with existing sarcomeres. This results in ventricular dilation while maintaining normal sarcomere lengths. The wall thickness normally increases in proportion to the increase in chamber radius. This type of hypertrophy is termed **eccentric hypertrophy,** and often accompanies systolic dysfunction.

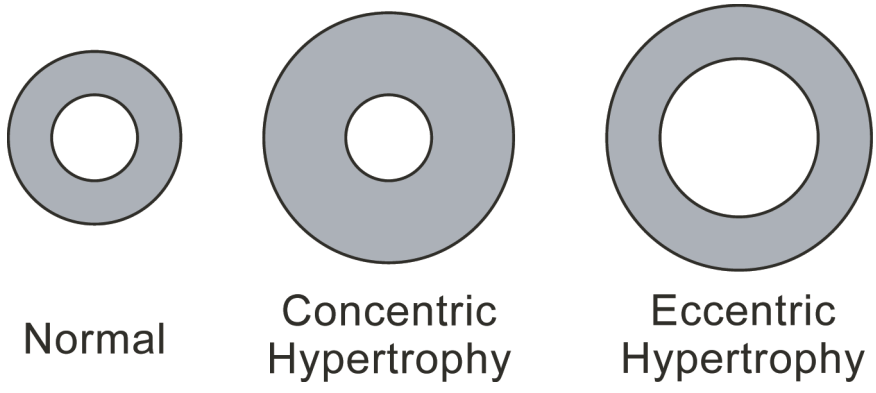

FIGURE 1 Concentric versus eccentric ventricular hypertrophy. With concentric hypertrophy, the ventricular wall thickens and the internal radius remains the same or is reduced. Eccentric hypertrophy occurs when the ventricle becomes chronically dilated; the wall thickness usually increases in proportion to the increase in radius.

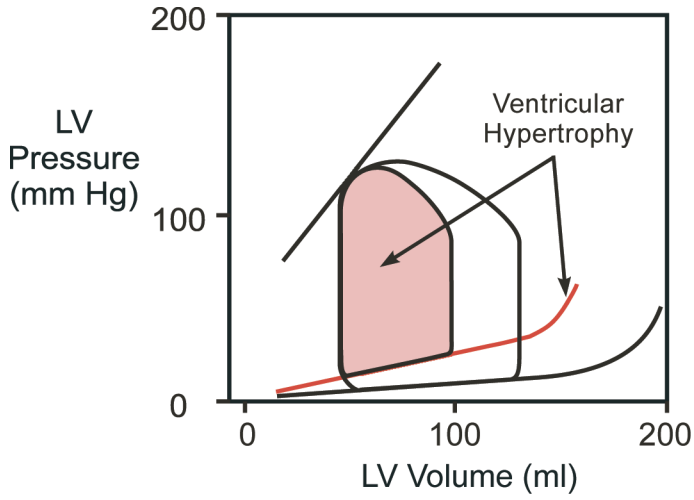

FIGURE 2 Effects of concentric hypertrophy on left ventricular pressure-volume loops. Hypertrophy (red loop) reduces compliance (increases the slope of the relationship between filling pressure and volume) leading to impaired filling (reduced end-diastolic volume), increased end-diastolic pressure, and reduced stroke volume (reduced width of pressure-volume loop). Left ventricular (*LV*) end-systolic volume may or may not change depending upon how afterload and inotropy change.

VENTRICULAR STROKE WORK

As defined by physics, work is the product of force and distance. Therefore, the work done to move an object of a given mass is the force applied to the object times the distance that the object moves. In the case of the work done to move a volume of fluid, work is defined as the product of the volume of fluid and the pressure required to move the fluid.

Stroke work (SW) refers to the work done by the ventricle to eject a volume of blood (i.e., stroke volume) into the aorta. The force that is applied to the volume of blood is the intraventricular pressure. Therefore, ***ventricular stroke work*** *can be estimated as the product of stroke volume (SV) and mean aortic pressure (MAP) during ejection* (Equation 1).

$$SW \cong SV \cdot MAP \qquad \text{Equation 1}$$

The use of aortic pressure instead of intraventricular pressure assumes that kinetic energy (see CD4 – Bernoulli) is negligible, which is generally true at resting cardiac outputs. Sometimes the calculation for stroke work is further simplified to stroke volume times mean aortic pressure.

Stroke work is best illustrated by using ventricular pressure-volume diagrams (see Chapter 4), in which stroke work is the area within the pressure-volume loop (Figure 1). This area represents the external work done by the ventricle to eject blood into the aorta.

Stroke work is sometimes used to assess ventricular function. If stroke work is plotted against ventricular preload, the resulting ventricular function curve appears qualitatively similar to a Frank-Starling curve (see Chapter 4). Like the Frank-Starling relationship, there is a family of curves, with each curve depending on the inotropic state of the ventricle.

Cardiac work *is the product of stroke work and heart rate,* which is the equivalent of the triple product of stroke volume, mean aortic pressure, and heart rate.

CRITICAL STENOSIS

The term "critical stenosis" refers to a narrowing of an artery (stenosis) that results in a significant reduction in maximal flow capacity in a distal vascular bed. A critical stenosis, while always reducing maximal flow capacity, may or may not reduce resting flow because of autoregulation of the distal vascular bed (see Chapter 7) and the development of collateral

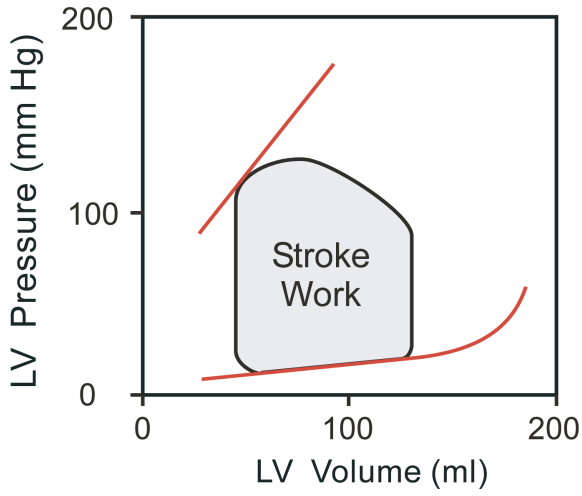

FIGURE 1 Ventricular stroke work. The area within the ventricular pressure-volume loop represents the left ventricular (*LV*) stroke work.

blood flow. The following discussion uses the coronary circulation as an example of the hemodynamics of a critical stenosis; however, the same principles apply to all vascular beds.

The degree of constriction resulting in a critical stenosis in the left anterior descending coronary artery (LAD) (Figure 1) is much greater than predicted by Poiseuille's equation (Equation 5-6) in which a 10% reduction in vessel radius would increase resistance by 52% in that single vessel. In fact, a 10% reduction in LAD radius would have virtually no hemodynamic effect on distal blood flow. The reason for this is two-fold: (1) the LAD normally has a very low resistance, and (2) the LAD is in series with the distal vascular bed that is supplied by the LAD (R_S), and the distal vascular bed is where most of the resis-

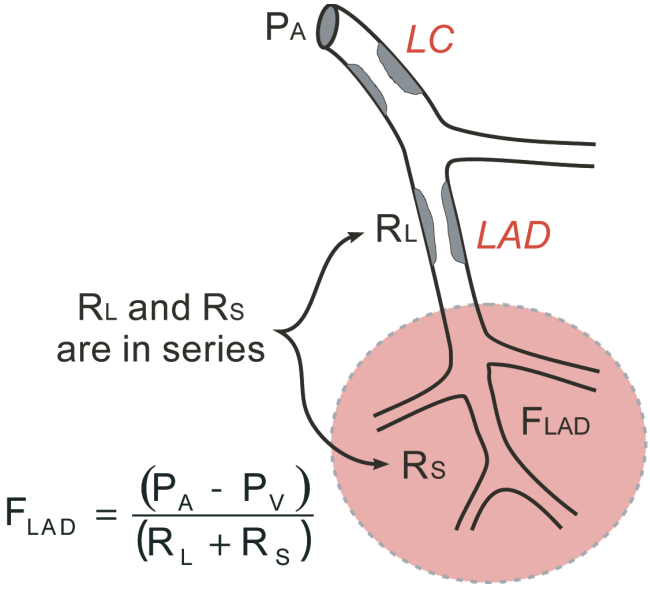

FIGURE 1 Model of the coronary circulation showing a stenotic left anterior descending (*LAD*) coronary artery. Because the resistances of the LAD (R_L) and the downstream smaller vessels supplied by the LAD (R_S) are in series, the LAD flow (F_{LAD}) is determined by aortic pressure (P_A) minus the venous pressure (P_V), divided by the sum of R_L and R_S.

tance resides. A critical stenosis in the LAD is not reached until the radius is reduced by at least 50%, which corresponds to a 75% decrease in cross-sectional area. Even a 50% reduction in radius will not impair resting flow, but it will reduce maximal flow capacity, which can lead to ischemia-induced chest pain during exertion (chronic stable angina; see CD7 – angina). Reducing the radius more than 75% (equivalent to a 94% decrease in cross-sectional area) significantly reduces resting blood flow (depending on the degree of collateralization). This can lead to chronic myocardial hypoxia. Therefore, it is commonly stated that the value for a critical stenosis is a 60 to 70% reduction in vessel diameter.

The concept of a critical stenosis can be explained by modeling the circulation as consisting of two series resistance components (see Chapter 5). Equation 1 describes the relationship between the resistance in the LAD (R_L, large vessel resistance), the resistance in the vascular beds supplied by the LAD (R_S, small vessel resistance) and the total resistance (R_T) when R_L and R_S are in series:

$$R_T = R_L + R_S \qquad \text{Equation 1}$$

It is important to note that distributing arteries such as the LAD have a relatively small resistance to flow compared to the distal microvasculature. Therefore, R_L is normally very small and may represent only 0.1% of R_T (i.e., $R_L = 0.001R_T$). If we use this value for the relative resistance and assume that $R_T = 100$, then $R_T = 0.1 + 99.9$. Using these numbers, decreasing the LAD radius by 50% increases R_L from 0.1 to 1.6, a 16-fold increase (from Poiseuille's equation). The new value of R_L, plus the original value of R_S (99.9), increases R_T from 100 to 101.5. Therefore, decreasing the radius of the LAD by 50% increases R_T by only 1.5%. A 75% reduction in LAD radius increases R_T by about 25%. These calculations assume that R_S does not decrease, which may occur because of autoregulation. If autoregulation does occur, then R_T would not decrease by as much as the above calculations show.

We can use the following equation to calculate the percent reduction in flow (F) when R_T increases:

$$F = \frac{(P_A - P_V)}{R_T} \qquad \text{Equation 2}$$

If we assume that the perfusion pressure ($P_A - P_V$) does not change, then a 25% increase in R_T reduces flow by 20%. Equations 1 and 2 can be combined (Equation 3) to show the effects of changes in R_L and R_S on flow:

$$F = \frac{(P_A - P_V)}{(R_T + R_S)} \qquad \text{Equation 3}$$

The above calculations assume non-turbulent, laminar flow. The presence of turbulence would lead to an even greater, disproportionate reduction in flow for a given reduction in vessel radius (see CD4 – turbulence).

As described previously, when the LAD becomes stenotic (increased R_L), resting blood flow does not necessarily decrease. The reason for this is that as R_L increases, R_S usually decreases due to autoregulation (response to acute stenosis) and collateralization (response to chronic stenosis). Although resting flow may not change, because R_L is increased, the minimal R_T will be increased, thereby limiting maximal blood flow.

The relationship between vessel radius and maximal distal blood flow in a vessel such as the LAD is shown in Figure 2. The figure shows that as the LAD is narrowed, the maximal distal flow capacity is reduced (because the minimal R_T is increased). Maximal coronary flow capacity falls dramatically once the stenosis reduces radius by more than 60% (84% decrease in cross-sectional area). The relationship drawn in this figure assumes that in the maximally dilated state, R_L is 1% of R_T, and that significant turbulence is not occurring. In the maximally dilated state, the reduced R_S causes the fractional resistance of R_L relative to R_T to increase. Therefore, in the maximally dilated state, R_L may be 1% of R_T, whereas in the non-dilated state, R_L may be only 0.1% of R_T.

The above analysis explains why interventional measures such as opening a narrowed coronary artery by inflating a balloon (balloon angioplasty) or placing a wire stent within the vessel to keep it open, or coronary bypass surgery are not usually conducted in patients

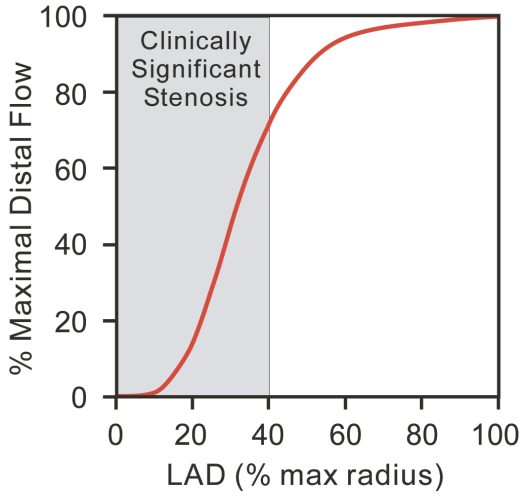

FIGURE 2 Effects of reducing left anterior descending (LAD) coronary artery radius on maximal distal blood flows. A 60% reduction in LAD radius (40% of max radius) decreases maximal distal flow capacity by more than 25%.

until one or more coronary arteries have stenotic lesions that represent more than a 60 to 70% reduction in lumen diameter.

VALSALVA MANEUVER

The Valsalva maneuver is sometimes used to assess autonomic reflex control of cardiovascular function in humans. It is performed by having the subject conduct a maximal, forced expiration against a closed glottis and holding this for at least 10 seconds. Contraction of the thoracic cage compresses the lungs and causes a large increase in intrapleural pressure (the pressure measured between the lining of the thorax and the lungs), which compresses the vessels within the thoracic. Aortic compression results in a transient rise in aortic pressure (Phase I of Figure 1). This results in a reflex bradycardia caused by baroreceptor activation. Because the thoracic vena cava also becomes compressed, venous return to the

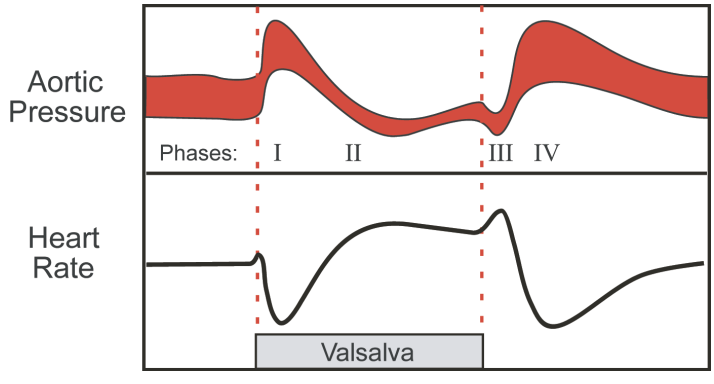

FIGURE 1 Effects of a Valsalva maneuver on aortic pressure and heart rate. During *Phase I,* which occurs at the beginning of the forced expiration, aortic pressure increases (due to aortic compression) and heart rate decreases reflexively. Aortic pressure falls during *Phase II* because compression of thoracic veins reduces venous return and cardiac output; reflex tachycardia occurs. *Phase III* begins when normal respiration resumes, and is characterized by a small transient fall in aortic pressure (because of removal of aortic compression) and a small increase in heart rate. Aortic pressure increases (and heart rate reflexively decreases) during *Phase IV* because resumption of normal cardiac output occurs while systemic vascular resistance is elevated from sympathetic activation that occurred during Phase II.

heart is compromised, causing cardiac output and aortic pressure to fall (Phase II). As aortic pressure falls, the baroreceptor reflex increases heart rate. A decrease in stroke volume accounts for the fall in pulse pressure. After several seconds, arterial pressure (both mean and pulse pressure) is reduced, and heart rate is elevated. When the subject begins breathing again, the sudden loss of compression on the aorta causes a small, transient dip in arterial pressure and a further reflex increase in heart rate (Phase III). When compression of the vena cava is removed, venous return suddenly increases causing a rapid rise in cardiac output several seconds later, which leads to a transient increase in arterial pressure (Phase IV). Arterial pressure overshoots during Phase IV because the systemic vascular resistance is increased by sympathetic activation that occurred during Phase II. Heart rate reflexively decreases during Phase IV in response to the transient elevation in arterial pressure.

ANGINA

An imbalance between oxygen delivery and oxygen demand, such that the oxygen supply/demand ratio is decreased, results in myocardial hypoxia. This stimulates pain receptors (nociceptors) within the heart and produces anginal pain and autonomic responses (see Chapter 6). Three different types of angina, all of which result from coronary artery disease, are described below.

Chronic stable angina is caused by chronic narrowing (i.e., stenosis) of coronary arteries due to atherosclerosis, and is typically observed in the large epicardial vessels. Coronary constriction limits coronary vasodilator reserve and maximal flow capacity (see CD5 –stenosis) so that as myocardial oxygen demand increases because of increased cardiac activity or increased workload, blood flow cannot increase proportionately to deliver adequate oxygen, resulting in cellular hypoxia (see Chapter 7). This is also termed "demand ischemia." There is usually a predictable pain threshold that is triggered by exertion, changes in emotional state, heavy meals, or cold weather, for example. Chronic stable angina, therefore, is precipitated by increases in oxygen demand.

Prinzmetal's (Variant) angina is generally thought to be due to acute coronary vasospasm that is often precipitated by stress, which activates sympathetic nerves that innervate the coronary vasculature. Vasospasm can occur at rest as well as during exercise. There is considerable evidence suggesting that damage to the coronary endothelium results in diminished production of nitric oxide, an important coronary vasodilator. The absence of nitric oxide leads to enhanced vasoconstrictor responses to sympathetic nerves innervating the coronary vessels, as well as to other vasoconstrictor influences. Prinzmetal's angina is categorized as "supply ischemia" because it results from an acute decrease in blood flow.

Unstable angina is not necessarily associated with exercise or stress, and its onset is therefore unpredictable. It is generally thought to be due to spontaneous thrombus formation within a coronary artery and therefore is refractory to the vasodilator actions of nitroglycerin. Endothelial dysfunction associated with coronary artery disease leads to reduced nitric oxide and prostacyclin production, both of which normally inhibit platelet adhesion and aggregation (see CD3 – nitric oxide and CD3 – prostaglandins). Unstable angina can be difficult to distinguish from acute myocardial infarction. Unstable angina is categorized as "supply ischemia" because it results from a decrease in blood flow.

Angina may also be precipitated by a combination of supply and demand ischemia. For example, diseased, stenotic coronary segments can undergo vasoconstriction during exercise (healthy arteries dilate). This probably occurs due to the absence of sufficient production of nitric oxide and prostacyclin by the vascular endothelium to counteract normal sympathetic-mediated effects on vascular α-adrenoceptors.

CAPILLARY PRESSURE

Capillary pressure (P_C) is determined by the upstream arterial pressure (P_A), the downstream venous pressure (P_V), and the precap-

illary (R_A) and postcapillary (R_V) resistances. These factors can be related quantitatively by using a simple vascular network model (Figure 1). If we assume that P_C represents a point between two series resistances (R_A and R_V), and the flow that enters in (F_I) and exits out (F_O) of this network is the same (i.e., there is conservation of flow), then we can derive Equation 1, which relates P_C to P_A, P_V, R_A and R_V:

$$P_C = \frac{\left(\frac{R_V}{R_A}\right)P_A + P_V}{1 + \left(\frac{R_V}{R_A}\right)} \qquad \text{Equation 1}$$

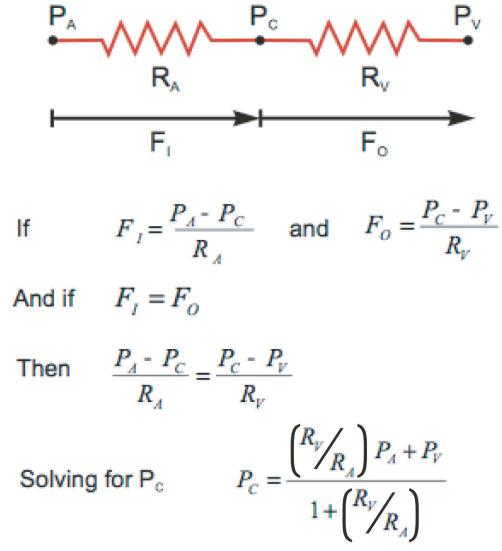

FIGURE 1 Factors determining capillary pressure. A series-coupled resistance model having precapillary and postcapillary resistance elements can be used to calculate mean capillary pressure (P_C) from arterial pressure (P_A), venous pressure (P_V), precapillary resistance (R_A) and postcapillary resistance (R_V). This model assumes that flow in (F_I) equals flow out (F_O).

We see from Equation 1 that capillary pressure is increased by increases in venous pressure, arterial pressure, and the post-to-precapillary resistance ratio (either increased postcapillary resistance or decreased precapillary resistance increases this ratio). Because the post-to-precapillary resistance ratio (R_V/R_A) is normally between 0.1 and 0.2, changes in venous pressure have a significantly greater effect on capillary pressure than changes in arterial pressure. This is illustrated by Equation 2, which shows the effects of P_A and P_V on P_C when R_V/R_A is 0.1.

$$P_C = \frac{0.1\,P_A + P_V}{1 + 0.1} = \frac{0.1\,P_A + P_V}{1.1} \qquad \text{Equation 2}$$

In this example, increasing P_A by 20 mm Hg increases P_C by 1.8 mm Hg, whereas increasing P_V by 20 mm Hg increases P_C by 18 mm Hg. This explains why venous pressure increases of 10 to 20 mm Hg in heart failure, for example, can cause severe systemic edema due to increased capillary pressure and fluid filtration, whereas increasing arterial pressure by the same amount causes only a small increase in capillary pressure and fluid filtration.

INTERSTITIAL COMPLIANCE

The fluid pressure within the interstitial space (P_i) of a tissue is determined by the volume (V) of fluid within the interstitium and the compliance (C) of the interstitium. Interstitial compliance is defined as the change in interstitial fluid volume (ΔV_i) divided by the change in interstitial fluid pressure (ΔP_i) as shown in Equation 1:

$$C = \frac{\Delta V_i}{\Delta P_i} \qquad \text{Equation 1}$$

This expression can be rearrange to:

$$\Delta P_i = \frac{\Delta V_i}{C} \qquad \text{Equation 2}$$

We see from Equation 2 that the change in interstitial fluid pressure (ΔP_i) equals the change in interstitial fluid volume (ΔV_i) divided by interstitial compliance (C). Therefore, an increase in interstitial fluid volume increases interstitial fluid pressure, and the magnitude of the change varies inversely with the compliance of the interstitium.

Figure 1 is a graphical representation of the relationship between interstitial fluid volume and pressure, and interstitial compliance. The slope of the relationship between interstitial volume and pressure is interstitial compliance. Note that the compliance decreases at higher interstitial volumes, which causes the pressure to increase disproportionately as volume increases. Some tissues and organs have

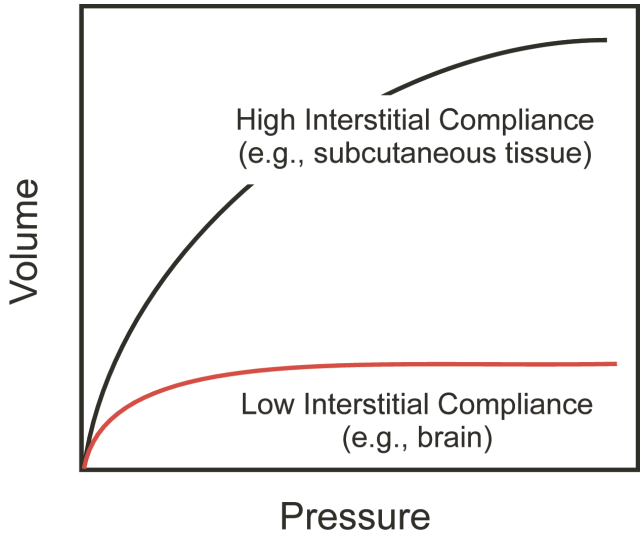

FIGURE 1 Effects of interstitial compliance on interstitial fluid volumes and pressures. Compliance is the change in interstitial volume divided by the change in interstitial pressure, which is the slope of the relationship between volume and pressure. Low interstitial compliance (e.g., brain tissue) causes large increases in interstitial fluid pressure when interstitial fluid volume increases, which can occur during cerebral edema or hemorrhage within the brain (stroke). In contrast, tissue with high interstitial compliance (e.g., subcutaneous tissues), show relatively small increases in interstitial pressure as interstitial volume increases.

a low interstitial compliance (e.g., brain, kidney) so that relatively small increases in interstitial volume can lead to large increases in interstitial pressure. A large increase in pressure can be very damaging to the tissues and lead to cellular dysfunction and death. In contrast, subcutaneous tissues have a relatively high interstitial compliance so that large increases in interstitial volume can occur with relatively small increases in interstitial pressure. Despite a relatively high compliance at low interstitial fluid volumes, subcutaneous interstitial pressures can still increase to high values at very high interstitial volumes during severe limb edema.

OSMOSIS AND OSMOTIC PRESSURE

Osmosis is the movement of water across a membrane from the side of high water concentration to the side of low concentration. Figure 1 is a model showing two chambers separated by a selectively permeable ("semipermeable") membrane that permits water, but not solutes, to diffuse across the membrane. If chamber A contains 150 mM NaCl and chamber B contains no solute, then the concentration of water in B is greater than its concentration in A. The concentration of water in A is diluted by the presence of the solutes, Na^+ and Cl^-. Because the concentration of water molecules is greater in B than in A, water moves across the membrane down its concentration gradient (i.e., from side B to A). If this movement of water is allowed to continue, the volume of A will increase and the volume of B will decrease. If, however, a hydrostatic pressure is applied to chamber A that is just sufficient to prevent water from moving from B to A, then the volume of A will not change. The hydrostatic pressure that is required to prevent the movement of water by osmosis is termed the **osmotic pressure**.

The osmotic pressure of a solution containing solute particles in water can be calculated using the **van't Hoff equation:**

$$\pi = nRTC$$

The osmotic pressure (π, usually expressed in mm Hg) equals the product of the number of

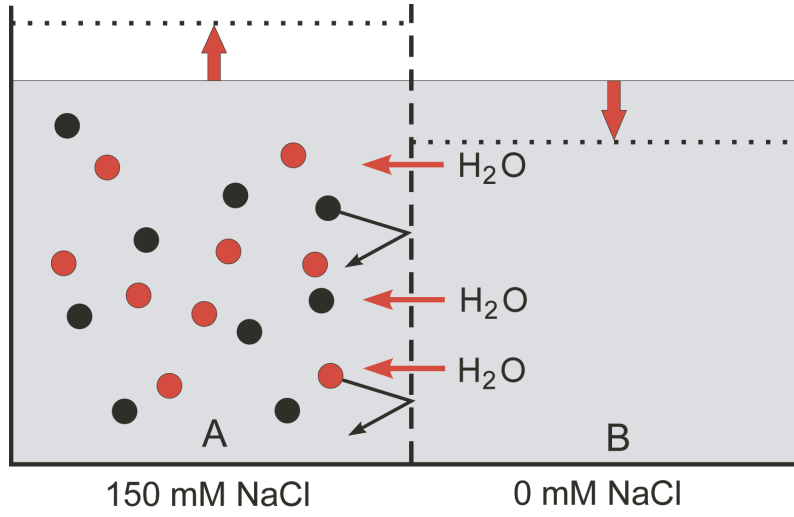

FIGURE 1 Osmosis. Chamber *A* contains 150 mM NaCl (red and black solute particles), whereas chamber *B* is pure water (H_2O). The two chambers are separated by a semi-permeable membrane that permits water, but not Na^+ or Cl^-, to move through the membrane. Because the concentration of water in B is greater than A, water moves by osmosis from B to A, down its concentration gradient. Over time, this leads to an increase in the volume of A (*up arrow*) and a decrease in the volume of B (*down arrow*).

dissociating particles (n), the ideal gas constant (R), the absolute temperature (T, degrees kelvin), and the molar concentration (C) of the solutes. If n and C are combined, then C represents the concentration in osmolarity (milliosmoles/liter; mOsm/L). In Figure 1, because NaCl dissociates in water to Na^+ and Cl^- (n=2), a 150 mM NaCl concentration (C) has an osmolar concentration (nC) of 300 mOsm.

Although the van't Hoff equation assumes very dilute solutions, it still approximates conditions found within the body. The measured osmolarity is usually less than the calculated osmolarity because of interactions between dissociated solute particles.

If the model shown in Figure 1 is changed so that chamber B contains NaCl at a concentration of 120 mM, then the concentration difference across the membrane ($\Delta C = 30$ mM) determines the osmotic pressure ($\pi = nRTDC$). Because NaCl dissociates into two ions, the net osmolarity across the membrane with this concentration difference is 60 mOsm/L.

As described in Chapter 8, the movement of water across the capillary endothelium depends upon hydrostatic pressures and oncotic (colloid osmotic) pressures rather than osmotic pressures. **Oncotic pressure** refers to the osmotic pressure exerted by non-permeable proteins on either side of the capillary endothelium. Because the ions in the plasma and interstitial fluid freely transverse the endothelial barrier, they do not contribute significantly to the osmotic forces that act upon the water molecules across capillaries.

PULMONARY CAPILLARY WEDGE PRESSURE

The measurement of pulmonary capillary wedge pressure (PCWP) provides an indirect assessment of left atrial pressure and is particularly useful in the diagnosis of left ventricular failure and mitral valve disease. The measurement is made as follows: A balloon-tipped, multi-lumen catheter (Swan-Ganz catheter) is advanced from a peripheral vein into the right atrium, passed into the right ventricle, then positioned within a branch of the pulmonary artery. There is one opening (port) at the tip of the catheter (distal to the balloon) and a second port several centimeters proximal to the balloon. These ports are connected to

pressure transducers. When properly positioned in a branch of the pulmonary artery, the distal port measures pulmonary artery pressure (approximately 25/15 mm Hg) and the proximal port measures right atrial pressure (approximately 0 to 4 mm Hg). The balloon (located behind the distal port) is then inflated with air using a syringe (the balloon volume is about 1 ml); this occludes the branch of the pulmonary artery. When this occurs, the pressure at the distal port rapidly falls, and after about 10 seconds, reaches a stable, lower value that is very close to left atrial pressure (normally about 8 to 10 mm Hg). The balloon is then deflated.

The pressure recorded during balloon inflation is similar to left atrial pressure because the occluded pulmonary artery, along with its distal branches that eventually connect to the pulmonary veins, acts as a long catheter that measures the blood pressure within the pulmonary veins (this pressure is virtually the same as mean left atrial pressure).

A PCWP exceeding 15 mm Hg suggests mitral stenosis, mitral insufficiency, aortic stenosis, aortic regurgitation, ventricular failure, or other cardiac defects or pathologies. When the PCWP exceeds 20 mm Hg, the transmission of this pressure back into the pulmonary vasculature increases pulmonary capillary hydrostatic pressure, which can lead to pulmonary congestion and edema.

PRESSURE NATRIURESIS

The kidneys play a central role in arterial pressure regulation through mechanisms related to sodium and water excretion. It has long been observed that acute increases in arterial pressure cause increased sodium and water excretion. This is termed **pressure natriuresis** or **pressure diuresis**. If an experiment is conducted in which arterial pressure is increased by infusing a systemic vasoconstrictor for several days, systemic vascular resistance and arterial pressure initially rise (Figure 1). After a day or two, arterial pressure returns to normal despite the sustained increase in systemic vascular resistance. The fall in arterial pressure is caused by a transient increase in sodium and water excretion that reduces blood volume and restores arterial pressure. When the arterial pressure is normalized, the sodium balance (sodium output/sodium intake) is also normalized, but at a reduced blood volume. If the changes in sodium excretion are plotted versus arterial pressure, a renal function curve (pressure natriuresis curve) is generated (see Figure 1). An increase in arterial pressure, brought about by increased systemic vascular resistance in this example, temporarily shifts the operating point on the renal function curve from A to B as the increased pressure increases sodium and water excretion. Then, as blood volume decreases in response to the natriuresis and diuresis, the arterial pressure falls back to its original operating point (A). The arterial pressure returns to its normal value because the reduction in blood volume reduces cardiac output through the Frank-Starling mechanism. These changes occur while the elevated systemic vascular resistance is being maintained by infusion of the vasoconstrictor. Therefore, the kidneys, by regulating blood volume, are ultimately responsible for the long-term regulation of arterial pressure.

If renal excretion of sodium and water is reduced either by extrinsic influences (e.g., increased circulating angiotensin II and aldosterone) or by intrinsic renal disease, then a higher arterial pressure (i.e., hypertension) is required to produce normal sodium and water excretion. This causes a rightward shift in the renal function curve (Figure 2). Therefore, when pressure natriuresis is impaired, a higher arterial pressure is required to maintain normal sodium balance. The higher arterial pressure is brought about by small reductions in sodium excretion (relative to sodium intake) due to impaired renal sodium handling, which over time increases blood volume and arterial pressure. Then, once the arterial pressure increases sufficiently to restore normal sodium excretion (to match the sodium intake), a new operating point is established (Point B in Figure 2).

For more details on conditions that alter pressure natriuresis curves see the following review article: Hall J: The kidney, hypertension, and obesity. *Hypertension* 2003;41: 625–633.

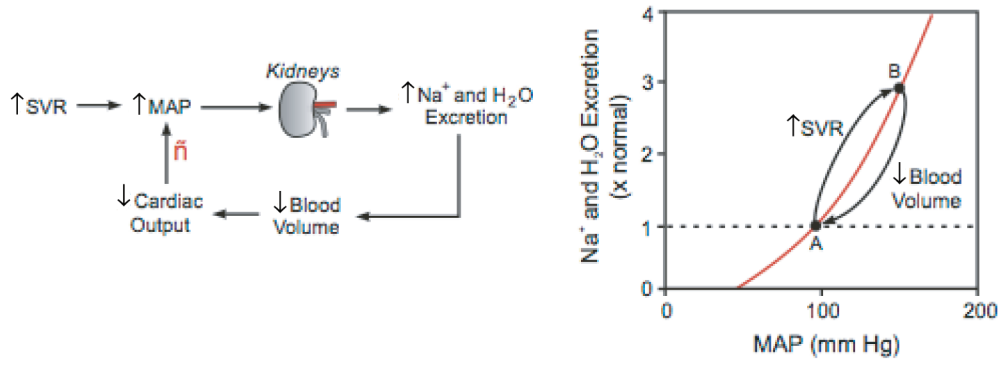

FIGURE 1 Pressure natriuresis. In the *left panel,* infusing a vasoconstrictor increases systemic vascular resistance (*SVR*) and mean arterial pressure (*MAP*). This causes pressure-induced natriuresis and diuresis (increased sodium and water excretion by the kidneys), which decreases blood volume and cardiac output (by the Frank-Starling mechanism) until arterial pressure is normalized. The *right panel* shows the renal function curve (pressure natriuresis curve), which depicts the relationship between renal excretion of sodium and water, and arterial pressure. If SVR is increased by infusing a vasoconstrictor, the arterial pressure and sodium (and water) excretion increase temporarily from a normal operating point *A* to point *B.* As blood volume (and cardiac output) decreases due to increased sodium and water excretion, the arterial pressure falls back to its normal operating point.

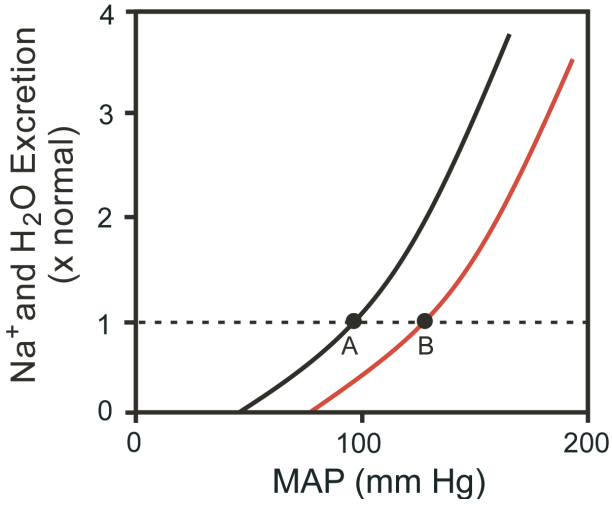

FIGURE 2 Effects of altered sodium excretion on arterial pressure. Impaired renal excretion of sodium and water (e.g., by increased angiotensin II, aldosterone or renal disease) increases blood volume and arterial pressure (from point *A* to *B*) as the normal renal function curve (black curve) shifts to the right (red curve). The arterial pressure increases to a level that is necessary to restore normal sodium and water excretion, thereby reestablishing normal sodium balance.

REYNOLDS NUMBER

The onset of turbulence under ideal conditions can be predicted by calculating the Reynolds number (Re) as shown in Equation 1:

$$\text{Re} = \frac{(V \cdot D \cdot \rho)}{\eta} \qquad \text{Equation 1}$$

(V = mean velocity, D = vessel diameter, ρ = blood density, and η = blood viscosity)

Above a critical Re, laminar flow is disrupted and turbulence occurs. The most important physiological determinant of Re is velocity. As blood flow velocity increases in a blood vessel or across a heart valve, turbulence does not gradually increase as the Reynolds number increases. Instead, laminar flow continues until a critical Re is reached, at which point, turbulence develops. Under ideal conditions (e.g., long, straight, smooth

blood vessels), the critical Re is relatively high, and laminar flow is normally present (see CD – turbulence). However, in branching vessels, or in vessels with atherosclerotic plaques protruding into the lumen, the critical Re is much lower so that turbulence can occur even at normal flow velocities.

Although vessel diameter is in the numerator of Equation 1, a decrease in diameter does not necessarily decrease Re. In fact, a decrease in vessel (or heart valve) diameter increases Re because a decrease in diameter causes a disproportionate increase in mean velocity (V). This occurs because velocity is proportional to the reciprocal of the radius (r) squared ($V \alpha 1/r^2$). This relationship is based upon the relationship between flow (F), velocity (V), and cross-sectional area (A) of a vessel, in which $F = V \cdot A$, and $A = \pi \cdot r^2$. As shown in Figure 1, if an arterial stenosis reduces the vessel diameter (or radius) to one-half its original diameter, mean velocity increases 4-fold. The net effect is a 2-fold increase in Re, bringing the Re closer to its critical value for turbulence to occur.

TURBULENT FLOW

Laminar flow is the normal condition for blood flow in most blood vessels. It is characterized by concentric layers of blood flowing down the length of a blood vessel (Figure 1). The orderly movement of adjacent layers of blood flow through a vessel helps to minimize energy losses in the flowing blood caused by viscous interactions between the adjacent layers and the wall of the blood vessel. **Turbulence** occurs when smoothly flowing, laminar flow becomes disrupted (see Figure 1). Turbulence is found distal to stenotic (narrowed) heart valves or arterial vessels, at vessel branch points, and in the ascending aorta at high cardiac ejection velocities (e.g., during exercise).

Turbulence results in characteristic sounds (e.g., ejection murmurs, carotid bruits) that can be heard with a stethoscope. Because higher velocities enhance turbulence (see CD – Reynolds), murmurs resulting from turbulence become louder whenever blood flow increases across narrowed valves or vessels. Elevated cardiac outputs across anatomically normal aortic valves can sometimes cause physiologic murmurs because of turbulence. This can occur in pregnant women who have elevated cardiac outputs and who may also have reduced hematocrit, which decreases blood viscosity. Both factors increase the Reynolds number (see CD – Reynolds) and thereby increase the likelihood of turbulence.

Turbulence causes increased energy loss and a greater pressure drop along a vessel

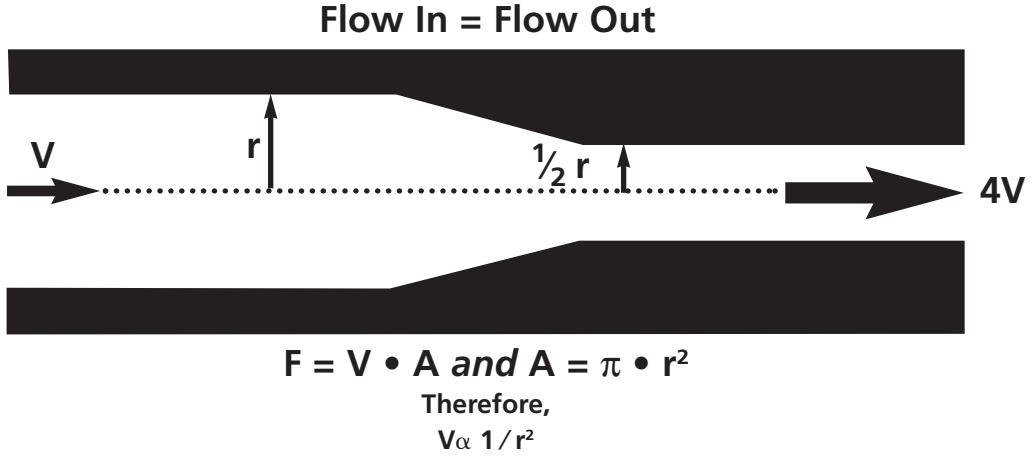

FIGURE 1 Effects of vessel narrowing on velocity. Because volume flow (*F*) equals mean velocity (*V*) times vessel cross-sectional area (*A*), and A is proportionate to the radius squared (r^2), $V \alpha 1/r^2$. Therefore, if radius is reduced to one-half normal, velocity increases 4-fold. This model assumes that flow does not change and that it is conserved (flow in = flow out).

length than predicted by the Poiseuille relationship (see Chapter 5). For example, as illustrated in Figure 2, if blood flow is increased 2-fold across a stenotic arterial segment, the pressure drop across the stenosis may increase 3 or 4-fold. The Poiseuille relationship predicts a 2-fold increase in the pressure drop across the lesion because the pressure drop is proportionate to flow under laminar flow conditions (Figure 3). Turbulence alters the

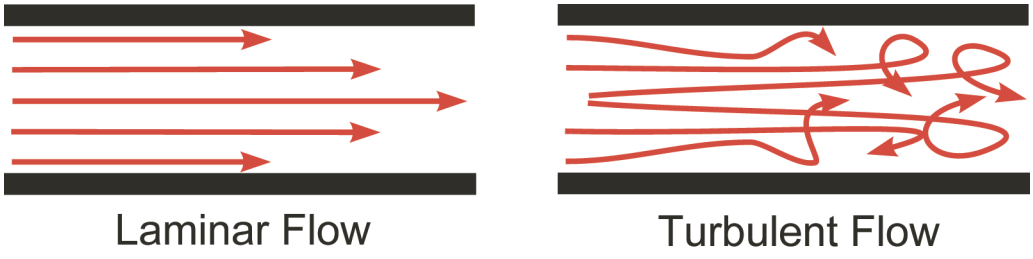

FIGURE 1 Laminar versus turbulent flow. In laminar flow, blood flows smoothly in concentric layers parallel with the axis of the blood vessel, with the highest velocity in the center of the vessel and the lowest velocity next to the endothelial lining of the vessel. When laminar flow becomes disrupted and turbulent, blood no longer flows in layers, but rather moves in different paths, often forming vortices.

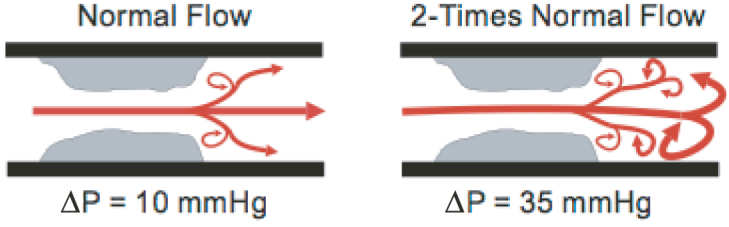

FIGURE 2 Effects of flow on turbulence. Increasing the flow across a stenotic lesion 2-fold causes a disproportionate increase in the pressure drop (ΔP) across the lesion due to increased turbulence; in this illustration, the ΔP may increase 3 or 4-fold instead of 2-fold as predicted by the Poiseuille relationship.

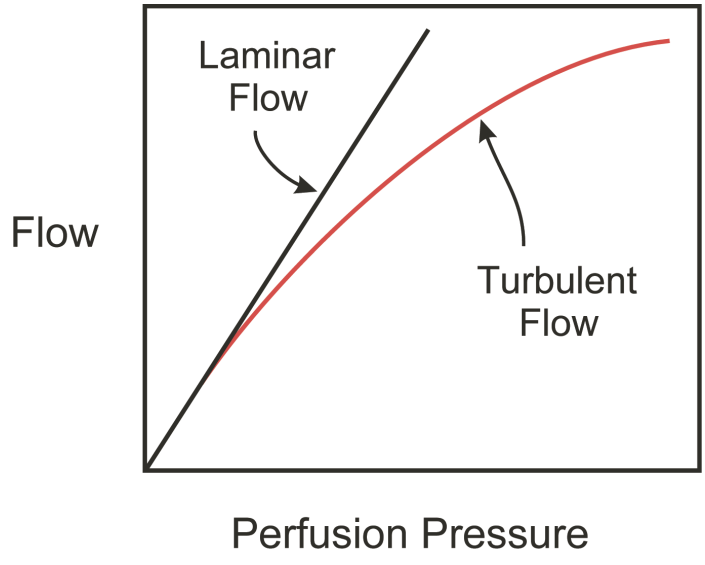

FIGURE 3 Effects of turbulence on the pressure-flow relationship. Turbulence decreases flow at any given perfusion pressure, or requires a greater perfusion pressure to drive a given flow. Turbulence is commonly found associated with stenotic heart valves or arterial vessels.

relationship between flow and perfusion pressure so that the relationship is no longer linear and proportionate as described by the Poiseuille relationship. Instead, a greater perfusion pressure is required to propel the blood at a given flow rate when turbulence is present. Alternatively, a given flow causes a greater pressure drop across a resistance than predicted simply by the radius and length of the resistance element because of increased energy losses associated with turbulence.

Supplemental Content

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Ion Permeability and Conductance
Reentry Mechanisms

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Formation and Physiological Actions of Endothelin-1
Formation and Physiological Actions of Metabolites of Arachidonic Acid

Chapter 4
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Chapter 9
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Other
Reynolds Number
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