Overview of the Cardiovascular System

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OBJECTIVES

The student understands the homeostatic role of the cardiovascular system, the basic principles of cardiovascular transport, and the basic structure and function of the components of the system.

- *Defines homeostasis.*
- *Identifies the major body fluid compartments and states the approximate volume of each.*
- *Lists three conditions, provided by the cardiovascular system, that are essential for regulating the composition of interstitial fluid (ie, the internal environment).*
- *Diagrams the blood flow pathways between the heart and other major body organs.*
- *States the relationship among blood flow, blood pressure, and vascular resistance.*
- *Predicts the relative changes in flow through a tube caused by changes in tube length, tube radius, fluid viscosity, and pressure difference.*
- *Identifies the chambers and valves of the heart and describes the pathway of blood flow through the heart.*
- *Defines cardiac output.*
- *Describes the pathway of action potential propagation in the heart.*
- *Lists the five factors essential to proper ventricular pumping action.*
- *States the relationship between ventricular filling and cardiac output (Starling's law of the heart) and describes its importance in the control of cardiac output.*
- *Identifies the distribution of sympathetic and parasympathetic nerves in the heart and lists the basic effects of these nerves on the heart.*
- *Lists the major different types of vessels in a vascular bed and describes the morphological differences among them.*
- *Describes the basic anatomical features and function of the different vessel types.*
- *Identifies the major mechanisms in vascular control and blood flow distribution.*
- *Describes the basic composition of the fluid and cellular portions of blood.*

HOMEOSTATIC ROLE OF THE CARDIOVASCULAR SYSTEM

A 19th-century French physiologist, Claude Bernard (1813–1878), first recognized that all higher organisms actively and constantly strive to prevent the external environment from upsetting the conditions necessary for life within the organism.

Thus, the temperature, oxygen concentration, pH, ionic composition, osmolarity, and many other important variables of our *internal environment* are closely controlled. This process of maintaining the "constancy" of our internal environment has come to be known as *homeostasis.* To accomplish this task, an elaborate material transport network, the cardiovascular system, has evolved.

Three compartments of watery fluids, known collectively as the *total body water*, account for approximately 60% of body weight. This water is distributed among the *intracellular*, *interstitial*, and *plasma* compartments, as indicated in Figure 1–1. Note that about two-thirds of our body water is contained within cells and communicates with the interstitial fluid across the plasma membranes of cells. Of the fluid that is outside cells (ie, extracellular fluid), only a small amount, the *plasma volume*, circulates within the cardiovascular system. Blood is composed of plasma and roughly an equal volume of formed elements (primarily red cells). The

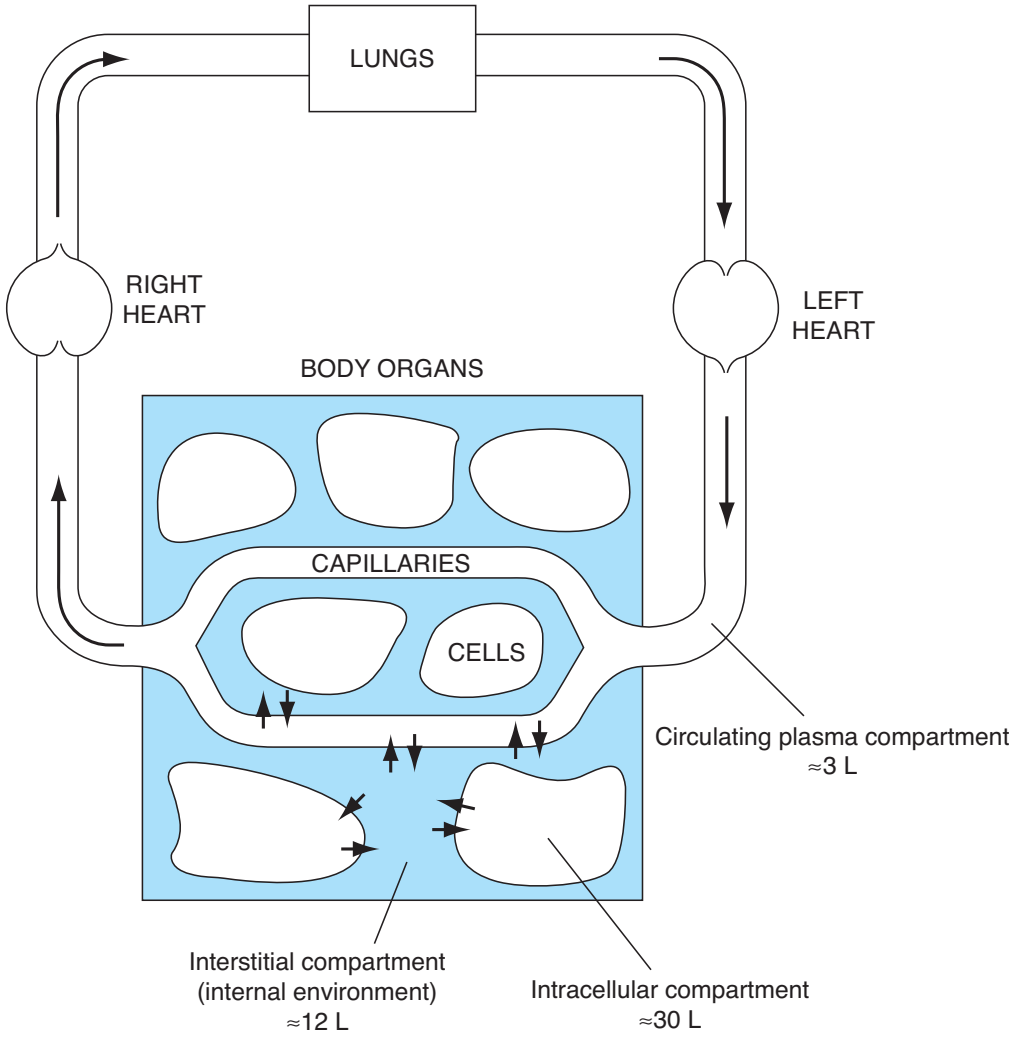


Figure 1–1. Major body fluid compartments with average volumes indicated for a 70-kg human. Total body water is approximately 60% of body weight.

circulating plasma fluid communicates with the interstitial fluid across the walls of small capillary vessels within organs.

The interstitial fluid is the immediate environment of individual cells. (It is the "internal environment" referred to by Bernard.) These cells must draw their nutrients from and release their products into the interstitial fluid. The interstitial fluid cannot, however, be considered a large reservoir for nutrients or a large sink for metabolic products, because its volume is less than half that of the cells that it serves.

The well-being of individual cells therefore depends heavily on the homeostatic mechanisms that regulate the composition of the interstitial fluid. This task is accomplished by continuously exposing the interstitial fluid to "fresh" circulating plasma fluid.

As blood passes through capillaries, solutes exchange between plasma and interstitial fluid by the process of diffusion. The net result of transcapillary diffusion is always that the interstitial fluid tends to take on the composition of the incoming blood. If, for example, potassium ion concentration in the interstitium of a particular skeletal muscle was higher than that in the plasma entering the muscle, then potassium would diffuse into the blood as it passes through the muscle's capillaries. Since this removes potassium from the interstitial fluid, its potassium ion concentration would decrease. It would stop decreasing when the net movement of potassium into capillaries no longer occurs, that is, when the concentration of the interstitial fluid reaches that of incoming plasma.

Three conditions are essential for this circulatory mechanism to effectively control the composition of the interstitial fluid: (1) there must be adequate blood flow through the tissue capillaries, (2) the chemical composition of the incoming (or arterial) blood must be controlled to be that which is optimal in the interstitial fluid, and (3) diffusion distances must be short. Figure 1–1 shows how the cardiovascular transport system operates to accomplish these tasks. As discussed earlier, substances are transported between cells and plasma in capillary vessels within organs by the process of diffusion. This transport occurs over extremely small distances because no cell in the body is located farther than approximately 10 μm from a capillary. Over such microscopic distances, *diffusion* is a very rapid process that can move huge quantities of material. Diffusion, however, is a very poor mechanism for moving substances from the capillaries of one organ, such as the lungs, to the capillaries of another organ that may be 1 m or more distant. Consequently, substances are transported between organs by the process of *convection*, by which the substances easily move along with blood flow because they are either dissolved or contained within blood. The relative distances involved in cardiovascular transport are not well illustrated in Figure 1–1. If the figure were drawn to scale, with 1 inch representing the distance from capillaries to cells within a calf muscle, then the capillaries in the lungs would have to be located about 15 miles away!

The overall functional arrangement of the cardiovascular system is illustrated in Figure 1–2. Since a functional rather than an anatomical viewpoint is expressed in this figure, the role of heart appears in three places: as the right heart pump, as the left heart pump, and as the heart muscle tissue. It is common practice to view the cardiovascular system as (1) the *pulmonary circulation*, composed of the right heart

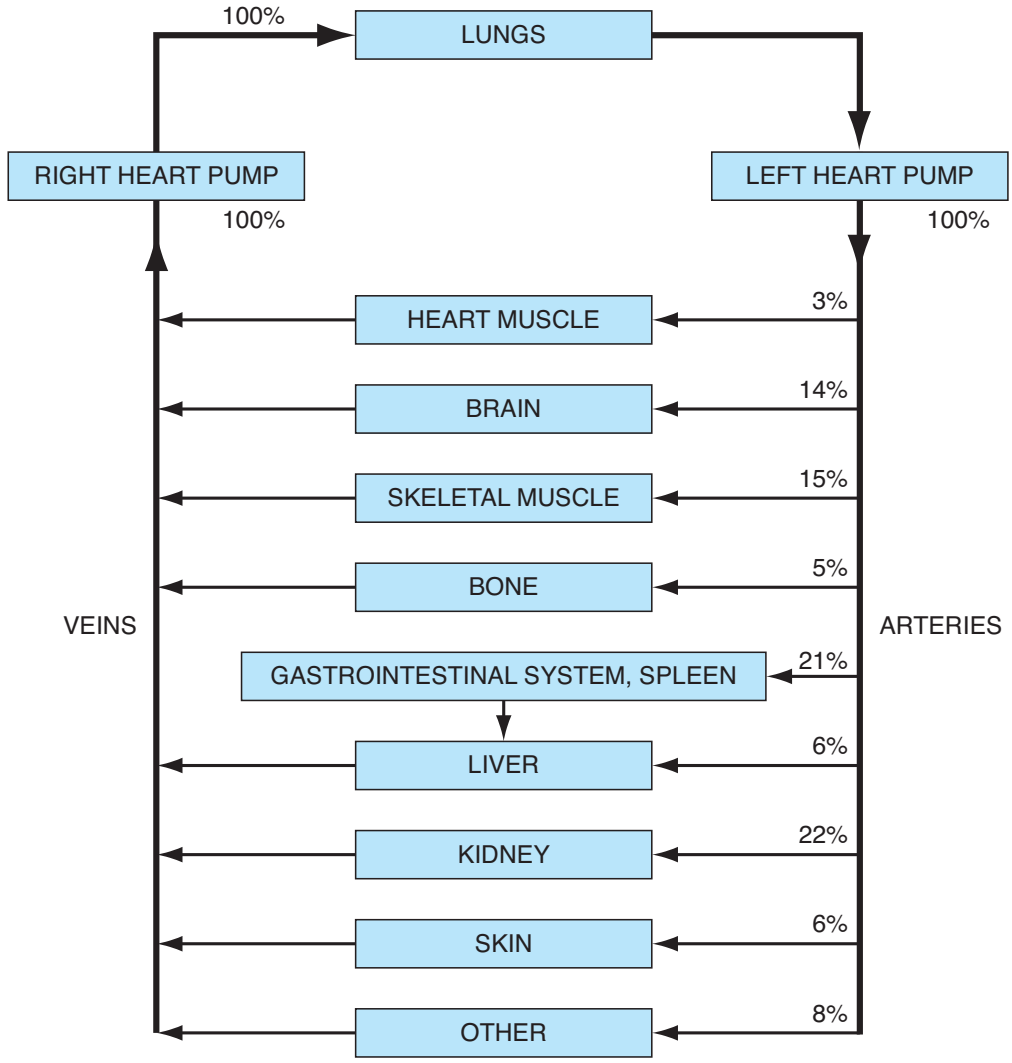


Figure 1–2. Cardiovascular circuitry, indicating the percentage distribution of cardiac output to various organ systems in a resting individual.

pump and the lungs, and (2) the *systemic circulation*, in which the left heart pump supplies blood to the systemic organs (all structures except the gas exchange portion of the lungs). The pulmonary and systemic circulations are arranged in series, that is, one after the other. Consequently, both the right and left hearts must pump an identical volume of blood per minute. This amount is called the *cardiac output.* A cardiac output of 5 to 6 L/min is normal for a resting individual.

As indicated in Figure 1–2, the systemic organs are functionally arranged in parallel (ie, side by side) within the cardiovascular system. There are two important consequences of this parallel arrangement. First, nearly all systemic organs receive blood of identical composition—that which has just left the lungs and is known as *arterial blood*. Second, the flow through any one of the systemic organs can be controlled independently of the flow through the other organs. Thus, for example,

the cardiovascular response to whole body exercise can involve increased blood flow through some organs, decreased blood flow through others, and unchanged blood flow through yet others.

Many of the organs in the body help perform the task of continually reconditioning the blood circulating in the cardiovascular system. Key roles are played by organs, such as the lungs, that communicate with the external environment. As is evident from the arrangement shown in Figure 1–2, any blood that has just passed through a systemic organ returns to the right heart and is pumped through the lungs, where oxygen and carbon dioxide are exchanged. Thus, the blood's gas composition is always reconditioned immediately after leaving a systemic organ.

Like the lungs, many of the systemic organs also serve to recondition the composition of blood, although the flow circuitry precludes their doing so each time the blood completes one circuit. The kidneys, for example, continually adjust the electrolyte composition of the blood passing through them. Because the blood conditioned by the kidneys mixes freely with all the circulating blood and because electrolytes and water freely pass through most capillary walls, the kidneys control the electrolyte balance of the entire internal environment. To achieve this, it is necessary that a given unit of blood pass often through the kidneys. In fact, the kidneys (under resting conditions) normally receive about one-fifth of the cardiac output. This greatly exceeds the amount of flow that is necessary to supply the nutrient needs of the renal tissue. This situation is common to organs that have a blood-conditioning function.

Blood-conditioning organs can also withstand, at least temporarily, severe reductions of blood flow. Skin, for example, can easily tolerate a large reduction in blood flow when it is necessary to conserve body heat. Most of the large abdominal organs also fall into this category. The reason is simply that because of their blood-conditioning functions, their normal blood flow is far in excess of that necessary to maintain their basal metabolic needs.

The brain, heart muscle, and skeletal muscles typify organs in which blood flows solely to supply the metabolic needs of the tissue. They do not recondition the blood for the benefit of any other organ. Normally, the blood flow to the brain and the heart muscle is only slightly greater than that required for their metabolism; hence, they do not tolerate blood flow interruptions well. Unconsciousness can occur within a few seconds after stoppage of cerebral flow, and permanent brain damage can occur in as little as 4 minutes without flow. Similarly, the heart muscle (myocardium) normally consumes approximately 75% of the oxygen supplied to it, and the heart's pumping ability begins to deteriorate within beats of a coronary flow interruption. As we shall see later, the task of providing adequate blood flow to the brain and the heart muscle receives a high priority in the overall operation of the cardiovascular system.

THE BASIC PHYSICS OF BLOOD FLOW

As outlined above, the task of maintaining interstitial homeostasis requires that an adequate quantity of blood flow continuously through each of the millions of capillaries in the body. In a resting individual, this adds up to a cardiac output

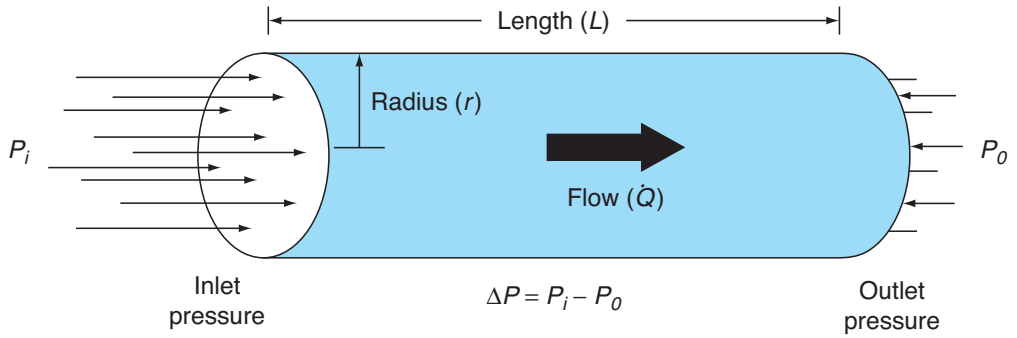


Figure 1–3. Factors influencing fluid flow through a tube.

of approximately 5 L/min (about 80 gallons/h). As people go about their daily lives, the metabolic rates and therefore the blood flow requirements in different organs and regions throughout the body change from moment to moment. Thus, the cardiovascular system must continuously adjust both the magnitude of cardiac output and how that cardiac output is distributed to different parts of the body. One of the most important keys to comprehending how the cardiovascular system operates is a thorough understanding of the relationship among the physical factors that determine the rate of fluid flow through a tube.

The tube depicted in Figure 1–3 might represent a segment of any vessel in the body. It has a certain length (L) and a certain internal radius (r) through which blood flows. Fluid flows through the tube only when the pressures in the fluid at the inlet and outlet ends (P_i and P_o) are unequal, that is, when there is a pressure difference (ΔP) between the ends. Pressure differences supply the driving force for flow. Because friction develops between the moving fluid and the stationary walls of a tube, vessels tend to resist fluid movement through them. This *vascular resistance* is a measure of how difficult it is to make fluid flow through the tube, that is, how much of a pressure difference it takes to cause a certain flow. The all-important relationship among flow, pressure difference, and resistance is described by the *basic flow equation* as follows:

$$\text{Flow} = \frac{\text{pressure difference}}{\text{resistance}}$$

$$\dot{Q} = \frac{\Delta P}{R}$$

where $\dot{Q}$ = flow rate (volume/time)
ΔP = pressure difference (mmHg[1])
R = resistance to flow (mmHg × time/volume)

[1] Although pressure is most correctly expressed in units of force per unit area, it is customary to express pressures within the cardiovascular system in millimeters of mercury. For example, mean arterial pressure may be said to be 100 mmHg because it is same as the pressure existing at the bottom of a mercury column 100 mm high. All cardiovascular pressures are expressed relative to atmospheric pressure, which is approximately 760 mmHg.

The basic flow equation may be applied not only to a single tube but also to complex networks of tubes, for example, the vascular bed of an organ or the entire systemic system. The flow through the brain, for example, is determined by the difference in pressure between cerebral arteries and veins divided by the overall resistance to flow through the vessels in the cerebral vascular bed. It should be evident from the basic flow equation that there are only two ways in which blood flow through any organ can be changed: (1) by changing the pressure difference across its vascular bed or (2) by changing its vascular resistance. Most often, it is changes in an organ's vascular resistance that cause the flow through the organ to change.

From the work of the French physician Jean Leonard Marie Poiseuille (1799–1869), who performed experiments on fluid flow through small glass capillary tubes, it is known that the resistance to flow through a cylindrical tube depends on several factors, including the radius and length of the tube and the viscosity of the fluid flowing through it. These factors influence resistance to flow as follows:

$$R = \frac{8L\eta}{\pi r^4}$$

where r = internal radius of the tube
L = tube length
η = fluid viscosity (Greek letter "*eta*")

Note that the internal radius of the tube is raised to the fourth power in this equation. Thus, even small changes in the internal radius of a tube have a very large influence on its resistance to flow. For example, halving the inside radius of a tube will increase its resistance to flow by 16-fold.

The preceding equations may be combined into one expression known as the *Poiseuille equation*, which includes all the terms that influence flow through a cylindrical vessel.[2]

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

Again, note that flow occurs only when a pressure difference exists. It is not surprising then that arterial blood pressure is an extremely important and carefully regulated cardiovascular variable. Also note once again that for any given pressure difference, tube radius has a very large influence on the flow through a tube. It is logical, therefore, that organ blood flows are regulated primarily through changes in the radius of vessels within organs. Although vessel length and blood viscosity

[2] Poiseuille's equation properly applies only to a homogeneous fluid flowing through rigid nontapered tubes with a certain flow pattern called *laminar flow*. Although not all these conditions are rigidly met for any vessel within the body, the approximation is close enough to permit general conclusions to be drawn from Poiseuille's equation.

are factors that influence vascular resistance, they are not variables that can be easily manipulated for the purpose of moment-to-moment control of blood flow.

In regard to the overall cardiovascular system as depicted in Figures 1–1 and 1–2, one can conclude that blood flows through the vessels within an organ only because a pressure difference exists between the blood in the arteries supplying the organ and the veins draining it. The primary job of the heart pump is to keep the pressure within arteries higher than that within veins. Normally, the average pressure in systemic arteries is near 100 mmHg, and the average pressure in systemic veins is near 0 mmHg.

Therefore, because the pressure difference (ΔP) is identical across all systemic organs, cardiac output is distributed among the various systemic organs solely on the basis of their individual resistances to flow. Because blood flows along the path of least resistance, organs with relatively low resistance receive relatively high flow.

THE HEART

Pumping Action

The heart lies in the center of the thoracic cavity and is suspended by its attachments to the great vessels within a thin fibrous sac called the *pericardium.* A small amount of fluid in the sac lubricates the surface of the heart and allows it to move freely during contraction and relaxation. Blood flow through all organs is passive and occurs only because arterial pressure is kept higher than venous pressure by the pumping action of the heart. The right heart pump provides the energy necessary to move blood through the pulmonary vessels, and the left heart pump provides the energy to move blood through the systemic organs.

The amount of blood pumped per minute from each ventricle (the *cardiac output,* CO) depends on the volume of blood ejected per beat (the *stroke volume,* SV) and the number of heartbeats per minute (the *heart rate,* HR) as follows:

$$\text{CO} = \text{SV} \times \text{HR}$$
$$\text{volume/minute} = \text{volume/beat} \times \text{beats/minute}$$

It should be evident from this relationship that all influences on cardiac output must act by changing either the heart rate or the stroke volume. These influences will be described in detail in subsequent chapters.

The pathway of blood flow through the chambers of the heart is indicated in Figure 1–4. Venous blood returns from the systemic organs to the right atrium via the superior and inferior venae cavae. It then passes through the *tricuspid valve* into the right ventricle and from there is pumped through the *pulmonic valve* into the pulmonary circulation via the pulmonary arteries. Oxygenated pulmonary venous blood flows in pulmonary veins to the left atrium and passes through the *mitral valve* into the left ventricle. From there it is pumped through the *aortic valve* into the aorta to be distributed to the systemic organs.

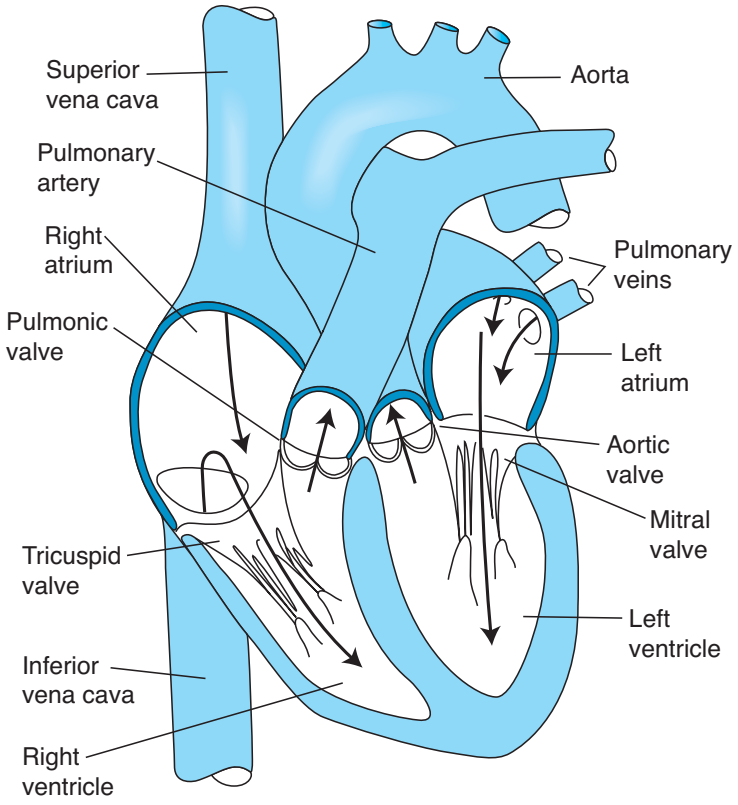


Figure 1–4. Pathway of blood flow through the heart.

Although the gross anatomy of the right heart pump is somewhat different from that of the left heart pump, the pumping principles are identical. Each pump consists of a ventricle, which is a closed chamber surrounded by a muscular wall, as illustrated in Figure 1–5. The valves are structurally designed to allow flow in only one direction and passively open and close in response to the direction of the pressure differences across them. Ventricular pumping action occurs because the volume of the intraventricular chamber is cyclically changed by rhythmic and synchronized contraction and relaxation of the individual cardiac muscle cells that lie in a circumferential orientation within the ventricular wall.

When the ventricular muscle cells are contracting, they generate a circumferential tension in the ventricular walls that causes the pressure within the chamber to increase. As soon as the ventricular pressure exceeds the pressure in the pulmonary artery (right pump) or aorta (left pump), blood is forced out of the chamber through the outlet valve as shown in Figure 1–5. This phase of the cardiac cycle during which the ventricular muscle cells are contracting is called *systole.* Because the pressure is higher in the ventricle than in the atrium during systole, the inlet or atrioventricular (AV) valve is closed. When the ventricular muscle cells relax, the pressure in the ventricle falls below that in the atrium, the AV valve opens, and the ventricle refills with blood, as shown on the right side in Figure 1–5. This portion of the cardiac cycle is called *diastole.* The outlet valve is closed during diastole because arterial pressure is

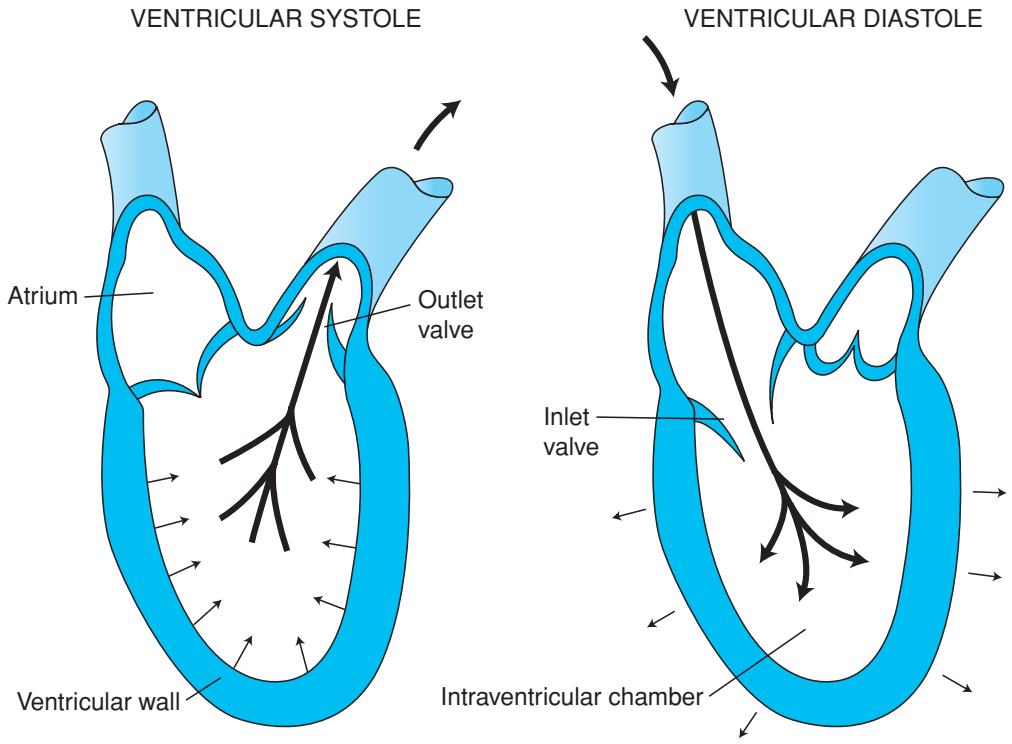


Figure 1–5. Ventricular pumping action.

greater than intraventricular pressure. After the period of diastolic filling, the systolic phase of a new cardiac cycle is initiated.

Excitation

Efficient pumping action of the heart requires a precise coordination of the contraction of millions of individual cardiac muscle cells. Contraction of each cell is triggered when an electrical excitatory impulse (*action potential*) sweeps over its membrane. Proper coordination of the contractile activity of the individual cardiac muscle cells is achieved primarily by the conduction of action potentials from one cell to the next via gap junctions that connect all cells of the heart into a functional syncytium (ie, acting as one synchronous unit). In addition, muscle cells in certain areas of the heart are specifically adapted to control the frequency of cardiac excitation, the pathway of conduction, and the rate of the impulse propagation through various regions of the heart. The major components of this specialized excitation and conduction system are shown in Figure 1–6. These include the *sinoatrial node* (SA node), the *atrioventricular node* (AV node), the *bundle of His,* and the right and left *bundle branches* made up of specialized cells called *Purkinje* fibers.

The SA node contains specialized cells that normally function as the heart's pacemaker and initiate the action potential that is conducted through the heart. The

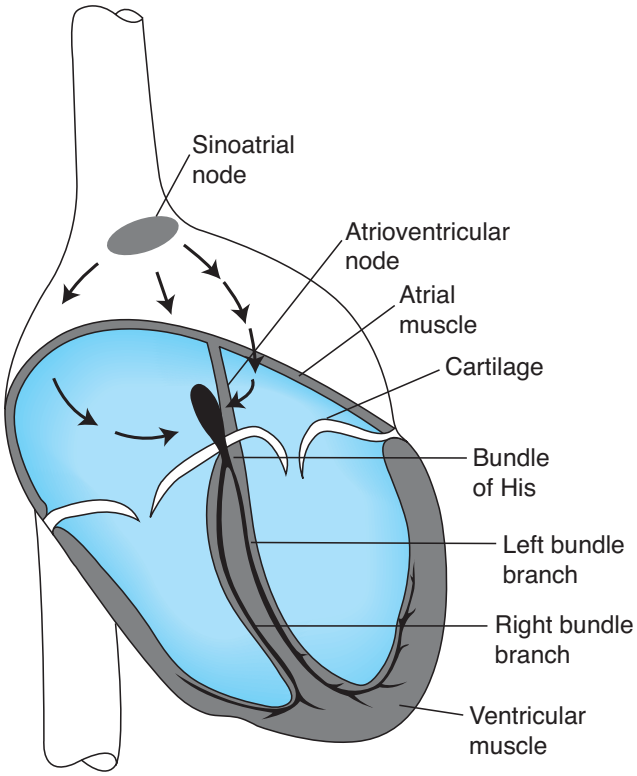


Figure 1–6. Electrical conduction system of the heart.

AV node contains slowly conducting cells that normally function to create a slight delay between atrial contraction and ventricular contraction. The Purkinje fibers are specialized for rapid conduction and ensure that all ventricular cells contract at nearly the same instant.

Requirements for Effective Operation

For effective, efficient ventricular pumping action, the heart must be functioning properly in five basic respects:

1. The contractions of individual cardiac muscle cells must occur at regular intervals and be synchronized (not *arrhythmic*).
2. The valves must open fully (not *stenotic*).
3. The valves must not leak (not *insufficient* or *regurgitant*).
4. The muscle contractions must be forceful (not *failing*).
5. The ventricles must fill adequately during diastole.

In the subsequent chapters, we will study in detail how these requirements are met in the normal heart.

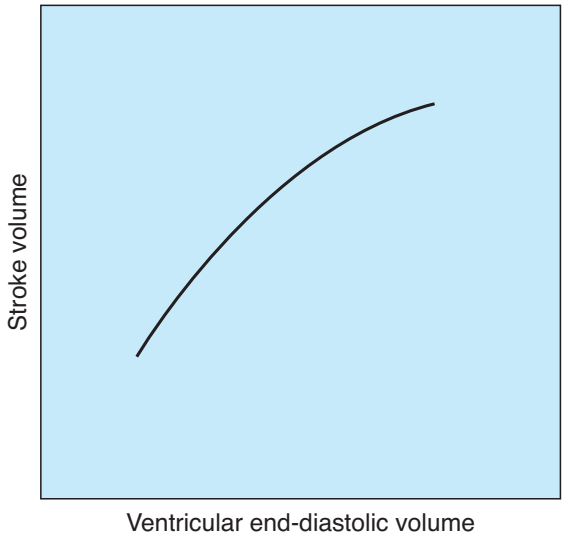


Figure 1–7. Starling's law of the heart.

Control of the Heart and Cardiac Output

Diastolic Filling

One of the most fundamental causes of variations in stroke volume was described by William Howell in 1884 and by Otto Frank in 1894 and formally stated by E. H. Starling in 1918. These investigators demonstrated that as cardiac filling increases during diastole, the volume ejected during systole also increases. As a consequence, and as illustrated in Figure 1–7, with other factors being equal, stroke volume increases as cardiac end-diastolic volume increases. This phenomenon (commonly referred to as Starling's law of the heart) is an intrinsic property of the cardiac muscle and is one of the primary regulators of cardiac output. The mechanisms responsible for this phenomenon depend largely on the cardiac muscle cells' length–tension relationship and will be described in detail in subsequent chapters.

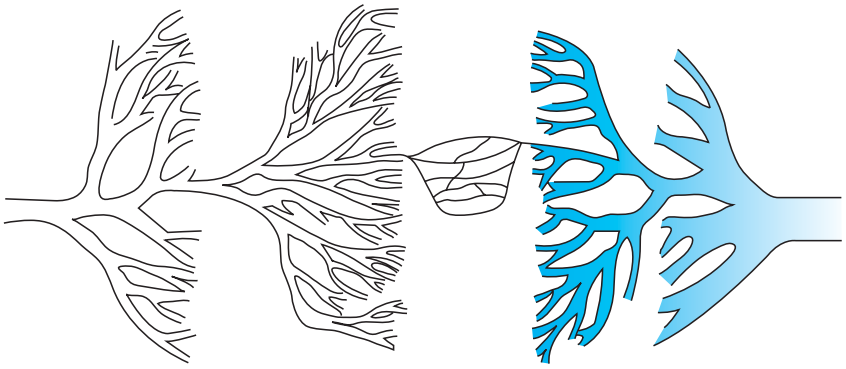
Autonomic Neural Influences

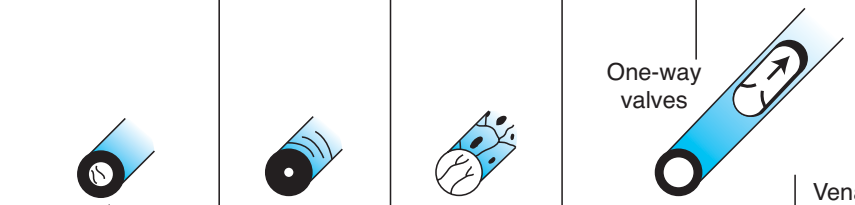
Although the heart can inherently beat on its own, cardiac function can be influenced profoundly by neural inputs from both the sympathetic and parasympathetic divisions of the autonomic nervous system. These inputs allow us to modify cardiac pumping as is appropriate to meet changing homeostatic needs of the body. All portions of the heart are richly innervated by *adrenergic sympathetic fibers.* When active, these sympathetic nerves release *norepinephrine* (noradrenaline) on cardiac cells. Norepinephrine interacts with β_1-adrenergic receptors on cardiac muscle cells to increase the heart rate, increase the action potential conduction velocity, and increase the force of contraction and rates of contraction and relaxation. Overall, sympathetic activation acts to increase cardiac pumping.

Cholinergic parasympathetic nerve fibers travel to the heart via the vagus nerve and innervate the SA node, the AV node, and the atrial muscle. When active, these parasympathetic nerves release *acetylcholine* on cardiac muscle cells. Acetylcholine interacts with *muscarinic* receptors on cardiac muscle cells to decrease the heart rate (SA node) and decrease the action potential conduction velocity (AV node). Parasympathetic nerves may also act to decrease the force of contraction of atrial (not ventricular) muscle cells. Overall, parasympathetic activation acts to decrease cardiac pumping. Usually, an increase in parasympathetic nerve activity is accompanied by a decrease in sympathetic nerve activity, and vice versa.

THE VASCULATURE

Blood that is ejected into the aorta by the left heart passes consecutively through many different types of vessels before it returns to the right heart. As illustrated in Figure 1–8, the major vessel classifications are *arteries*, *arterioles*, *capillaries*, *venules*,





	ARTERIES		ARTERIOLES	CAPILLARIES	VENULES	VEINS	
	Aorta						Venae cavae
Internal diameter	2.5 cm	0.4 cm	30 μm	5 μm	70 μm	0.5 cm	3 cm
Wall thickness	2 mm	1 mm	20 μm	1 μm	7 μm	0.5 mm	1.5 mm
Number	1	160	5×10^7	10^{10}	10^8	200	2
Total cross-sectional area	4.5 cm^2	20 cm^2	400 cm^2	4500 cm^2	4000 cm^2	40 cm^2	18 cm^2

Figure 1–8. Structural characteristics of the peripheral vascular system.

and *veins*. These consecutive vascular segments are distinguished from one another by differences in their physical dimensions, morphological characteristics, and function. One thing that all these vessels have in common is that they are lined with a contiguous single layer of endothelial cells. In fact, this is true for the entire circulatory system including the heart chambers and even the valve leaflets.

Some representative physical characteristics of these major vessel types are shown in Figure 1–8. It should be realized, however, that the vascular bed is a continuum and that the transition from one type of vascular segment to another does not occur abruptly. The total cross-sectional area through which blood flows at any particular level in the vascular system is equal to the sum of the cross-sectional areas of all the individual vessels arranged in parallel at that level. The number and total cross-sectional area values presented in Figure 1–8 are estimates for the entire systemic circulation.

Arteries are thick-walled vessels that contain, in addition to some smooth muscle, a large component of elastin and collagen fibers. Primarily because of the elastin fibers, which can stretch to twice their unloaded length, arteries can expand to accept and temporarily store some of the blood ejected by the heart during systole and then, by passive recoil, supply this blood to the organs downstream during diastole. The aorta is the largest artery and has an internal (lumenal) diameter of approximately 25 mm. Arterial diameter decreases with each consecutive branching, and the smallest arteries have diameters of approximately 0.1 mm. The consecutive arterial branching pattern causes an exponential increase in arterial numbers. Thus, although individual vessels get progressively smaller, the total cross-sectional area available for blood flow within the arterial system increases to severalfold that in the aorta. Arteries are often referred to as *conduit* vessels because they have relatively low and unchanging resistance to flow.

Arterioles are smaller and structured differently than arteries. In proportion to lumen size, arterioles have much thicker walls with more smooth muscle and less elastic material than do arteries. Because arterioles are so muscular, their diameters can be actively changed to regulate the blood flow through peripheral organs. Despite their minute size, arterioles are so numerous that in parallel their collective cross-sectional area is much larger than that at any level in arteries. Arterioles are often referred to as *resistance* vessels because of their high and changeable resistance, which regulates peripheral blood flow through individual organs.

Capillaries are the smallest vessels in the vasculature. In fact, red blood cells with diameters of 7 μm must deform to pass through them. The capillary wall consists of a single layer of endothelial cells that separate the blood from the interstitial fluid by only approximately 1 μm. Capillaries contain no smooth muscle and thus lack the ability to change their diameters actively. They are so numerous that the total collective cross-sectional area of all the capillaries in systemic organs is more than 1000 times that of the root of the aorta. Given that capillaries are approximately 0.5 mm in length, the total surface area available for exchange of material between blood and interstitial fluid can be calculated; it exceeds 100 m^2. For obvious reasons, capillaries are viewed as the *exchange* vessels of the cardiovascular system. In addition to the transcapillary diffusion of solutes that occurs across these vessel walls, there

can sometimes be net movements of fluid (volume) into and/or out of capillaries. For example, tissue swelling (*edema*) is a result of net fluid movement from plasma into the interstitial space.

After leaving capillaries, blood is collected in venules and veins and returned to the heart. Venous vessels have very thin walls in proportion to their diameters. Their walls contain smooth muscle, and their diameters can actively change. Because of their thin walls, venous vessels are quite distensible. Therefore, their diameters change passively in response to small changes in transmural distending pressure (ie, the difference between the internal and external pressures across the vessel wall). Venous vessels, especially the larger ones, also have one-way valves that prevent reverse flow. As will be discussed later, these valves are especially important in the cardiovascular system's operation during standing and during exercise. It turns out that peripheral venules and veins normally contain more than 50% of the total blood volume. Consequently, they are commonly thought of as the *capacitance* vessels. More importantly, *changes* in venous volume greatly influence cardiac filling and therefore cardiac pumping. Thus, peripheral veins actually play an extremely important role in controlling cardiac output.

Control of Blood Vessels

Blood flow through individual vascular beds is profoundly influenced by changes in the activity of sympathetic nerves innervating arterioles. These nerves release norepinephrine at their endings that interacts with *α-adrenergic* receptors on the smooth muscle cells to cause contraction and thus arteriolar constriction. The reduction in arteriolar diameter increases vascular resistance and decreases blood flow. These neural fibers provide the most important means of *reflex* control of vascular resistance and organ blood flow.

Arteriolar smooth muscle is also very responsive to changes in the local chemical conditions within an organ that accompany changes in the metabolic rate of the organ. For reasons to be discussed later, increased tissue metabolic rate leads to arteriolar dilation and increased tissue blood flow.

Venules and veins are also richly innervated by sympathetic nerves and constrict when these nerves are activated. The mechanism is the same as that involved with arterioles. Thus, increased sympathetic nerve activity is accompanied by decreased venous volume. The importance of this phenomenon is that venous constriction tends to increase cardiac filling and therefore cardiac output via Starling's law of the heart.

There is no important neural or local metabolic control of either arterial or capillary vessels.

BLOOD

Blood is a complex fluid that serves as the medium for transporting substances between the tissues of the body and performs a host of other functions as well. Normally, approximately 40% of the volume of whole blood is

occupied by blood cells that are suspended in the watery fluid, *plasma*, which accounts for the rest of the volume. The fraction of blood volume occupied by cells is termed as the *hematocrit*, a clinically important parameter.

$$\text{Hematocrit} = \text{cell volume/total blood volume}$$

Blood Cells

Blood contains three general types of "formed elements": red cells, white cells, and platelets (see Appendix A). All are formed in bone marrow from a common stem cell. Red cells are by far the most abundant. They are specialized to carry oxygen from the lungs to other tissues by binding oxygen to *hemoglobin*, an iron-containing heme protein concentrated within red blood cells. Because of the presence of hemoglobin, blood can transport 40 to 50 times the amount of oxygen that plasma alone could carry. In addition, the hydrogen ion buffering capacity of hemoglobin is vitally important to the blood's capacity to transport carbon dioxide.

A small, but important, fraction of the cells in blood is white cells or *leukocytes*. Leukocytes are involved in immune processes. Appendix A gives more information on the types and function of leukocytes. Platelets are small cell fragments that are important in the blood-clotting process.

Plasma

Plasma is the liquid component of blood and, as indicated in Appendix B, is a complex solution of electrolytes and proteins. *Serum* is the fluid obtained from a blood sample after it has been allowed to clot. For all practical purposes, the composition of serum is identical to that of plasma except that it contains none of the clotting proteins.

Inorganic *electrolytes* (inorganic ions such as sodium, potassium, chloride, and bicarbonate) are the most concentrated solutes in plasma. Of these, sodium and chloride are by far the most abundant and, therefore, are primarily responsible for plasma's normal osmolarity of about 300 mOsm/L. To a first approximation, the "stock" of the plasma soup is a 150-m*M* solution of sodium chloride. Such a solution is called "isotonic saline" and has many clinical uses as a fluid that is compatible with cells.

Plasma normally contains many different *proteins.* Most plasma proteins can be classified as *albumins*, *globulins*, or *fibrinogen* on the basis of different physical and chemical characteristics used to separate them. More than 100 distinct plasma proteins have been identified and each presumably serves some specific function. Many plasma proteins are involved in blood clotting or immune/defense reactions. Many others are important carrier proteins for a variety of substances including fatty acids, iron, copper, vitamin D, and certain hormones.

Proteins do not readily cross capillary walls and, in general, their plasma concentrations are much higher than their concentrations in the interstitial fluid. As will be discussed, plasma proteins play an important osmotic role in transcapillary

fluid movement and consequently in the distribution of extracellular volume between the plasma and interstitial compartments. *Albumin* plays an especially strong role in this regard simply because it is by far the most abundant of the plasma proteins.

Plasma also serves as the vehicle for transporting nutrients and waste products. Thus, a plasma sample contains many small organic molecules such as glucose, amino acids, urea, creatinine, and uric acid whose measured values are useful in clinical diagnosis.

FOUNDATION FOR SUBSEQUENT CHAPTERS

This first chapter has presented an overall description of the design of the cardiovascular system. Some important, basic, bottom-line principles that should help you understand many aspects of cardiovascular function have been included. (See the study questions at the end of this chapter, for example.)

Subsequent chapters will expand these concepts in much greater detail, but we urge students not to lose sight of the overall picture presented in this chapter. It may be useful to repeatedly refer back to this material.

KEY CONCEPTS

1. *The primary role of the cardiovascular system is to maintain homeostasis in the interstitial fluid.*
2. *The physical law that governs cardiovascular operation is that flow through any segment is equal to pressure difference across that segment divided by its resistance to flow; ie,* $\dot{Q} = \Delta P/R$.
3. *The heart pumps blood by rhythmically filling and ejecting blood from the ventricular chambers that are served by passive one-way inlet and outlet valves.*
4. *Changes in heart rate and stroke volume (and therefore cardiac output) can be accomplished by alterations in ventricular filling and by alterations in autonomic nerve activity to the heart.*
5. *Blood flow through individual organs is regulated by changes in the diameter of their arterioles.*
6. *Changes in arteriolar diameter can be accomplished by alterations in sympathetic nerve activity and by variations in local conditions.*
7. *Blood is a complex suspension of red cells, white cells, and platelets in plasma that is ideally suited to carry gases, salts, nutrients, and waste molecules throughout the system.*

STUDY QUESTIONS

1–1. Which organ in the body always receives the most blood flow?

1–2. Whenever skeletal muscle blood flow increases, blood flow to other organs must decrease. True or false?

1–3. When a heart valve does not close properly, a sound called a "murmur" can often be detected as the valve leaks. Would you expect a leaky aortic valve to cause a systolic or diastolic murmur?

1–4. Slowing of action potential conduction through the AV node will slow the heart rate. True or false?

1–5. Calculate cardiac output from the following data:

Pulmonary arterial pressure = 20 mmHg
Pulmonary venous pressure = 0 mmHg
Pulmonary vascular resistance = 4 mmHg × min/L

1–6. a. Determine the vascular resistance of a resting skeletal muscle from the following data:

Mean arterial pressure = 100 mmHg
Mean venous pressure = 0 mmHg
Blood flow to the muscle = 5 mL/min

b. Assume that when the muscle is exercising, the resistance vessels dilate so that their internal radius doubles. If blood pressure does not change, what is the blood flow through the exercising muscle?

c. What is the vascular resistance of this exercising skeletal muscle?

1–7. Usually, an individual who has lost a significant amount of blood is weak and does not reason very clearly. Why would blood loss have these effects?

1–8. What direct cardiovascular consequences would you expect from an intravenous injection of norepinephrine?

1–9. What direct cardiovascular effects would you expect from an intravenous injection of a drug that stimulates α-adrenergic receptors but not β-adrenergic receptors?

1–10. Individuals with high arterial blood pressure (hypertension) are often treated with drugs that block β-adrenergic receptors. What is the rationale for such treatment?

1–11. The clinical laboratory reports a serum sodium ion value of 140 mEq/L in a blood sample you have taken from a patient. What does this tell you about the sodium ion concentration in plasma, in interstitial fluid, and in intracellular fluid?

1–12. An individual has had the "flu" for 3 days with severe vomiting and diarrhea. How is this likely to influence his or her hematocrit?

1–13. Which of the following manipulations would produce the greatest decrease in blood flow through a given vascular bed?

a. halve the length of the capillaries
b. double the viscosity of the blood
c. halve the pressure gradient across the bed
d. double the radius of the venuoles
e. halve the radius of the arterioles

1–14. Arteries play which of the following functional roles in the systemic vascular system?

a. as conduit vessels
b. as capacitance vessels
c. as resistance vessels
d. as exchange vessels

1–15. You need to determine the correct dose of an IV drug that distributes only within the extracellular space. Which of the following values would be the closest estimate of the extracellular fluid volume of a healthy young adult male weighing 100 kg (220 lb)?

a. 3 L
b. 5 L
c. 8 L
d. 10 L
e. 20 L

Characteristics of Cardiac Muscle Cells

2

OBJECTIVES

The student understands the ionic basis of the spontaneous electrical activity of cardiac muscle cells:

- *Describes how membrane potentials are created across semipermeable membranes by transmembrane ion concentration differences.*
- *Defines equilibrium potential and knows its normal value for potassium and sodium ions.*
- *States how membrane potential reflects a membrane's relative permeability to various ions.*
- *Defines resting potential and action potential.*
- *Describes the characteristics of "fast" and "slow" response action potentials.*
- *Identifies the refractory periods of the cardiac cell electrical cycle.*
- *Defines threshold potential and describes the interaction between ion channel conditions and membrane potential during the depolarization phase of the action potential.*
- *Defines pacemaker potential and describes the basis for rhythmic electrical activity of cardiac cells.*
- *Lists the phases of the cardiac cell electrical cycle and states the membrane's permeability alterations responsible for each phase.*

The student knows the normal process of cardiac electrical excitation:

- *Describes gap junctions and their role in cardiac excitation.*
- *Describes the normal pathway of action potential conduction through the heart.*
- *Indicates the timing at which various areas of the heart are electrically excited and identifies the characteristic action potential shapes and conduction velocities in each major part of the conduction system.*
- *States the relationship between electrical events of cardiac excitation and the P, QRS, and T waves, the PR interval, and the ST segment of the electrocardiogram.*

The student understands the factors that control the heart rate and action potential conduction in the heart:

- *States how diastolic potentials of pacemaker cells can be altered to produce changes in the heart rate.*
- *Describes how cardiac sympathetic and parasympathetic nerves alter the heart rate and conduction of cardiac action potentials.*
- *Defines the terms* chronotropic *and* dromotropic.

The student understands the contractile processes of cardiac muscle cells:

- *Lists the subcellular structures responsible for cardiac muscle cell contraction.*
- *Defines and describes the* excitation–contraction *process.*
- *Defines* isometric, isotonic, *and* afterloaded *contractions of the cardiac muscle.*
- *Identifies the influence of altered preload on the tension producing and shortening capabilities of the cardiac muscle.*
- *Describes the influence of altered afterload on the shortening capabilities of the cardiac muscle.*
- *Defines the terms* contractility *and* inotropic state *and describes the influence of altered contractility on the tension producing and shortening capabilities of the cardiac muscle.*
- *Describes the effect of altered sympathetic neural activity on the cardiac inotropic state.*
- *States the relationships between ventricular volume and muscle length, between intraventricular pressure and muscle tension and the law of Laplace.*

Cardiac muscle cells are responsible for providing the power to drive blood through the circulatory system. Coordination of their activity depends on an electrical stimulus that is regularly initiated at an appropriate rate and reliably conducted through the entire heart. Mechanical pumping action depends on a robust contraction of the muscle cells that results in repeating cycles of tension development, shortening and relaxation. In addition, mechanisms to adjust the excitation and contraction characteristics must be available to meet the changing demands of the circulatory system. This chapter focuses on these electrical and mechanical properties of cardiac muscle cells that underlie normal heart function.

ELECTRICAL ACTIVITY OF CARDIAC MUSCLE CELLS

In all striated muscle cells, contraction is triggered by a rapid voltage change called an *action potential* that occurs on the cell membrane. Cardiac muscle cell action potentials differ sharply from those of skeletal muscle cells in three important ways that promote synchronous rhythmic excitation of the heart: (1) they can be self-generating; (2) they can be conducted directly from cell to cell; and (3) they have long duration, which precludes fusion of individual twitch contractions. To understand these special electrical properties of the cardiac muscle and how cardiac function depends on them, the basic electrical properties of excitable cell membranes must first be reviewed.

Membrane Potentials

All cells have an electrical potential (voltage) across their membranes. Such *membrane potentials* are caused by a separation of electrical charges across the membrane itself. The only way that the membrane potential can change is for electrical charges to move across (ie, current to flow through) the cell membrane.

There are two important corollaries to this statement: (1) the rate of change of membrane voltage is directly proportional to the net current across the membrane and (2) membrane voltage is stable (ie, unchanging) only when there is no net current across the membrane.

Unlike a wire, current across cell membranes is not carried by electrons but by the movement of ions through the cell membrane. The three ions that are the most important determinants of cardiac membrane potentials are sodium (Na^+) and calcium (Ca^{2+}), which are more concentrated in the interstitial fluid than they are inside cells, and potassium (K^+), which is more concentrated in intracellular than interstitial fluid. In general, such ions are very insoluble in lipids. Consequently, they cannot pass into or out of a cell through the lipid bilayer of the membrane itself. Instead, these ions cross the membrane only via various protein structures that are embedded in and span across the lipid cell wall. There are three general types of such transmembrane protein structures that are involved in ion movement across the cell membrane: (1) ion *channels*, (2) ion *exchangers*, and (3) ion *pumps*.[1] All are very specific for particular ions. For example, a "sodium channel" is a transmembrane protein structure that allows only Na^+ ions to pass into or out of a cell according to the net electrochemical forces acting on Na^+ ions.

The subsequent discussion concentrates on ion channel operation because ion channels (as opposed to transporters and pumps) are responsible for the resting membrane potential and for the rapid changes in membrane potential that constitute the cardiac cell action potential. Ion channels are under complex control and can be "opened," "closed," or "inactivated." The net result of the status of membrane channels to a particular ion is commonly referred to as the membrane's *permeability* to that ion. For example, "high permeability to sodium" implies that many of the Na^+ ion channels are in their open state at that instant. Precise timing of the status of ion channels accounts for the characteristic membrane potential changes that occur when cardiac cells are activated.

Figure 2–1 shows how ion concentration differences can generate an electrical potential across the cell membrane. Consider first, as shown at the top of this figure, a cell that (1) has K^+ more concentrated inside the cell than outside, (2) is permeable only to K^+ (ie, only K^+ channels are open), and (3) has no initial transmembrane potential. Because of the concentration difference, K^+ ions (positive charges) will diffuse out of the cell. Meanwhile, negative charges, such as protein anions, cannot leave the cell because the membrane is impermeable to them. Thus, the K^+ efflux will make the cytoplasm just inside the cell membrane more electrically negative (deficient in positively charged ions) and at the same time make the interstitial fluid just outside the cell membrane more electrically positive (rich in positively charged ions). Now K^+ ion, being positively charged, is attracted to regions of electrical negativity. Therefore, when K^+ diffuses out of a cell, it creates an electrical potential

[1] "Channels" can be thought of as passive ion-specific holes in the membrane through which a particular ion will move according to the electrochemical forces acting on it. "Exchangers" are passive devices that couple the movement of two or more specific ions across the membrane according to the collective net electrochemical forces acting on all the ions involved. "Pumps" use the chemical energy of splitting ATP to move ions across the cell membrane against prevailing electrochemical forces.

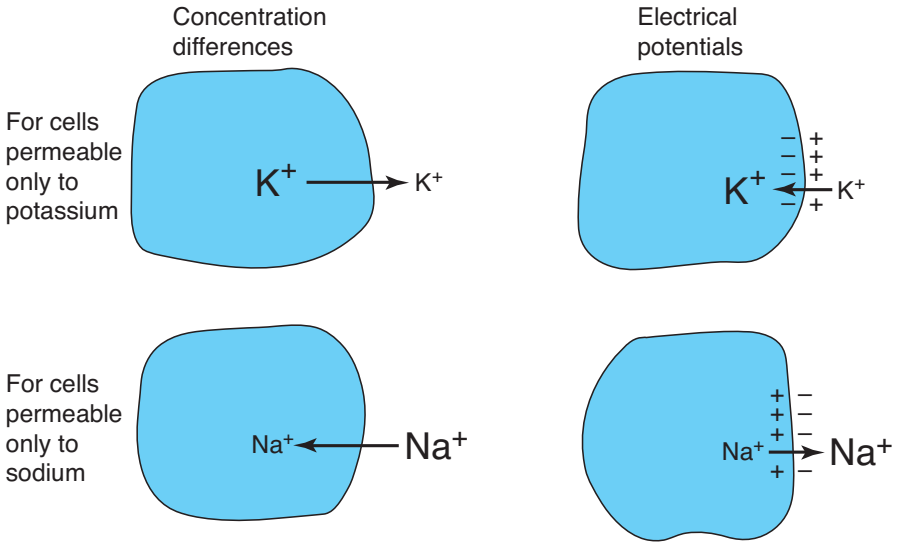


Figure 2–1. Electrochemical basis of membrane potentials.

across the membrane that tends to attract it back into the cell. There exists one membrane potential called the *potassium equilibrium potential* at which the electrical forces tending to pull K^+ into the cell exactly balance the concentration forces tending to drive K^+ out. When the membrane potential has this value, there is no *net* movement of K^+ across the membrane. With the normal concentrations of approximately 145 m*M* K^+ inside cells and 4 m*M* K^+ in the extracellular fluid, the K^+ equilibrium potential is roughly −90 mV (more negative inside than outside by nine-hundredths of a volt).[2] A membrane that is permeable only to K^+ will inherently and rapidly (essentially instantaneously) develop the potassium equilibrium potential. In addition, membrane potential changes require the movement of so few ions that concentration differences are not significantly affected by the process.

As depicted in the bottom half of Figure 2–1, similar reasoning shows how a membrane permeable only to Na^+ would have the *sodium equilibrium potential* across it. The sodium equilibrium potential is approximately +70 mV, with the normal extracellular Na^+ concentration of 140 m*M* and intracellular Na^+ concentration of 10 m*M*. Real cell membranes, however, are never permeable to just Na^+ or just K^+. When a membrane is permeable to both of these ions, the membrane potential will lie somewhere between the Na^+ equilibrium potential and the K^+ equilibrium potential. Just what membrane potential will exist at any instant depends on the relative permeability of the membrane to Na^+ and K^+. The more permeable the membrane is to K^+ than to Na^+, the closer the membrane potential will be to −90 mV. Conversely, when the permeability to Na^+ is high relative to the

[2] The equilibrium potential (E_{eq}) for any ion (X^z) is determined by its intracellular and extracellular concentrations as indicated in the Nernst equation:

$$E_{eq} = \frac{-61.5\ \text{mV}}{z} \log_{10} \frac{[X^z]\text{inside}}{[X^z]\text{outside}}$$

permeability to K^+, the membrane potential will be closer to +70 mV.[3] A *stable* membrane potential that lies between the sodium and potassium equilibrium potentials implies that there is no *net* current across the membrane. This situation may well be the result of opposite but balanced sodium and potassium currents across the membrane.

Because of low or unchanging permeability or low concentration, roles played by ions other than Na^+ and K^+ in determining membrane potential are usually minor and often ignored. However, as discussed later, calcium ions (Ca^{2+}) do participate in the cardiac muscle action potential. Like Na^+, Ca^{2+} is more concentrated outside cells than inside. The equilibrium potential for Ca^{2+} is approximately +100 mV, and the cell membrane tends to become more positive on the inside when the membrane's permeability to Ca^{2+} rises.

Under resting conditions, most heart muscle cells have membrane potentials that are quite close to the potassium equilibrium potential. Thus, both electrical and concentration gradients favor Na^+ and Ca^{2+} entry into the resting cell. However, the very low permeability of the resting membrane to Na^+ and Ca^{2+}, in combination with an energy-requiring sodium pump that extrudes Na^+ from the cell, prevents Na^+ and Ca^{2+} from gradually accumulating inside the resting cell.[4,5]

Cardiac Cell Action Potentials

Action potentials of cells from different regions of the heart are not identical but have varying characteristics that are important to the overall process of cardiac excitation.

Some cells within a specialized conduction system have the ability to act as pacemakers and to spontaneously initiate action potentials, whereas ordinary cardiac muscle cells do not (except under unusual conditions). Basic membrane electrical features of an ordinary cardiac muscle cell and a cardiac pacemaker-type cell are shown in Figure 2–2. Action potentials from these cell types are referred to as

"fast-response" and "slow-response" action potentials, respectively. As shown in Figure 2–2A, fast-response action potentials are characterized by a rapid depolarization (phase 0) with a substantial overshoot (positive inside voltage), a rapid reversal of the overshoot potential (phase 1), a long plateau (phase 2), and a repolarization (phase 3) to a stable, high (ie, large negative) resting membrane potential (phase 4). In comparison, the slow-response action potentials are characterized by a slower initial depolarization phase, a lower amplitude overshoot,

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[3] A quantitative description of how Na^+ and K^+ concentrations and the relative permeability (P_{Na}/P_K) to these ions affect membrane potential (E_m) is given by the following equation:

$$E_m = -61.5\,\text{mV}\log_{10}\left(\frac{[K^+]_i + P_{Na}/P_K[Na^+]_i}{[K^+]_o + P_{Na}/P_K[Na^+]_o}\right)$$

[4] The sodium pump not only removes Na^+ from the cell but also pumps K^+ into the cell. Because more Na^+ is pumped out than K^+ is pumped in (3:2), the pump is said to be electrogenic. The resting membrane potential becomes slightly less negative than normal when the pump is abruptly inhibited.

[5] The steep sodium gradient also promotes Ca^{2+} removal from the cytoplasm via a sodium/calcium exchanger.

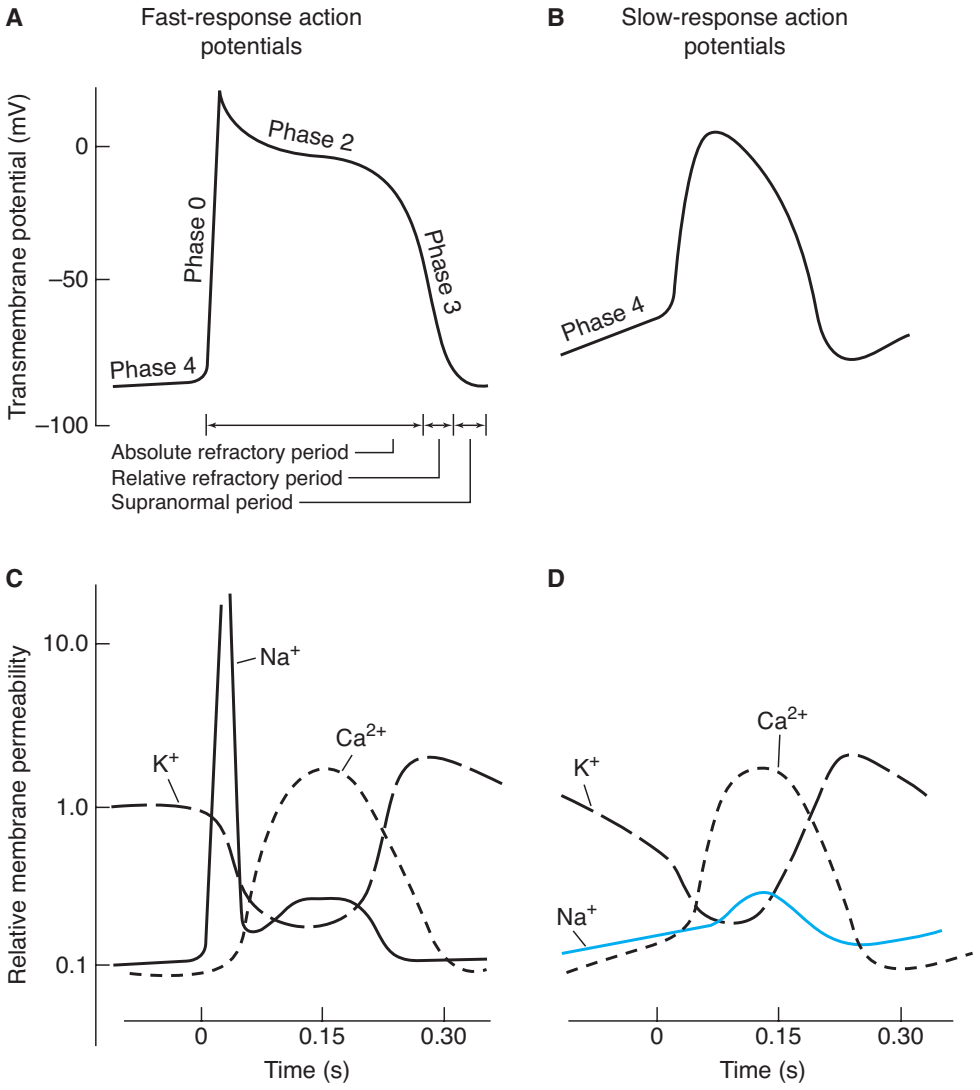

Figure 2–2. Time course of membrane potential (A and B) and ion permeability changes (C and D) that occur during "fast-response" (*left*) and "slow-response" (*right*) action potentials.

a shorter and less stable plateau phase, and a repolarization to an unstable, slowly depolarizing "resting" potential (Figure 2–2B). The unstable resting potential seen in pacemaker cells with slow-response action potentials is variously referred to as *phase 4 depolarization*, *diastolic depolarization*, or *pacemaker potential.* Such cells are usually found in the sinoatrial (SA) and atrioventricular (AV) nodes.

As indicated at the bottom of Figure 2–2A, cells are in an absolute refractory state during most of the action potential (ie, they cannot be stimulated to fire another action potential). Near the end of the action potential, the membrane is relatively refractory and can be reexcited only by a larger than normal stimulus. Immediately after the action potential, the membrane is transiently hyperexcitable and is said to be in a "vulnerable" or "supranormal" period. Similar alterations in

membrane excitability occur during slow action potentials but at present are not well characterized.

Recall that the membrane potential of any cell at any given instant depends on the relative permeability of the cell membrane to specific ions. As in all excitable cells, cardiac cell *action* potentials are the result of transient changes in the ionic permeability of the cell membrane that are triggered by an initial depolarization. Figures 2–2C and 2–2D indicate the changes in the membrane's permeabilities to K^+, Na^+, and Ca^{2+} that produce the various phases of the fast- and slow-response action potentials.[6] Note that during the resting phase, the membranes of both types of cells are more permeable to K^+ than to Na^+ or Ca^{2+}. Therefore, the membrane potentials are close to the potassium equilibrium potential (of −90 mV) during this period. In pacemaker-type cells, at least three mechanisms are thought to contribute to the slow depolarization of the membrane observed during the diastolic interval. First, there is a progressive decrease in the membrane's permeability to K^+ during the resting phase, and second, the permeability to Na^+ increases slightly. The gradual increase in the Na^+/K^+ permeability ratio will cause the membrane potential to move slowly away from the K^+ equilibrium potential (−90 mV) in the direction of the Na^+ equilibrium potential. Third, there is a slight increase in the permeability of the membrane to calcium ions, which results in an inward movement of these positively charged ions and also contributes to the diastolic depolarization.

When the membrane potential depolarizes to a certain *threshold* potential in either type of cell, major rapid alterations in the permeability of the membrane to specific ions are triggered. Once initiated, these permeability changes cannot be stopped and they proceed to completion.

The characteristic rapid rising phase of the fast-response action potential is a result of a sudden increase in Na^+ permeability. This produces what is referred to as the *fast inward current* of Na^+ and causes the membrane potential to move rapidly toward the sodium equilibrium potential. As indicated in Figure 2–2C, this period of very high sodium permeability (phase 0) is short-lived.[7] Development and maintenance of a depolarized *plateau* state (phase 2) is accomplished by the interactions of at least three separate processes: (1) a sustained reduction in K^+ permeability, (2) a slowly developed and sustained increase in the membrane's permeability to Ca^{2+}, and (3) electrogenic action of an Na^+/Ca^{2+} exchanger in which three Na^+ ions move into the cell in exchange for a single Ca^{2+} ion moving out of the cell.

The initial fast inward current is small (or even absent) in cells that have slow-response action potentials. The slow rising phase of these action potentials is therefore primarily a result of an inward movement of Ca^{2+} ions. In both types of cells,

[6] The membrane's permeability to a particular ion is not synonymous with the transmembrane current of that ion. The transmembrane current of any ion is the product of the membrane's permeability to it times the electrochemical driving forces acting on it. For example, the resting membrane is quite permeable to K^+ but there is little net K^+ movement because the resting membrane potential is very close to the potassium equilibrium potential.

[7] This is followed by a very brief increase in potassium permeability (not shown in Figure 2–2C) that allows a brief outward going potassium current (i_{To}) that contributes to the early repolarization (phase 1).

the membrane is repolarized (phase 3) to its original resting potential as the K^+ permeability increases and the Ca^{2+} and Na^+ permeabilities return to their low resting values. These late permeability changes produce what is referred to as the *delayed outward current.*

The overall smoothly graded permeability changes that produce action potentials are the net result of alterations in each of the many individual ion channels within the plasma membrane of a single cell.[8] These ion channels are generally made up of very long polypeptide chains that loop repeatedly across the cell membrane. These loops form a hollow channel between the intra- and extracellular fluids that are structurally quite specific for certain ions. The open/closed status of the channels can be altered by configurational changes in parts of the molecules within the channel ("gates") so that when open, ions move down their electrochemical gradient either into or out of the cell (high permeability). It is a largely unsolved mystery as to what specific mechanisms control the operation of these channels and cause the timing of their operation to so stereotypically follow the onset of a cardiac action potential. Some of the current thinking about these processes is presented later. Certain types of channels are called *voltage-gated channels* (or voltage-operated channels) because their probability of being open varies with membrane potential. Other types of channels, called *ligand-gated channels* (or receptor-operated channels), are activated by certain neurotransmitters or other specific signal molecules. Table 2–1 lists some of the major currents and channel types involved in cardiac cell electrical activity.

Some of the voltage-gated channels respond to a sudden onset, sustained change in membrane potential by only a brief period of activation. However, changes in membrane potential of slower onset but the same magnitude may fail to activate these channels at all. To explain such behavior, it is postulated that these channels have two independently operating "gates"—an *activation gate* and an *inactivation gate*—both of which must be open for the channel as a whole to be open. Both these gates respond to changes in membrane potential but do so with different voltage sensitivities and time courses.

These concepts are illustrated in Figure 2–3. In the resting state, with the membrane polarized to near −80 mV, the activation or *m* gate of the fast Na^+ channel is closed, but its inactivation or *h* gate is open (Figure 2–3A). With a rapid depolarization of the membrane to threshold, the Na^+ channels will be activated strongly to allow an inrush of positive sodium ions that further depolarizes the membrane and thus initiates a "fast" response action potential as illustrated in Figure 2–3B. This occurs because the *m* gate responds to membrane depolarization by opening more quickly than the *h* gate responds by closing. Thus, a rapid depolarization to threshold is followed by a brief, but strong, period of Na^+ channel activation wherein the *m* gate is open but the *h* gate has yet to close.

[8] The experimental technique of *patch clamping* has made it possible to study the operation of individual ion channels. The patch clamp data indicate that a single channel is either open or closed at any instant in time; there are no graded states of partial opening. What is graded is the percentage of time that a given channel spends in the open state, and the total number of channels that are currently in the open state.

Table 2–1. Characteristics of Important Cardiac Ion Channels in Order of Their Participation in an Action Potential

Current	Channel	Gating mechanism	Functional role
i_{K1}	K^+ channel (inward rectifier)	Voltage	Maintains high K^+ permeability during phase 4 Its decay contributes to diastolic depolarization Its suppression during phases 0 to 2 contributes to plateau
i_{Na}	Na^+ channel (fast)	Voltage	Accounts for phase 0 of action potential Inactivation may contribute to phase 1 of action potential
i_{To}	K^+ channel (transient outward)	Voltage	Contributes to phase 1 of action potential
i_{Ca}	Ca^{2+} channel (slow inward, L channels)	Both	Contributes to phase 2 of action potential Inactivation may contribute to phase 3 of action potential Is enhanced by sympathetic stimulation and β-adrenergic agents
i_K	K^+ channel (delayed rectifier)	Voltage	Causes phase 3 of action potential Is enhanced by increased intracellular Ca^{2+}
i_{KATP}	K^+ channel (ATP-sensitive)		Increases K^+ permeability when [ATP] is low
i_{KACh}	K^+ channel (acetylcholine-activated)	Ligand	Responsible for effects of vagal stimulation Decreases diastolic depolarization (and the heart rate) Hyperpolarizes resting membrane potential Shortens phase 2 of the action potential
i_f ("funny")	Na^+ (pacemaker current)	Both	Is activated by hyperpolarization and contributes to the diastolic depolarization Is enhanced by sympathetic stimulation and β-adrenergic agents Is suppressed by vagal stimulation

The initial membrane depolarization also causes the activation (d) gate of the Ca^{2+} channel to open after a brief delay. This permits the slow inward current of Ca^{2+} ions, which helps maintain the depolarization through the plateau phase of the action potential (Figure 2–3C). Ultimately, repolarization occurs because of both a delayed inactivation of the Ca^{2+} channel (by closure of the f gates) and an opening of K^+ channels (which are not shown in Figure 2–3). Multiple

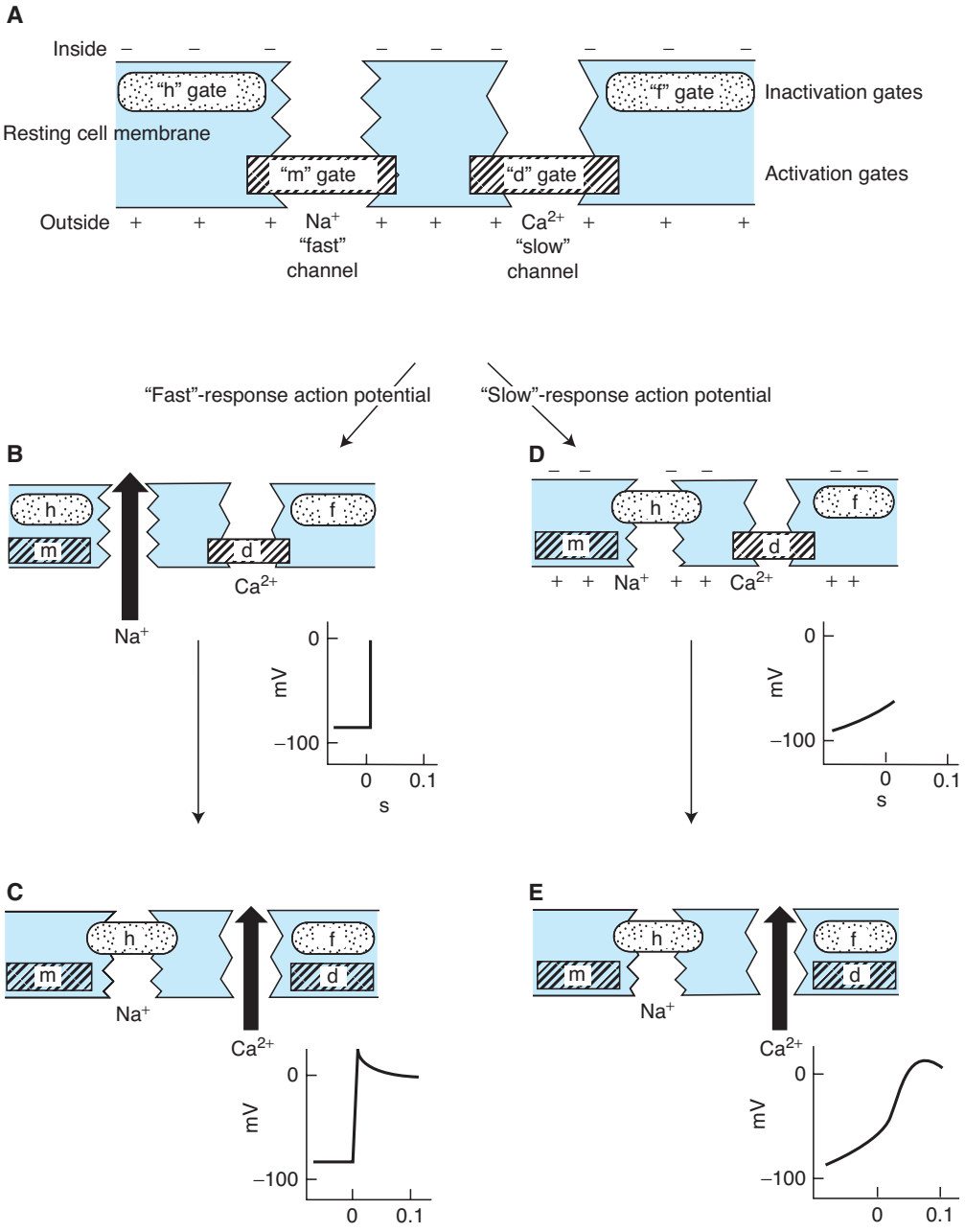

Figure 2–3. A conceptual model of cardiac membrane ion channels: at rest (**A**), during the initial phases of the fast-response (**B** and **C**), and the slow-response action potentials (**D** and **E**).

factors influence the operation of K^+ channels. For example, high intracellular Ca^{2+} concentration contributes to activation of K^+ channels during repolarization.

The *h* gates of sodium channels remain closed during the remainder of the action potential, effectively inactivating the Na^+ channel and contributing to the long cardiac refractory period, which lasts until the end of phase 3. With

repolarization, both gates of the sodium channel return to their original position and the channel is now ready to be reactivated by a subsequent depolarization.

The slow-response action potential shown in the right half of Figure 2–3 differs from the fast-response action potential primarily because of the lack of a strong activation of the fast Na^+ channel at its onset. This is a direct consequence of a slow depolarization to the threshold potential. Slow depolarization gives the inactivating *h* gates time to close even as the activating *m* gates are opening (Figure 2–3D). Thus, in a slow-response action potential, there is no initial period where all the sodium channels of a cell are essentially open at once. The depolarization beyond threshold is slow and caused primarily by the influx of Ca^{2+} through slow channels (Figure 2–3E).

Although cells in certain areas of the heart typically have fast-type action potentials and cells in other areas normally have slow-type action potentials, it is important to recognize that all cardiac cells are potentially capable of having either type of action potential, depending on how fast they depolarize to the threshold potential. As we shall see, rapid depolarization to the threshold potential is usually an event forced on a cell by the occurrence of an action potential in an adjacent cell. Slow depolarization to threshold occurs when a cell itself spontaneously and gradually loses its resting polarization, which normally happens only in the SA node. A *chronic* moderate depolarization of the resting membrane (caused, for example, by moderately high extracellular K^+ concentration) can inactivate the fast channels (by closing the *h* gates) without inactivating the slow Ca^{2+} channels. Under these conditions, all cardiac cell action potentials will be of the slow type. Large, sustained depolarizations, however, can inactivate both the fast and slow channels and thus make the cardiac muscle cells completely inexcitable.

Conduction of Cardiac Action Potentials

Action potentials are conducted over the surface of individual cells because active depolarization in any one area of the membrane produces local currents in the intracellular and extracellular fluids that passively depolarize immediately adjacent areas of the membrane to their voltage threshold for active depolarization.

In the heart, cardiac muscle cells are connected end-to-end by structures called *intercalated disks*. These disks contain the following: (1) *firm mechanical attachments* between adjacent cell membranes by proteins called *adherins* in structures called *desmosomes* and (2) *low-resistance electrical connections* between adjacent cells through channels formed by proteins called *connexin* in structures called *gap junctions*. Figure 2–4 shows schematically how these gap junctions allow action potential propagation from cell to cell.

Cells B, C, and D are shown in the resting phase with more negative charges inside than outside. Cell A is shown in the plateau phase of an action potential and has more positive charges inside than outside. Because of the gap junctions, electrostatic attraction can cause a local current flow (ion movement) between the depolarized membrane of active cell A and the polarized membrane of resting cell B, as indicated

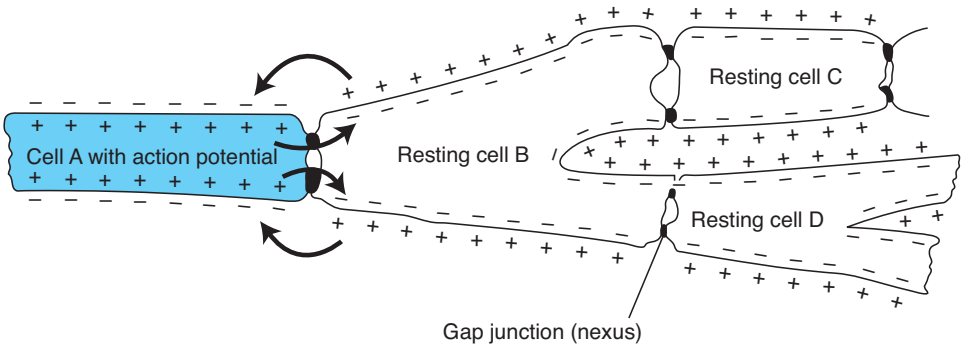

Figure 2–4. Local currents and cell-to-cell conduction of cardiac muscle cell action potentials.

by the arrows in the figure. This ion movement depolarizes the membrane of cell B. Once the local currents from active cell A depolarize the membrane of cell B near the gap junction to the threshold level, an action potential will be triggered at that site and will be conducted over cell B. Because cell B branches (a common morphological characteristic of cardiac muscle fibers), its action potential will evoke action potentials on cells C and D. This process is continued through the entire myocardium. Thus, an action potential initiated at *any* site in the myocardium will be conducted from cell to cell throughout the entire myocardium.

The speed at which an action potential propagates through a region of cardiac tissue is called the *conduction velocity*. The conduction velocity varies considerably in different areas in the heart and is determined by three variables. First, conduction velocity is directly dependent on the diameter of the muscle fiber involved. Thus, conduction over small-diameter cells in the AV node is significantly slower than conduction over large-diameter cells in the ventricular Purkinje system. Second, conduction velocity is also directly dependent on the intensity of the local depolarizing currents, which are in turn directly determined by the rate of rise of the action potential. Rapid depolarization favors rapid conduction. Third, conduction velocity is dependent on the capacitive and/or resistive properties of the cell membranes, gap junctions, and cytoplasm. Electrical characteristics of gap junctions can be influenced by external conditions that promote phosphorylation/dephosphorylation of the connexin proteins.

Details of the overall consequences of the cardiac conduction system are shown in Figure 2–5. As noted earlier, the specific electrical adaptations of various cells in the heart are reflected in the characteristic shape of their action potentials that are shown in the right half of Figure 2–5. Note that the action potentials shown in Figure 2–5 have been positioned to indicate the time when the electrical impulse that originates in the SA node reaches other areas of the heart. Cells of the SA node act as the heart's normal pacemaker and determine the heart rate. This is because the spontaneous depolarization of the resting membrane is most rapid in SA nodal cells, and they reach their threshold potential before cells elsewhere.

The action potential initiated by an SA nodal cell first spreads progressively through the atrial wall. Action potentials from cells in two different regions of the

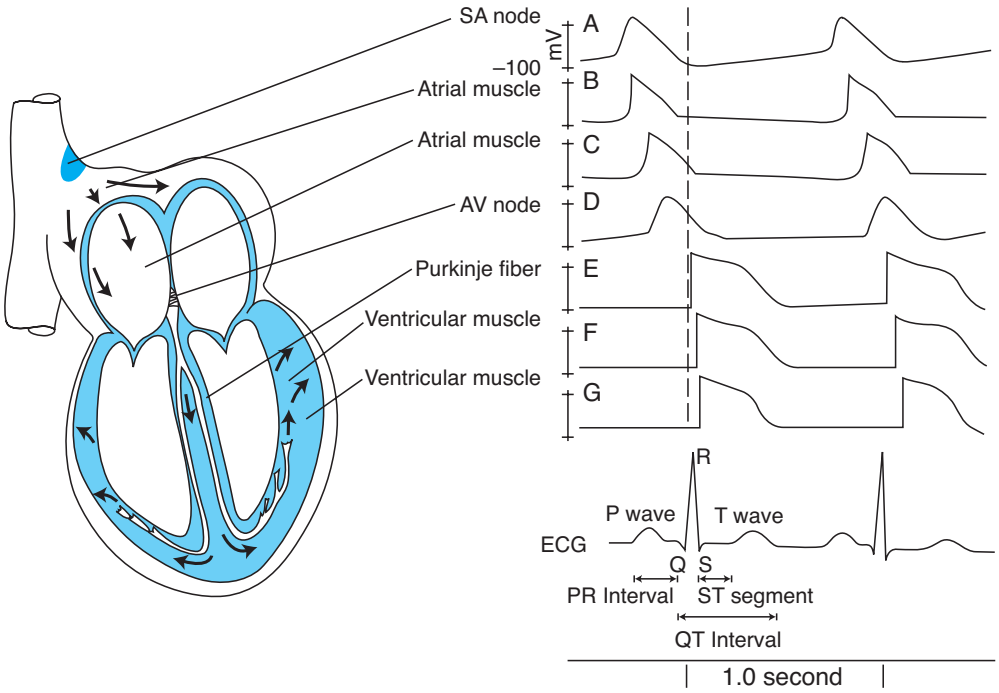

Figure 2–5. Electrical activity of the heart: single-cell voltage recordings (traces A to G) and lead II electrocardiogram.

atria are shown in Figure 2–5: one close to the SA node and one more distant from the SA node. Both cells have similarly shaped action potentials, but their temporal displacement reflects the fact that it takes some time for the impulse to spread over the atria. As shown in Figure 2–5, action potential conduction is greatly slowed as it passes through the AV node. This is because of the small size of the AV nodal cells and the slow rate of rise of their action potentials. Since the AV node delays the transfer of the cardiac excitation from the atria to the ventricles, atrial contraction can contribute to ventricular filling just before the ventricles contract. Note also that AV nodal cells have a faster spontaneous depolarization during the resting period than other cells of the heart except those of the SA node. The AV node is sometimes referred to as a latent pacemaker, and in many pathological situations it (rather than the SA node) controls the heart rhythm.

Because of sharply rising action potentials and other factors, such as large cell diameters, electrical conduction is extremely rapid in Purkinje fibers. This allows the Purkinje system to transfer the cardiac impulse to cells in many areas of the ventricle nearly in unison. Action potentials from muscle cells in two areas of the ventricle are shown in Figure 2–5. Because of the high conduction velocity in ventricular tissue, there is only a small discrepancy in their time of onset. Note in Figure 2–5 that the ventricular cells which are the last to depolarize have shorter duration action potentials and thus are the first to repolarize. The physiological importance of this unexpected behavior is not clear, but it does have an influence on the electrocardiograms that is discussed in Chapter 4.

Electrocardiograms

Fields of electrical potential caused by the electrical activity of the heart extend through the extracellular fluid of the body and can be measured with electrodes placed on the body surface. *Electrocardiography* provides a record of how the voltage between two points on the body surface changes with time as a result of the electrical events of the cardiac cycle. At any instant of the cardiac cycle, the electrocardiogram indicates the net electrical field that is the summation of many weak electrical fields being produced by voltage changes occurring on individual cardiac cells at that instant. When a large number of cells are simultaneously depolarizing or repolarizing, large voltages are observed on the electrocardiogram. Because the electrical impulse spreads through the heart tissue in a consistent pathway, the temporal pattern of voltage change recorded between two points on the body surface is also consistent and will repeat itself with each heart cycle.

The lower trace of Figure 2–5 represents a typical recording of the voltage changes normally measured between the right arm and the left leg as the heart goes through two cycles of electrical excitation; this record is called a lead II electrocardiogram and is discussed in detail in Chapter 4. The major features of an electrocardiogram are the *P wave,* the PR interval, the *QRS complex*, the QT interval, and the *T wave.* The P wave corresponds to atrial depolarization; the PR interval to the conduction time through the atria and AV node: the QRS complex, to ventricular depolarization; the QT interval to the duration of ventricular systole and the T wave, to ventricular repolarization.

Control of Heart Beating Rate

Normal rhythmic contractions of the heart occur because of spontaneous electrical pacemaker activity (automaticity) of cells in the SA node. The interval between heartbeats (and thus the heart rate) is determined by how long it takes the membranes of these pacemaker cells to spontaneously depolarize to the threshold level. The SA nodal cells fire at a spontaneous or *intrinsic rate* (≈100 beats per minute) in the absence of any outside influences. Outside influences *are* required, however, to increase or decrease automaticity from its intrinsic level.

The two most important outside influences on automaticity of SA nodal cells come from the autonomic nervous system. Fibers from both the sympathetic and parasympathetic divisions of the autonomic system terminate on cells in the SA node, and these fibers can modify the intrinsic heart rate. Activating the cardiac sympathetic nerves (increasing cardiac sympathetic *tone*) increases the heart rate. Increasing the cardiac parasympathetic tone slows the heart rate. As shown in Figure 2–6, both the parasympathetic and sympathetic nerves influence the heart rate by altering the course of spontaneous depolarization of the resting potential in SA pacemaker cells.

Cardiac parasympathetic fibers, which travel to the heart through the *vagus* nerves, release the transmitter substance *acetylcholine* on SA nodal cells. Acetylcholine increases the permeability of the resting membrane to K^+ and decreases the diastolic

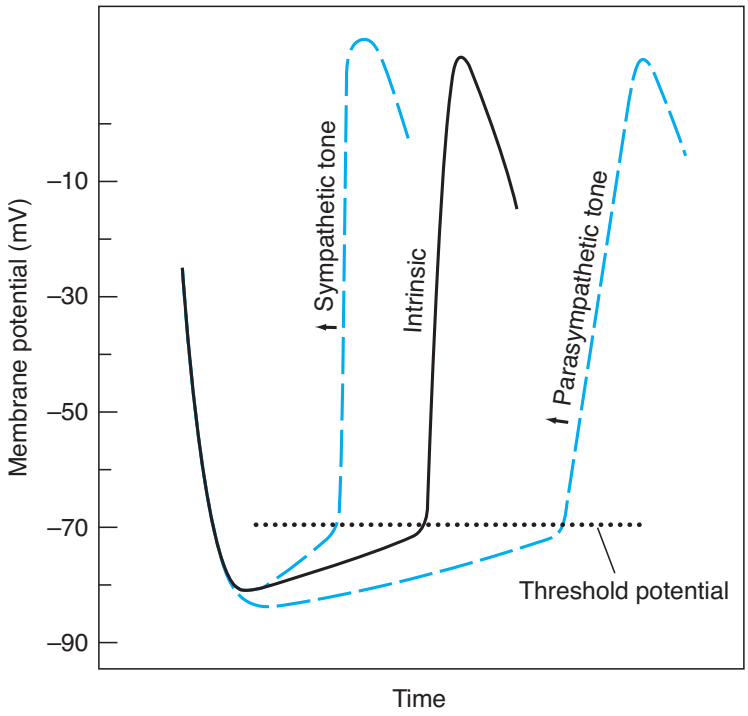

Figure 2–6. The effect of sympathetic and parasympathetic tone on pacemaker potential.

permeability to Na^+.[9] As indicated in Figure 2–6, these permeability changes have two effects on the resting potential of cardiac pacemaker cells: (1) they cause an initial hyperpolarization of the resting membrane potential by bringing it closer to the K^+ equilibrium potential and (2) they slow the rate of spontaneous depolarization of the resting membrane. Both of these effects increase the time between beats by prolonging the time required for the resting membrane to depolarize to the threshold level. Because there is normally some continuous *tonic* activity of cardiac parasympathetic nerves, the normal resting heart rate is approximately 70 beats per minute.

Sympathetic nerves release the transmitter substance *norepinephrine* on cardiac cells. In addition to other effects discussed later, norepinephrine acts on SA nodal cells to increase the inward currents carried by Na^+ (i_f) and by Ca^{2+} during the diastolic interval.[10] These changes will increase the heart rate by increasing the rate of diastolic depolarization as shown in Figure 2–6.

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[9] Acetylcholine interacts with muscarinic receptors on the SA nodal cell membrane that in turn are linked to inhibitory G proteins, G_i. The activation of G_i has two effects: (1) an increase in K^+ conductance resulting from an increased opening of the K_{Ach} channels and (2) a suppression of adenylate cyclase leading to a fall in intracellular cyclic adenosine monophosphate, which reduces the inward-going pacemaker current carried by Na^+ (i_f).

[10] Norepinephrine interacts with β_1-adrenergic receptors on the SA nodal cell membrane that in turn are linked to stimulatory G proteins, G_s. The activation of G_s increases adenylate cyclase, leading to an increase in intracellular cyclic AMP that increases the open-state probability of the pacemaker Na^+ current channel (i_f).

In addition to sympathetic and parasympathetic nerves, there are many (usually less important) factors that can alter the heart rate. These include a number of ions and circulating hormones, as well as physical influences such as temperature and atrial wall stretch. All act by somehow altering the time required for the resting membrane to depolarize to the threshold potential. An abnormally high concentration of Ca^{2+} in the extracellular fluid, for example, tends to decrease the heart rate by shifting the threshold potential. Factors that increase the heart rate are said to have a *positive chronotropic effect.* Those that decrease the heart rate have a *negative chronotropic effect.*

Besides their effect on the heart rate, autonomic fibers also influence the conduction velocity of action potentials through the heart. Increases in sympathetic activity increase conduction velocity (have a *positive dromotropic effect*), whereas increases in parasympathetic activity decrease conduction velocity (have a *negative dromotropic effect*). These effects are most notable at the AV node and can influence the duration of the PR interval.

MECHANICAL ACTIVITY OF THE HEART

Cardiac Muscle Contraction

Contraction of the cardiac muscle cell is initiated by the action potential signal acting on intracellular organelles to evoke tension generation and/or shortening of the cell. In this section, we describe (1) the subcellular processes involved in coupling the excitation to the contraction of the cell (EC coupling) and (2) the mechanical properties of cardiac cells.

Basic histological features of cardiac muscle cells are quite similar to those of skeletal muscle cells and include (1) an extensive myofibrillar structure made up of parallel interdigitating thick and thin filaments arranged in serial units called *sarcomeres*, which are responsible for the mechanical processes of shortening and tension development[11]; (2) a complex internal compartmentation of the cytoplasm by an intracellular membrane system called the *sarcoplasmic reticulum* (SR), which sequesters calcium during the diastolic interval with the help of the calcium-storage protein *calsequestrin*; (3) regularly spaced, extensive invaginations of the cell

[11] Proteins making up the thick and thin filaments are collectively referred to as "contractile proteins." The *thick filament* consists of a protein called *myosin*, which has a long straight tail with two globular heads each of which contains an ATP-binding site and an actin-binding site; light chains are loosely associated with the heads and their phosphorylation may regulate (or modulate) muscle function. The *thin filament* consists of several proteins including *actin*—two α-helical strands of polymerized subunits (g-actin) with sites that interact with the heads of myosin molecules to form cross-bridges with the thick filaments; *tropomyosin*—a regulatory fibrous-type protein lying in the groove of the actin α-helix, which prevents actin from interacting with myosin when the muscle is at rest; and *troponin*—a regulatory protein consisting of three subunits: *troponin C*, which binds calcium ions during activation and initiates the configurational changes in the regulatory proteins that expose the actin site for cross-bridge formation; *troponin T*, which anchors the troponin complex to tropomyosin; and *troponin I*, which participates in the inhibition of actin–myosin interaction at rest. In addition, the macromolecule, *titin*, extends from the Z disk to the M line and contributes significantly to the passive stiffness of cardiac muscle over its normal working range.

membrane (sarcolemma), called *T tubules*, which appear to be connected to parts of the SR ("junctional" SR) by dense strands ("feet") and which carry the action potential signal to the inner parts of the cell; and (4) a large number of mitochondria that provide the oxidative phosphorylation pathways needed to ensure a ready supply of adenosine triphosphate (ATP) to meet the high metabolic needs of the cardiac muscle. Students are encouraged to consult a histology textbook for specific cellular, morphological details.

Excitation–Contraction Coupling

Muscle action potentials trigger mechanical contraction through a process called *excitation–contraction coupling*, which is illustrated in Figure 2–7. The major event of excitation–contraction coupling is a dramatic rise in the intracellular free Ca^{2+} concentration. The "resting" intracellular free Ca^{2+} concentration is less than 0.1 μM. In contrast, during maximum activation of the contractile apparatus, the intracellular free Ca^{2+} concentration reaches nearly 100 μM. When the wave of depolarization passes over the muscle cell membrane and down the T tubules, Ca^{2+} is released from the SR into the intracellular fluid.

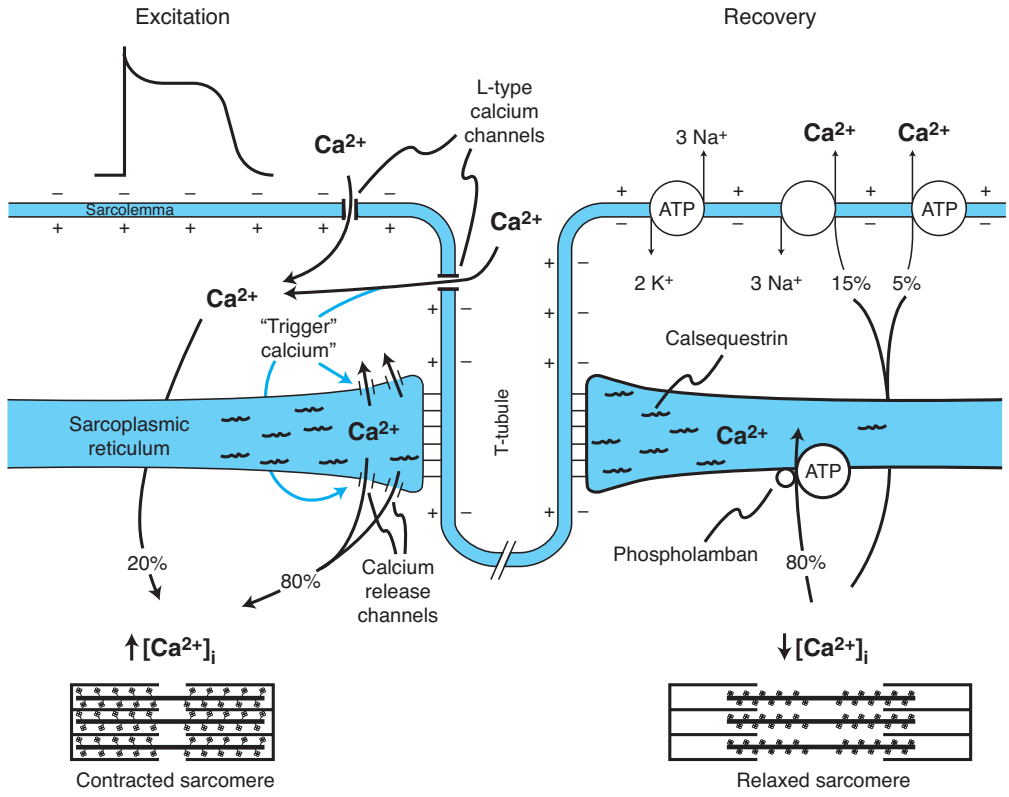

Figure 2–7. Excitation–contraction coupling and sarcomere shortening.

As indicated on the left side of Figure 2–7, the specific trigger for this release appears to be the entry of calcium into the cell via the L-type calcium channels and an increase in Ca^{2+} concentration in the region just under the sarcolemma on the surface of the cell and throughout the t-tubular system. Unlike the skeletal muscle, this highly localized increase in calcium is essential for triggering the massive release of calcium from the SR. This *calcium-induced calcium release* is a result of opening calcium-sensitive release channels on the SR.[12] Although the amount of Ca^{2+} that enters the cell during a single action potential is quite small compared with that released from the SR, it is essential not only for triggering the SR calcium release but also for maintaining adequate levels of Ca^{2+} in the intracellular stores over the long run.

When the intracellular Ca^{2+} level is high (>1.0 μM), links called *cross-bridges* form between two types of filaments found within the muscle. Sarcomere units, as depicted in the lower part of Figure 2–7, are joined end to end at Z lines to form *myofibrils*, which run the length of the muscle cell. During contraction, thick and thin filaments slide past one another to shorten each sarcomere and thus the muscle as a whole. The bridges form when the regularly spaced myosin heads from thick filaments attach to regularly spaced sites on the actin molecules in the thin filaments. Subsequent deformation of the bridges results in a pulling of the actin molecules toward the center of the sarcomere. This actin–myosin interaction requires energy from ATP. In resting muscles, the attachment of myosin to the actin sites is inhibited by troponin and tropomyosin. Calcium causes muscle contraction by interacting with troponin C to cause a configurational change that removes the inhibition of the actin sites on the thin filament. Because a single cross-bridge is a very short structure, gross muscle shortening requires that cross-bridges repetitively form, produce incremental movement between the myofilaments, detach, form again at a new actin site, and so on in a cyclic manner.

There are several processes that participate in the reduction of intracellular Ca^{2+} that terminates the contraction. These processes are illustrated on the right side of Figure 2–7. Approximately 80% of the calcium is actively taken back up into the SR by the action of Ca^{2+}-ATPase pumps located in the network part of the SR.[13] About 20% of the calcium is extruded from the cell into the extracellular fluid either via the Na^{+}–Ca^{2+} exchanger located in the sarcolemma[14] or via sarcolemmal Ca^{2+}-ATPase pumps.

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[12] These channels may be blocked by the plant alkaloid ryanodine and are activated by the methylxanthine caffeine. These agents are chemical tools used to assess properties of these SR channels.

[13] The action of these pumps is regulated by the protein phospholamban. When this protein is phosphorylated (eg, by the action of norepinephrine), the rate of Ca^{2+} resequestration is increased and the rate of relaxation is enhanced.

[14] The Na^{+}–Ca^{2+} exchanger is powered by the sodium gradient across the sarcolemma, which, in turn, is maintained by the Na^{+}/K^{+}-ATPase. This exchanger is electrogenic in that three Na^{+} ions move into the cell in exchange for each Ca^{2+} ion that moves out. This net inward movement of positive charge may contribute to the maintenance of the plateau phase of the action potential. The cardiac glycoside, digitalis, slows down the Na^{+}/K^{+} pump and thus reduces the sodium gradient, which, in turn, results in an increase in intracellular Ca^{2+}. This mechanism contributes to the positive effect of cardiac glycosides on the contractile force of the failing heart.

Excitation–contraction coupling in the cardiac muscle is different from that in the skeletal muscle in that it may be modulated; different intensities of actin–myosin interaction (contraction) can result from a single action potential trigger in the cardiac muscle. The mechanism for this is largely dependent on variations in the amount of Ca^{2+} reaching the myofilaments and therefore the number of cross-bridges activated during the twitch. This ability of the cardiac muscle to vary its contractile strength—that is, change its *contractility*—is extremely important to cardiac function, as discussed in a later section of this chapter.

The duration of the cardiac muscle cell contraction is approximately the same as that of its action potential. Therefore, the electrical refractory period of a cardiac muscle cell is not over until the mechanical response is completed. As a consequence, heart muscle cells cannot be activated rapidly enough to cause a fused (tetanic) state of prolonged contraction. This is fortunate because intermittent contraction and relaxation are essential for the heart's pumping action.

Cardiac Muscle Cell Mechanics

The cross-bridge interaction that occurs after a muscle is activated to contract gives the muscle the potential to develop force and/or shorten. Whether it does one, the other, or some combination of the two depends primarily on what is allowed to happen by the external constraints placed on the muscle during the contraction. For example, activating a muscle whose ends are held rigidly causes it to develop tension, but it cannot shorten. This is called an *isometric* ("fixed length") contraction. The force that a muscle produces during an isometric contraction indicates its maximum ability to develop tension. At the other extreme, activating an unrestrained muscle causes it to shorten without force development because it has nothing to develop force against. This type of contraction is called an *isotonic* ("fixed tension") contraction. Under such conditions, a muscle shortens with its maximum possible velocity (called V_{max}), which is determined by the maximum possible rate of cross-bridge cycling. Adding load to the muscle decreases the velocity and extent of its shortening. Thus, the course of a muscle contraction depends on both the inherent capabilities of the muscle and the external constraints placed on the muscle during contraction. Muscle cells in the ventricular wall operate under different constraints during different phases of each cardiac cycle. To understand ventricular function, the manner in which the cardiac muscle behaves when constrained in several different ways must first be examined.

Isometric Contractions: Length–Tension Relationships

The influence of muscle length on the behavior of the cardiac muscle during isometric contraction is illustrated in Figure 2–8. The top panel shows the experimental arrangement for measuring muscle force at rest and during contraction at three different lengths. The middle panel shows time records of muscle tensions recorded at each of the three lengths in response to an external stimulus, and the bottom panel shows a graph of the resting and peak tension results plotted against muscle length.

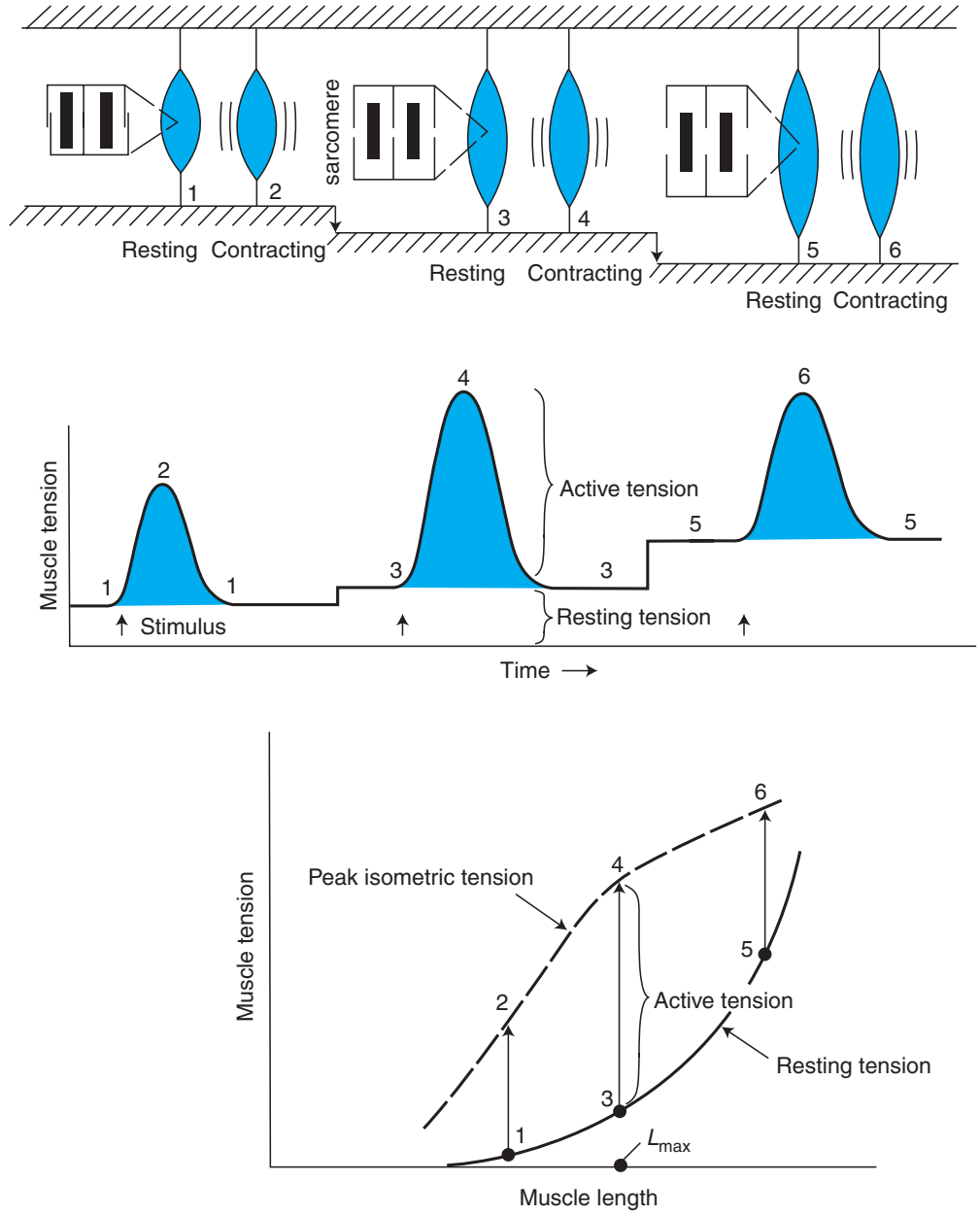

Figure 2–8. Isometric contractions and the effect of muscle length on resting tension and active tension development.

The first important fact illustrated in Figure 2–8 is that force is required to stretch a resting muscle to different lengths. This force is called the *resting tension.* The lower curve in the graph in Figure 2–8 shows the resting tension measured at different muscle lengths and is referred to as the *resting length–tension curve.* When a muscle is stimulated to contract while its length is held constant, it develops an additional component of tension called *active* or *developed tension.* The *total tension* exerted by a muscle during contraction is the sum of the active and resting tensions.

The second important fact illustrated in Figure 2–8 is that the active tension developed by the cardiac muscle during the course of an isometric contraction depends very much on the muscle length at which the contraction occurs. Active tension development is maximum at some intermediate length referred to as L_{max}. Little active tension is developed at very short or very long muscle lengths. Normally, the cardiac muscle operates at lengths well below L_{max} so that increasing muscle length increases the tension developed during an isometric contraction.

There are three separate mechanisms that have been proposed to explain the relationship between muscle length and developed tension. The first mechanism to be identified suggests that this relationship depends on the *extent of overlap* of the thick and thin filaments in the sarcomere at rest. Histological studies indicate that the changes in the resting length of the whole muscle are associated with proportional changes in the individual sarcomeres. Peak tension development occurs at sarcomere lengths of 2.2 to 2.3 μm. At sarcomere lengths shorter than approximately 2.0 μm, the opposing thin filaments may overlap or buckle and thus interfere with active tension development as shown at the top of Figure 2–8. At long sarcomere lengths, overlap may be insufficient for optimal cross-bridge formation.

The second (and perhaps more important) mechanism is based on a length-dependent change in *sensitivity* of the myofilaments to calcium. At short lengths only a fraction of the potential cross-bridges are apparently activated by a given increase in intracellular calcium. At longer lengths, more of the cross-bridges become activated, leading to an increase in active tension development. This change in calcium sensitivity occurs immediately after a change in length with no time delay. The "sensor" responsible for the length-dependent activation of the cardiac muscle seems to reside with the troponin C molecule, but how it happens is not fully understood.

The third mechanism rests on the observation that within several minutes after increasing the resting length of the cardiac muscle, there is an increase in the *amount* of calcium that is released with excitation, which is coupled to a further increase in force development. It is thought that stretch-sensitive ion channels in the cell membranes may be responsible for this delayed response.

To what extent each of these mechanisms is contributing to the length dependency of cardiac contractile force at any instant is neither clear nor very important in this discussion. The important point is that the dependence of active tension development on muscle length is a fundamental property of the cardiac muscle that has extremely powerful effects on heart function.

Isotonic and Afterloaded Contractions

During what is termed *isotonic* ("fixed load") contraction, a muscle shortens against a constant load. A muscle contracts isotonically when lifting a fixed weight such as the 1-g load shown in Figure 2–9. Such a 1-g weight placed on a resting muscle will result in some specific resting muscle length, which is determined by the muscle's resting length–tension curve. If the muscle were to contract isometrically at this length, it would be capable of generating a certain amount of tension, for example, 4.5 g as indicated by the dashed line in the graph in Figure 2–9. A contractile tension

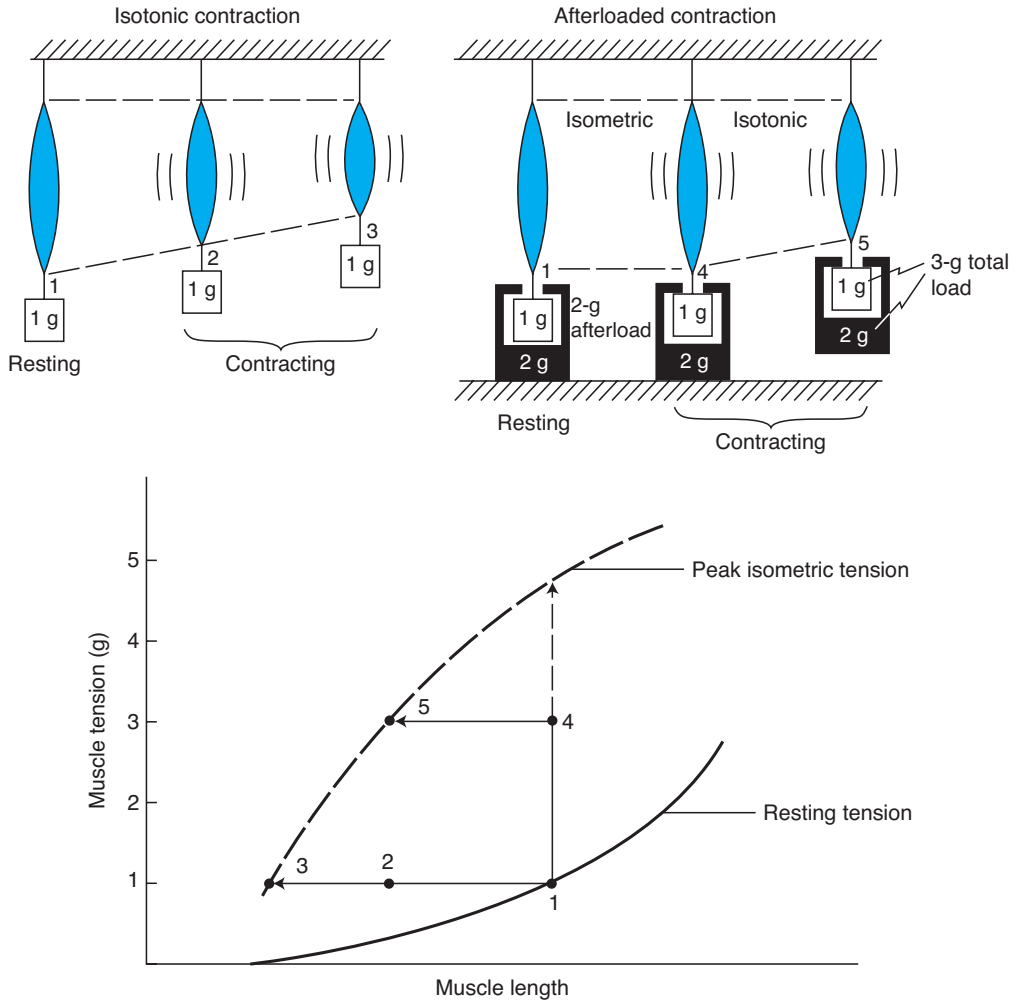

Figure 2–9. Relationship of isotonic and afterloaded contractions to the cardiac muscle length–tension diagram.

of 4.5 g obviously cannot be generated while lifting a 1-g weight. When a muscle has contractile potential in excess of the tension it is actually developing, it shortens. Thus in an isotonic contraction, muscle length decreases at constant tension, as illustrated by the horizontal arrow from point 1 to point 3 in Figure 2–9. As the muscle shortens, however, its contractile potential inherently decreases, as indicated by the downward slope of the peak isometric tension curve in Figure 2–9. There exists some short length at which the muscle is capable of generating only 1 g of tension, and when this length is reached, shortening must cease.[15] Thus, the curve

[15] In reality, muscle shortening requires some time and the duration of a muscle twitch contraction is limited because intracellular Ca^{2+} levels are elevated only briefly following the initiation of a membrane action potential. For this and possibly other reasons, isotonic shortening may not actually proceed quite as far as the isometric tension development curve on the length–tension diagram suggests is possible. Because this complication does not alter the general correspondence between a muscle's isometric and isotonic performance, we choose to ignore it.

on the cardiac muscle length–tension diagram that indicates how much isometric tension a muscle can develop at various lengths also establishes the limit on how far muscle shortening can proceed with different loads.

Figure 2–9 also shows a complex type of muscle contraction called an *afterloaded isotonic contraction*, in which the load on the muscle at rest, the *preload*, and the load on the muscle during contraction, the *total load*, are different. In the example of Figure 2–9, the preload is equal to 1 g, and because an additional 2-g weight (the *afterload*) is engaged during contraction, the total load equals 3 g.

Because preload determines the resting muscle length, both isotonic contractions shown in Figure 2–9 begin from the same length. Because of the different loading arrangement, however, the afterloaded muscle must increase its total tension to 3 g before it can shorten. This initial tension will be developed isometrically and can be represented as going from point 1 to point 4 on the length–tension diagram. Once the muscle generates enough tension to equal the total load, its tension output is fixed at 3 g and it will now shorten isotonically because its contractile potential still exceeds its tension output. This isotonic shortening is represented as a horizontal movement on the length–tension diagram along the line from point 4 to point 5. As in any isotonic contraction, shortening must cease when the muscle's tension-producing potential is decreased sufficiently by the length change to be equal to the load on the muscle. Note that the afterloaded muscle shortens less than the non-afterloaded muscle, even though both muscles began contracting at the same initial length. The factors that affect the extent of cardiac muscle shortening during an afterloaded contraction are of special interest to us, because, as we shall see, stroke volume is determined by how far the cardiac muscle shortens under these conditions.

Cardiac Muscle Contractility

A number of factors in addition to initial muscle length can affect the tension-generating potential of the cardiac muscle. *Any intervention that increases the peak isometric tension that a muscle can develop at a* fixed length *is said to increase cardiac muscle contractility.* Such an agent is said to have a *positive inotropic effect* on the heart.

The most important physiological regulator of cardiac muscle contractility is norepinephrine. When norepinephrine is released on cardiac muscle cells from sympathetic nerves, it has not only the chronotropic effect on the heart rate discussed earlier but also a pronounced, positive inotropic effect that causes cardiac muscle cells to contract more rapidly and forcefully.

The positive effect of norepinephrine on the isometric tension-generating potential is illustrated in Figure 2–10A. When norepinephrine is present in the solution bathing the cardiac muscle, the muscle will, *at every length*, develop more isometric tension when stimulated than it would in the absence of norepinephrine. In short, norepinephrine raises the peak isometric tension curve on the cardiac muscle

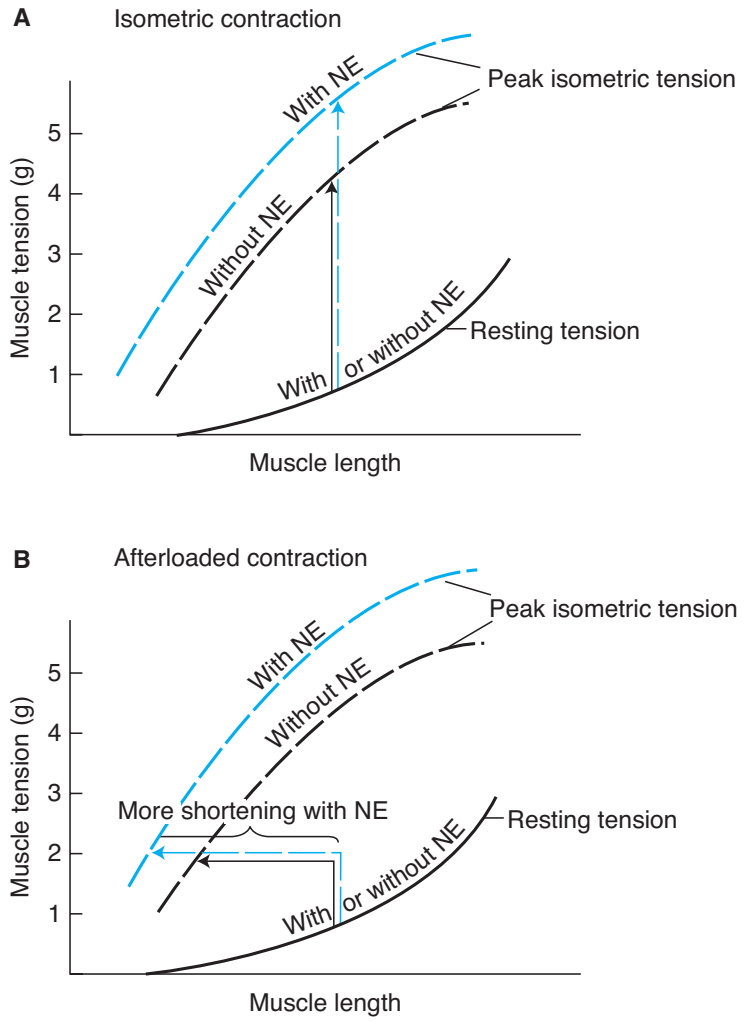

Figure 2–10. The effect of norepinephrine (NE) on isometric (**A**) and afterloaded (**B**) contractions of the cardiac muscle.

length–tension graph. Norepinephrine is said to increase cardiac muscle contractility because it enhances the forcefulness of muscle contraction *even when length is constant.* Changes in contractility and initial length can occur simultaneously, but by definition a change in *contractility* must involve a shift from one peak isometric length–tension curve to another.

Figure 2–10B shows how raising the peak isometric length–tension curve with norepinephrine increases the amount of shortening in afterloaded contractions of the cardiac muscle. With preload and total load constant, more shortening occurs in the presence of norepinephrine than in its absence. This is because when contractility is increased, the tension-generating potential is equal to the total load at a shorter muscle length. Note that norepinephrine has no effect on the resting length–tension relationship of the cardiac muscle. Thus, norepinephrine causes increased shortening

by changing the final but not the initial muscle length associated with afterloaded contractions.

The cellular mechanism of the norepinephrine effect on contractility is mediated by its interaction with a β_1-adrenergic receptor. The signaling pathway involves an activation of the G_s protein–cAMP–protein kinase A, which then phosphorylates the Ca^{2+} channel, increasing the inward calcium current during the plateau of the action potential. This increase in calcium influx not only contributes to the magnitude of the rise in intracellular Ca^{2+} for a given beat but also loads the internal calcium stores, which allows more to be released during subsequent depolarizations. This increase in free Ca^{2+} during activation allows more cross-bridges to be formed and greater tension to be developed.

Because norepinephrine also causes phosphorylation of the regulatory protein, *phospholamban*, on the sarcoplasmic reticular Ca^{2+}-ATPase pump, the rate of calcium retrapping into the SR is enhanced and the rate of relaxation is increased. This is called a *positive lusitropic effect.* In addition to more rapid calcium retrapping by the SR, there is a norepinephrine-induced decrease in the action potential duration. This effect is achieved by a potassium channel alteration, occurring in response to the elevated intracellular $[Ca^{2+}]$ that increases potassium permeability, terminates the plateau phase of the action potential, and contributes to the early relaxation. Such shortening of the systolic interval is helpful in the presence of elevated heart rates that might otherwise significantly compromise diastolic filling time.

Enhanced parasympathetic activity has been shown to have a small negative inotropic effect on the heart. In the atria, where this effect is most pronounced, the negative inotropic effect is thought to be due to a shortening of the action potential and a decrease in the amount of Ca^{2+} that enters the cell during the action potential.

Changes in the heart rate also influence cardiac contractility. Recall that a small amount of extracellular Ca^{2+} enters the cell during the plateau phase of each action potential. As the heart rate increases, more Ca^{2+} enters the cells per minute. There is a buildup of intracellular Ca^{2+} and a greater amount of Ca^{2+} is released into the sarcoplasm with each action potential. Thus, a sudden increase in beating rate is followed by a progressive increase in contractile force to a higher plateau. This behavior is called the *staircase phenomenon* (or treppe). Changes in contractility produced by this intrinsic mechanism are sometimes referred to as *homeometric autoregulation.* The importance of such rate-dependent modulation of contractility in normal ventricular function is not clear at present.

RELATING CARDIAC MUSCLE CELL MECHANICS TO VENTRICULAR FUNCTION

Certain geometric factors dictate how the length–tension relationships of cardiac muscle fibers in the ventricular wall determine the volume and pressure relationships of the ventricular chamber. The actual relationships are complex because the shape of the ventricle is complex. The ventricle is often modeled as either a cylinder or a sphere, although its actual shape lies somewhere between the

two. Because cardiac muscle cells are oriented circumferentially in the ventricular wall, either model can be used to illustrate three important functional points:

1. An increase in ventricular volume causes an increase in ventricular circumference and therefore an increase in the length of the individual cardiac muscle cells (and vice versa). Thus, the extent of diastolic filling of the ventricle determines the "preload."
2. At any given ventricular volume, an increase in the tension of individual cardiac muscle cells in the wall causes an increase in intraventricular pressure (and vice versa).
3. As ventricular volume decreases (ie, as the ventricular radius decreases), a lesser total (collective) force is required by the muscle cells in the ventricular walls to produce any given intraventricular pressure (and vice versa).

The last point is a reflection of the *law of Laplace* that states the physical relationship that must exist between total wall tension and internal pressure in any hollow vessel with circular containing walls. Regardless of whether the ventricle is envisioned as a hollow cylinder or a hollow sphere, the law of Laplace says that the *total* wall tension (T) depends on both intraventricular pressure (P) and its internal radius (r) as $T = P \times r$.

One implication of the law of Laplace is that the muscle cells in the ventricular wall have a somewhat easier job of producing internal pressure at the end of ejection (when the radius is small) than at the beginning of ejection (when the radius is large). More importantly, the law of Laplace has important clinical relevance in pathological situations such as "cardiac dilation" and "cardiac hypertrophy." These are discussed in detail in Chapter 11.

The importance of all these relationships will become more apparent in the subsequent chapter as we consider how cardiac muscle cell behavior determines how the heart functions as a pump.

KEY CONCEPTS

Cardiac myocyte membrane potentials are a result of the relative permeability of the membrane to various ions and their concentration differences across the membrane.

Action potentials of cardiac myocytes are a result of changes in the membrane's permeability to various ions.

Action potentials of cardiac myocytes have long plateau phases that generate long refractory periods and preclude summated or tetanic contractions.

Action potentials are spontaneously generated by pacemaker cells in the SA node and are conducted from cell to cell via gap junctions throughout the entire heart.

5. *The rate of spontaneous diastolic depolarization of the SA nodal cells (and thus the heart rate) is modulated by the autonomic nervous system.*

6. *Excitation of the cardiac myocyte initiates contraction by increasing the cytosolic calcium level that activates the contractile apparatus.*

7. *Mechanical response of the myocyte depends on preload (determined by the initial resting length), afterload (determined by the tension that needs to be developed), and contractility (the degree of activation of the contractile apparatus dependent on the amount of calcium released on activation).*

8. *The cardiac myocyte length–tension relationships are correlated with changes in volume and pressure in the intact ventricle.*

STUDY QUESTIONS

2–1. *Small changes in extracellular potassium ion concentrations have major effects on cell membrane potentials.*
   a. *What will happen to the potassium equilibrium potential of cardiac muscle cells when interstitial $[K^+]$ (ie, $[K^+]_o$) is elevated?*
   b. *What effect will this have on the cells' resting membrane potential?*
   c. *What effect will this have on the cells' excitability?*

2–2. *Cardiac survival during cardiac transplantation is improved by perfusing donor hearts with cardioplegic solutions containing approximately 20 mM KCl. Why is this high potassium concentration helpful?*

2–3. *There are several classes of drugs that are useful for treating various cardiac arrhythmias. Identify the primary effects of each of the following classes of drugs on cardiac myocyte characteristics:*
   a. *What are the effects of sodium channel blockers on the PR interval of the ECG? On the duration of the QRS complex?*
   b. *What are the effects of calcium channel blockers on the rate of firing of SA nodal cells? On the rate of conduction of the action potential through the AV node? On myocardial contractility?*
   c. *What are the effects of potassium channel blockers on action potential duration? On refractory periods?*

2–4. *Very high sympathetic neural activity to the heart can lead to tetanic concentration of the cardiac muscle. True or false?*

2–5. *An increase in which of the following (with the others held constant) will result in an increase in the amount of active shortening of a cardiac muscle cell?*
   a. *preload*
   b. *afterload*
   c. *contractility*

2–6. What happens when an intervention promotes early activation of the "delayed rectifier" K^+ channel (I_K) in a cardiac muscle?

a. The resting potential is increased (hyperpolarized).
b. The action potential duration is decreased.
c. The action potential amplitude is decreased.
d. The action potential conduction velocity is increased.
e. The absolute refractory period is prolonged.

2–7. Action potential conduction velocity in cardiac muscle tissue is influenced by all of the following except

a. cell diameter
b. resting membrane potential
c. extracellular potassium concentration
d. rate of rise (phase 0) of the action potential
e. duration of the plateau phase (phase 2) of the action potential

2–8. The primary route of removal of $[Ca^{2+}]$ from the sarcoplasm during relaxation of a cardiac muscle cell is by

a. active transport out of the cell
b. passive exchange with extracellular sodium
c. active transport into the sarcoplasmic reticulum
d. trapping of calcium by troponin in the myofilaments
e. passive movement out of the cell via L-type calcium channels

The Heart Pump

3

OBJECTIVES

The student knows the basic electrical and mechanical events of the cardiac cycle:

- *Correlates the electrocardiographic events with the mechanical events during the cardiac cycle.*
- *Lists the major distinct phases of the cardiac cycle as delineated by valve opening and closure.*
- *Describes the pressure and volume changes in the atria, the ventricles, and the aorta during each phase of the cardiac cycle.*
- *Defines and states normal values for (1) ventricular end-diastolic volume, end-systolic volume, stroke volume, diastolic pressure, and peak systolic pressure, and (2) aortic diastolic pressure, systolic pressure, and pulse pressure.*
- *States similarities and differences between mechanical events in the left and right heart pump.*
- *States the origin of the heart sounds.*
- *Diagrams the relationship between left ventricular pressure and volume during the cardiac cycle.*

The student understands the factors that determine cardiac output:

- *Defines cardiac output and cardiac index.*
- *States the relationship between cardiac output, the heart rate, and stroke volume.*
- *Identifies the major determinants of stroke volume.*
  - *States the Frank–Starling law of the heart.*
  - *Predicts the effect of altered ventricular preload on stroke volume and the ventricular pressure–volume relationship.*
  - *Predicts the effect of altered ventricular afterload on stroke volume and the ventricular pressure–volume relationship.*
  - *Predicts the effect of altered ventricular contractility (inotropic state) on stroke volume and the ventricular pressure–volume relationship.*
- *Draws a family of cardiac function curves describing the relationship between filling pressure and cardiac output under various levels of sympathetic tone.*
- *The student identifies the factors that influence myocardial oxygen consumption.*

The repetitive, synchronized contraction and relaxation of the cardiac muscle cells provide the forces necessary to pump blood through the systemic and pulmonary circulations. In this chapter, we describe (1) basic mechanical features of this cardiac pump, (2) factors that influence and/or regulate the cardiac output, and (3) sources of energy and energy costs required for myocardial activity.

CARDIAC CYCLE

Left Pump

The mechanical function of the heart can be described by the pressure, volume, and flow changes that occur within it during one cardiac cycle. A cardiac cycle is defined as one complete sequence of contraction and relaxation. The normal mechanical events of a cycle of the left heart pump are correlated in Figure 3–1. This important figure summarizes a great deal of information and should be studied carefully.

Ventricular Diastole

The *diastolic phase*[1] of the cardiac cycle begins with the opening of the atrioventricular (AV) valves. As shown in Figure 3–1, the mitral valve opens when left ventricular pressure falls below left atrial pressure and the period of ventricle filling begins. Blood that had previously accumulated in the atrium behind the closed mitral valve empties rapidly into the ventricle, and this causes an initial drop in atrial pressure. Later, the pressures in both chambers slowly rise together as the atrium and ventricle continue passively filling in unison with blood returning to the heart through the veins.

Atrial contraction is initiated near the end of ventricular diastole by the depolarization of the atrial muscle cells, which causes the P wave of the electrocardiogram. As the atrial muscle cells develop tension and shorten, atrial pressure rises and an additional amount of blood is forced into the ventricle. At normal heart rates, atrial contraction is not essential for adequate ventricular filling. This is evident in Figure 3–1 from the fact that the ventricle has nearly reached its maximum or *end-diastolic volume* before atrial contraction begins. Atrial contraction plays an increasingly significant role in ventricular filling as heart rate increases because the time interval between beats for passive filling becomes progressively shorter with increased heart rate. Note that throughout diastole, atrial and ventricular pressures are nearly identical. This is because a normal open mitral valve has very little resistance to flow and thus only a very small atrial–ventricular pressure difference is necessary to produce ventricular filling.

Ventricular Systole

Ventricular systole begins when the action potential breaks through the AV node and sweeps over the ventricular muscle—an event heralded by the QRS complex of the electrocardiogram. Contraction of the ventricular muscle cells causes intraventricular pressure to rise above that in the atrium, which causes abrupt closure of the AV valve.

Pressure in the left ventricle continues to rise sharply as the ventricular contraction intensifies. When the left ventricular pressure exceeds that in the aorta, the aortic valve opens. The period between mitral valve closure and aortic valve opening is referred to as the *isovolumetric contraction phase* because during this interval the

[1] The atria and ventricles do not beat simultaneously. Usually, and unless otherwise noted, systole and diastole denote phases of ventricular operation.

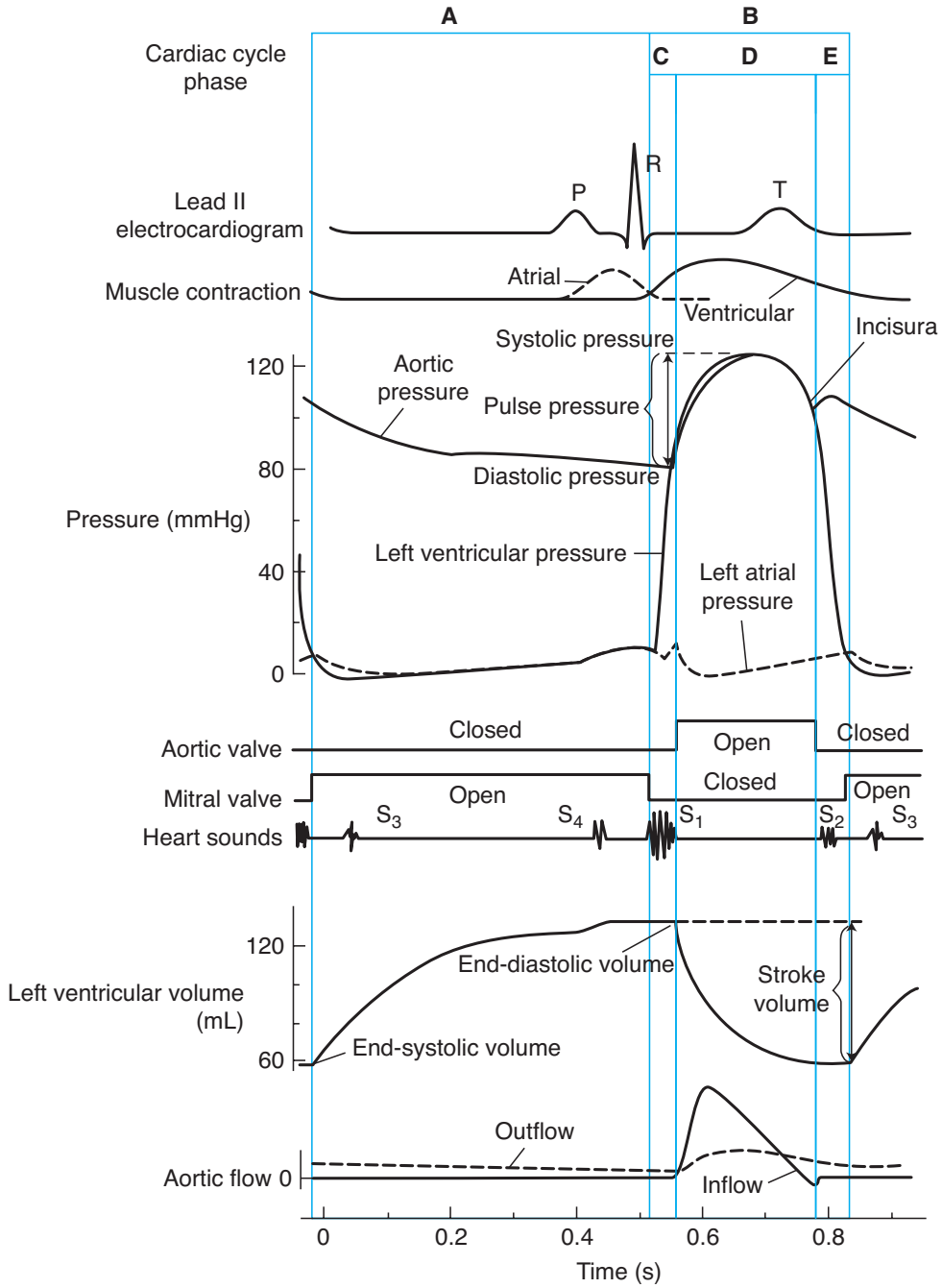

Figure 3–1. Cardiac cycle—left heart pump. Cardiac cycle phases: **A**, diastole; **B**, systole that is divided into three periods; **C**, isovolumetric contraction; **D**, ejection; and **E**, isovolumetric relaxation.

ventricle is a closed chamber with a fixed volume. Ventricular ejection begins with the opening of the aortic valve. In early ejection, blood enters the aorta rapidly and causes the pressure there to rise. Pressure builds simultaneously in both the ventricle and the aorta as the ventricular muscle cells continue to contract in early systole. This interval is often called the *rapid ejection period.*

Left ventricular and aortic pressures ultimately reach a maximum called *peak systolic pressure*. At this point the strength of ventricular muscle contraction begins to wane. Muscle shortening and ejection continue, but at a reduced rate. Aortic pressure begins to fall because blood is leaving the aorta and large arteries faster than blood is entering from the left ventricle. Throughout ejection, very small pressure differences exist between the left ventricle and the aorta because the aortic valve orifice is so large that it presents very little resistance to flow.

Eventually, the strength of the ventricular contraction diminishes to the point where intraventricular pressure falls below aortic pressure. This causes abrupt closure of the aortic valve. A dip, called the *incisura* or *dicrotic notch*, appears in the aortic pressure trace because a small volume of aortic blood must flow backward to fill the space behind the aortic valve leaflets as they close. After aortic valve closure, intraventricular pressure falls rapidly as the ventricular muscle relaxes. For a brief interval, called the *isovolumetric relaxation phase*, the mitral valve is also closed. Ultimately, intraventricular pressure falls below atrial pressure, the AV valve opens, and a new cardiac cycle begins.

Note that atrial pressure progressively rises during ventricular systole because blood continues to return to the heart and fill the atrium. The elevated atrial pressure at the end of systole promotes rapid ventricular filling once the AV valve opens to begin the next heart cycle.

The ventricle has reached its minimum or *end-systolic volume* at the time of aortic valve closure. The amount of blood ejected from the ventricle during a single beat, the *stroke volume*, is equal to ventricular end-diastolic volume minus ventricular end-systolic volume.

The aorta distends or balloons out during systole because more blood enters the aorta than leaves it. During diastole, the arterial pressure is maintained by the elastic recoil of walls of the aorta and other large arteries. Nonetheless, aortic pressure gradually falls during diastole as the aorta supplies blood to the systemic vascular beds. The lowest aortic pressure, reached at the end of diastole, is called *diastolic pressure*. The difference between diastolic and peak systolic pressures in the aorta is called the arterial *pulse pressure*. Typical values for systolic and diastolic pressures in the aorta are 120 and 80 mmHg, respectively.

At a normal resting heart rate of about 70 beats per minute, the heart spends approximately two-thirds of the cardiac cycle in diastole and one-third in systole. When increases in the heart rate occur, both diastolic and systolic intervals become shorter. Action potential durations are shortened and conduction velocity is increased. Contraction and relaxation rates are also enhanced. This shortening of the systolic interval tends to blunt the potential adverse effects of increases in the heart rate on diastolic filling time.

Right Pump

Because the entire heart is served by a single electrical excitation system, similar mechanical events occur essentially simultaneously in both the left and right sides of the heart. Both ventricles have synchronous systolic and

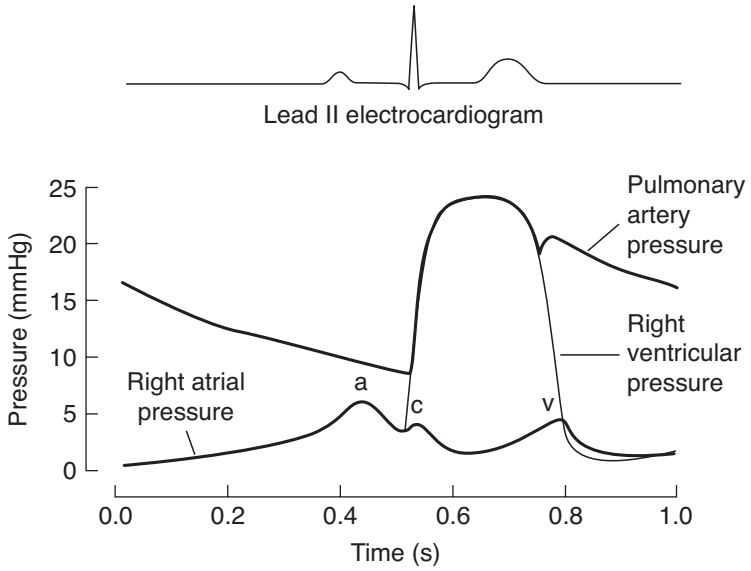

Figure 3–2. Cardiac cycle—right heart pump.

diastolic periods, and the valves of the right and left sides of the heart normally open and close nearly in unison. Because the two sides of the heart are arranged in series in the circulation, they must pump the same amount of blood and therefore must have identical stroke volumes.

The major difference between the right and left pumps is in the magnitude of the peak systolic pressure. The pressures developed by the right side of the heart as shown in Figure 3–2 are considerably lower than those for the left side of the heart (Figure 3–1). This is because the lungs provide considerably less resistance to blood flow than that offered collectively by the systemic organs. Therefore, less arterial pressure is required to drive the cardiac output through the lungs than through the systemic organs. Typical pulmonary artery systolic and diastolic pressures are 24 and 8 mmHg, respectively.

The pressure pulsations that occur in the right atrium are transmitted in retrograde fashion to the large veins near the heart. These pulsations, shown on the atrial pressure trace in Figure 3–2, can be visualized in the neck over the jugular veins in a recumbent individual. They are collectively referred to as the *jugular venous pulse* and can provide clinically useful information about the heart. Atrial contraction produces the first pressure peak called the *a* wave. The *c* wave, which follows shortly thereafter, coincides with the onset of ventricular systole and is caused by an initial bulging of the tricuspid valve into the right atrium. Right atrial pressure falls after the *c* wave because of atrial relaxation and a downward displacement of the tricuspid valve during ventricular emptying. Right atrial pressure then begins to increase toward a third peak, the *v* wave, as the central veins and right atrium fill behind a closed tricuspid valve with blood returning to the heart from the peripheral organs. With the opening of the tricuspid valve at the conclusion of ventricular systole, right atrial pressure again falls as blood moves into the relaxed right ventricle.

Shortly afterward, right atrial pressure begins to rise once more toward the next *a* wave as returning blood fills the central veins, the right atrium, and right ventricle together during diastole.

Heart Sounds

A phonocardiographic record of the heart sounds, which occur in the cardiac cycle, is included in Figure 3–1. These sounds are normally heard by *auscultation* with a stethoscope placed on the chest. The first heart sound, S_1, occurs at the beginning of systole because of the abrupt closure of the AV valves, which produces vibrations of the cardiac structures and the blood in the ventricular chambers. S_1 can be heard most clearly by placing the stethoscope over the apex of the heart. Note that this sound occurs immediately after the QRS complex of the electrocardiogram.

The second heart sound, S_2, arises from the closure of the aortic and pulmonic valves at the beginning of the period of isovolumetric relaxation. This sound is heard at near the end of the T wave in the electrocardiogram. The pulmonic valve usually closes slightly after the aortic valve. Because this discrepancy is enhanced during the inspiratory phase of the respiratory cycle, inspiration causes what is referred to as the *physiological splitting of the second heart sound.* The discrepancy in valve closure during inspiration may range from 30 to 60 ms. One of the factors that lead to prolonged ejection of the right ventricle during inspiration is that the decreased intrathoracic pressure that accompanies inspiration transiently enhances venous return and diastolic filling of the right side of the heart. For reasons that are detailed later in this chapter, this extra filling volume will be ejected but a little extra time is required to do so.

The third and fourth heart sounds, shown in Figure 3–1, are not normally present. When they are present, however, they, along with S_1 and S_2, produce what are called *gallop rhythms* (resembling the sound of a galloping horse). When present, the third heart sound occurs shortly after S_2 during the period of rapid passive ventricular filling and, in combination with heart sounds S_1 and S_2, produces what is called *ventricular gallop rhythm.* Although S_3 may sometimes be detected in normal children, it is heard more commonly in patients with left ventricular failure. The fourth heart sound, which occasionally is heard shortly before S_1, is associated with atrial contraction and rapid active filling of the ventricle. Thus, the combination of S_1, S_2, and S_4 sounds produces what is called an *atrial gallop rhythm.* The presence of S_4 often indicates an increased ventricular diastolic stiffness, which can occur with several cardiac disease states.

Cardiac Cycle Pressure–Volume and Length–Tension Relationships

Intraventricular pressure and volume are intimately linked to the tension and length of the cardiac muscle cells in the ventricular wall through purely geometric and physical laws. Figures 3–3A and 3–3B show the correspondence between a ventricular pressure–volume loop and a cardiac muscle length–tension

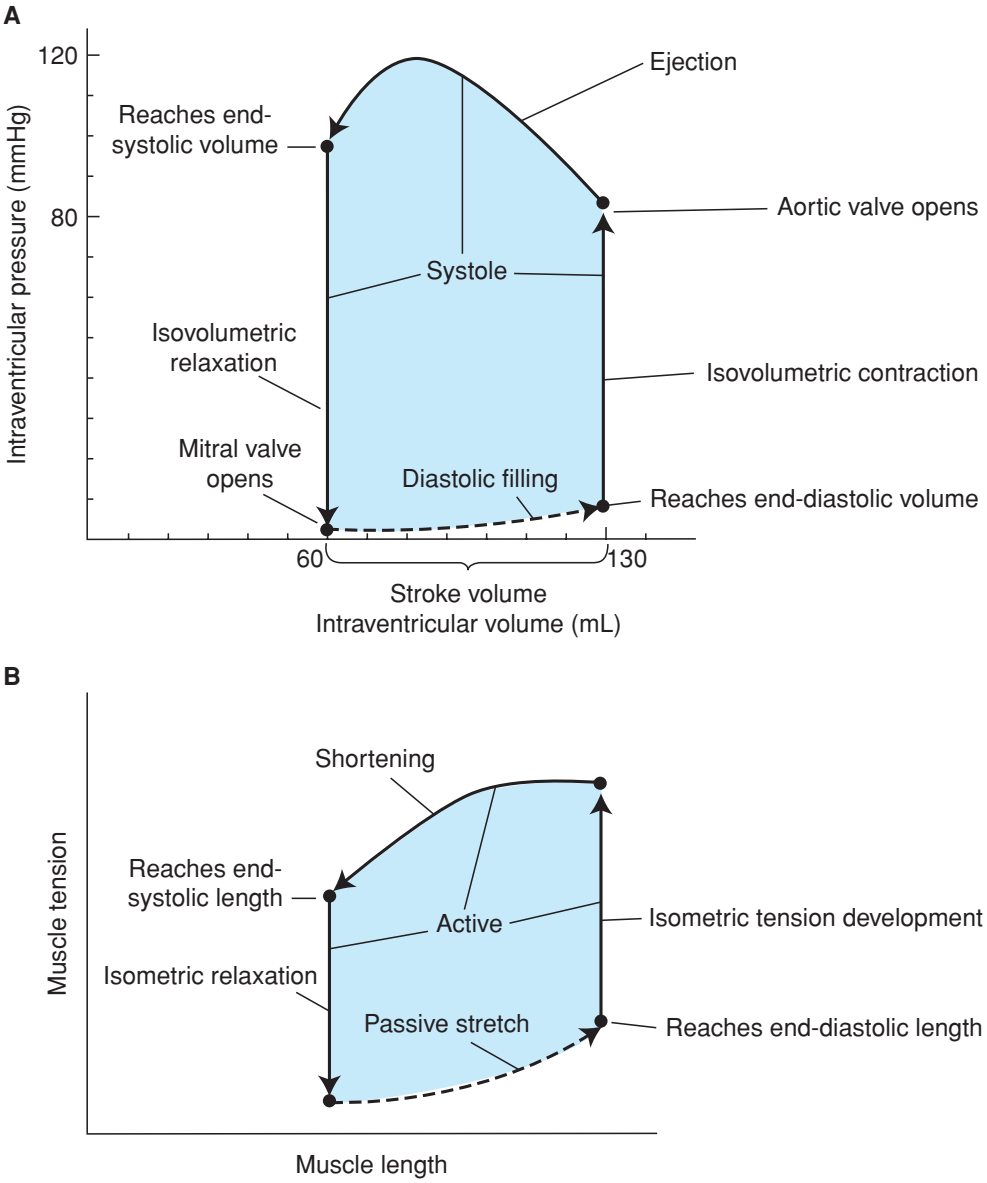

Figure 3–3. (**A**) Left ventricular pressure–volume cycle and (**B**) corresponding cardiac muscle length–tension cycle.

loop during one cardiac cycle. This fact makes it clear that cardiac muscle length–tension behavior is the underlying basis for ventricular function. Note that in Figure 3–3, each major phase of the ventricular cardiac cycle has a corresponding phase of cardiac muscle length and tension change. During diastolic ventricular filling, for example, the progressive increase in ventricular pressure causes a corresponding increase in muscle tension, which passively stretches the resting cardiac muscle to greater lengths along its resting length–tension curve. End-diastolic ventricular pressure is referred to as *ventricular preload* because it sets the end-diastolic ventricular

volume and therefore the resting length of the cardiac muscle fibers at the end of diastole.

At the onset of systole, the ventricular muscle cells develop tension isometrically and intraventricular pressure rises accordingly. After the intraventricular pressure rises sufficiently to open the outlet valve, ventricular ejection begins as a consequence of ventricular muscle shortening. Systemic arterial pressure is often referred to as the *ventricular afterload* because it determines the tension that must be developed by cardiac muscle fibers before they can shorten.[2]

During cardiac ejection, the cardiac muscle is simultaneously generating active tension *and* shortening (ie, an afterloaded isotonic contraction). The magnitude of ventricular volume change during ejection (ie, stroke volume) is determined simply by how far ventricular muscle cells are able to shorten during contraction. This, as already discussed, depends on the length–tension relationship of the cardiac muscle cells and the load against which they are shortening. Once shortening ceases and the output valve closes, the cardiac muscle cells relax isometrically. Ventricular wall tension and intraventricular pressure fall in unison during isovolumetric relaxation.

DETERMINANTS OF CARDIAC OUTPUT

Cardiac output (liters of blood pumped by *each* of the ventricles per minute) is an extremely important cardiovascular variable that is continuously adjusted so that the cardiovascular system operates to meet the body's moment-to-moment transport needs. In going from rest to strenuous exercise, for example, the cardiac output of an average person will increase from approximately 5.5 to perhaps 15 L/min. The extra cardiac output provides the exercising skeletal muscles with the additional nutritional supply needed to sustain an increased metabolic rate. To understand the cardiovascular system's response not only to exercise but to all other physiological or pathological demands placed on it, we must understand what determines and therefore controls cardiac output.

As stated in Chapter 1, cardiac output is the product of the heart rate and stroke volume (CO = HR × SV). Therefore, all changes in cardiac output must be produced by changes in the heart rate and/or stroke volume.

Factors influencing the heart rate do so by altering the characteristics of the diastolic depolarization of the pacemaker cells as discussed in Chapter 2 (Figure 2–6). Recall that variations in activity of the sympathetic and parasympathetic nerves leading to cells of the sinoatrial (SA) node constitute the most important regulators of the heart rate. Increases in sympathetic activity increase the heart rate, whereas increases in parasympathetic activity decrease the heart rate. These neural inputs have

[2] This designation is somewhat misleading for at least two reasons. First, arterial pressure is more analogous to ventricular total load than to ventricular afterload. Second, because of the law of Laplace, the actual wall tension that needs to be generated to attain a given intraventricular pressure also depends on the ventricular radius (tension = pressure × radius). Thus, the larger the end-diastolic volume, the greater the tension required to develop sufficient intraventricular pressure to open the outflow valve. We choose, however, to ignore these complications at this time.

immediate effects (within one beat) and therefore can cause very rapid adjustments in cardiac output.

INFLUENCES ON STROKE VOLUME

Effect of Changes in Ventricular Preload: Frank–Starling Law of the Heart

The volume of blood that the heart ejects with each beat can vary significantly. One of the most important factors responsible for these variations in stroke volume is the extent of cardiac filling during diastole. This concept is introduced in Chapter 1 (Figure 1–7) and is known as Starling's law of the heart. To review (and to reemphasize its importance), this law states that, with other factors equal, *stroke volume increases as cardiac filling increases*. As shown below, this phenomenon is based on the intrinsic mechanical properties of myocardial muscle.

Figure 3–4A illustrates how increasing muscle preload will increase the extent of shortening during a subsequent contraction with a fixed total load. Recall from

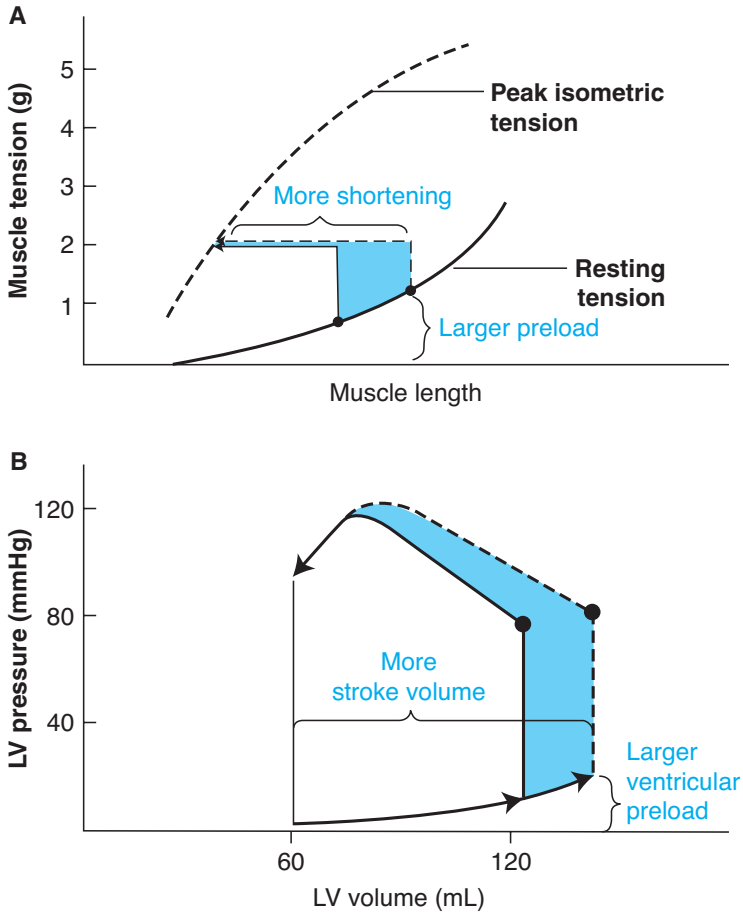

Figure 3–4. The effect of increased in preload on (**A**) cardiac muscle shortening during afterloaded contractions and (**B**) ventricular stroke volume.

the nature of the resting length–tension relationship that an increased preload is necessarily accompanied by increased initial muscle fiber length. As described in Chapter 2, when a muscle starts from a greater length, it has more distance to shorten before it reaches the length at which its tension-generating capability is no longer greater than the load on it. The same behavior is exhibited by cardiac muscle cells when they are actually operating in the ventricular wall. Increases in ventricular preload increase both end-diastolic volume and stroke volume almost equally, as illustrated in Figure 3–4B.

The precise relationship between cardiac preload (cardiac filling pressure) and end-diastolic volume has especially important physiological and clinical consequences. Although the actual relationship is somewhat curvilinear, especially at very high filling pressures, it is nearly linear over the normal operating range of the heart. The low slope of this relationship indicates the incredible distensibility of the normal ventricle during diastole (eg, a change in filling pressure of only 1 mmHg normally will change end-diastolic volume by about 25 mL). As discussed in Chapter 11, one major form of cardiac failure is called "diastolic failure" and is characterized by a decidedly abnormal relationship between cardiac filling pressure and end-diastolic volume.

It should be noted in Figure 3–4A that increasing preload increases initial muscle length without significantly changing the final length to which the muscle shortens against a constant total load. Thus, increasing ventricular filling pressure increases stroke volume primarily by increasing end-diastolic volume. As shown in Figure 3–4B, this is not accompanied by a significant alteration in end-systolic volume.

Effect of Changes in Ventricular Afterload

As stated previously, systemic arterial pressure is usually taken to be the left ventricular "afterload". A slight complication is that arterial pressure varies between a diastolic value and a systolic value during each cardiac ejection. Usually, however, we are interested in *mean* ventricular afterload and take this to be *mean* arterial pressure.

Figure 3–5A shows how increased afterload, at constant preload, has a negative effect on cardiac muscle shortening. Again, this is simply a consequence of the fact that muscle cannot shorten beyond the length at which its peak isometric tension-generating potential equals the total load on it. Thus, shortening must stop at a greater muscle length when afterload is increased.

Normally, mean ventricular afterload is quite constant, because mean arterial pressure is held within tight limits by the cardiovascular control mechanisms described later. In many pathological situations such as hypertension and aortic valve obstruction, however, ventricular function is adversely influenced by abnormally high ventricular afterload. When this occurs, stroke volume may be decreased as shown by the changes in the pressure–volume loop in Figure 3–5B. Under these conditions, note that stroke volume is decreased because end-systolic volume is increased.

The relationship between end-systolic pressure and end-systolic volume obtained at a constant preload but different afterloads is indicated by the dotted

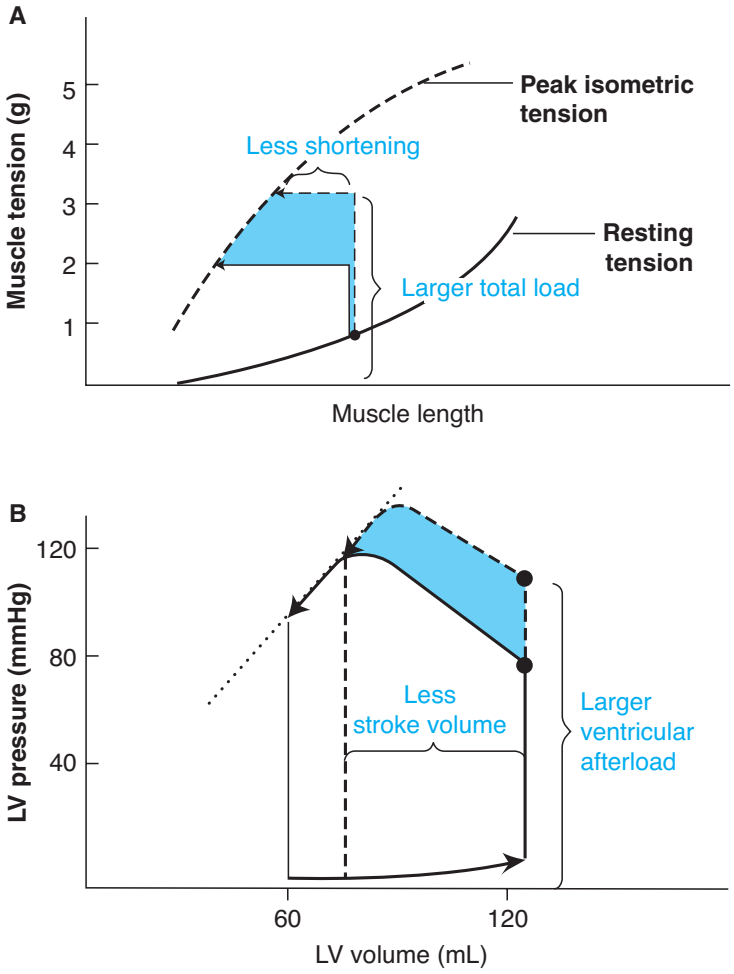

Figure 3–5. The effect of increased in afterload on (**A**) cardiac muscle shortening during afterloaded contractions and (**B**) ventricular stroke volume.

line in Figure 3–5B. In a normally functioning heart, the effect of changes in afterload on end-systolic volume (and therefore stroke volume) is quite small (about 0.5 mL/mmHg). However, in what is termed "systolic cardiac failure," the effect of afterload on end-systolic volume is greatly enhanced. Thus, the slope of this line can be used clinically to assess the systolic function of the heart as discussed further in Chapter 11.

Effect of Changes in Cardiac Muscle Contractility

Recall that activation of the sympathetic nervous system results in release of norepinephrine from cardiac sympathetic nerves, which increases contractility of the individual cardiac muscle cells. This results in an upward shift of the peak isometric length–tension curve. As shown in Figure 3–6A, such a shift will result in an increase in the shortening of a muscle contracting with constant preload and total load. Thus, as shown in Figure 3–6B, the norepinephrine released by sympathetic nerve stimulation will increase ventricular stroke volume by decreasing the end-systolic volume, without directly influencing the end-diastolic volume.

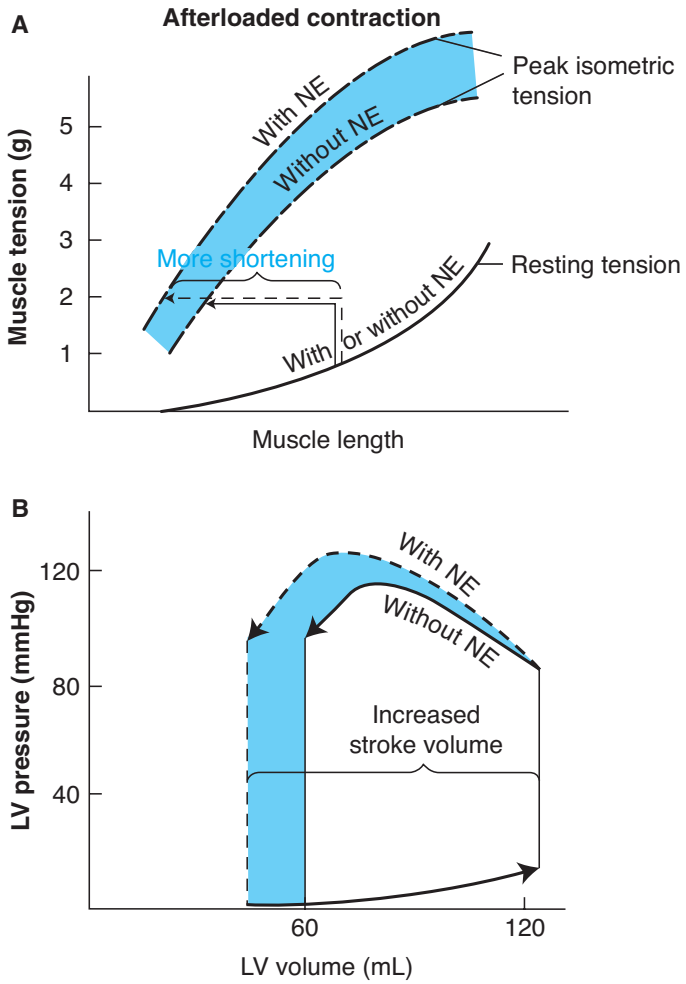

Figure 3–6. The effect of norepinephrine (NE) on (**A**) cardiac muscle shortening during afterloaded contractions and (**B**) ventricular stroke volume.

In addition to this change in the extent of myocyte shortening, an increase in contractility will also cause an increase in the *rates* of myocyte tension development and of shortening. This will result in an increase in the *rate* of isovolumetric pressure development and the *rate* of ejection during systole.

SUMMARY OF DETERMINANTS OF CARDIAC OUTPUT

The major influences on cardiac output are summarized in Figure 3–7. The heart rate is controlled by chronotropic influences on the spontaneous electrical activity of SA nodal cells. Cardiac parasympathetic nerves have a negative chronotropic effect, and sympathetic nerves have a positive chronotropic effect on the SA node. Stroke volume is controlled by influences on the contractile performance of the ventricular cardiac muscle—in particular, its degree of shortening in the afterloaded situation. The three distinct influences on stroke volume are contractility, preload, and afterload. Increased cardiac sympathetic nerve activity tends to increase stroke

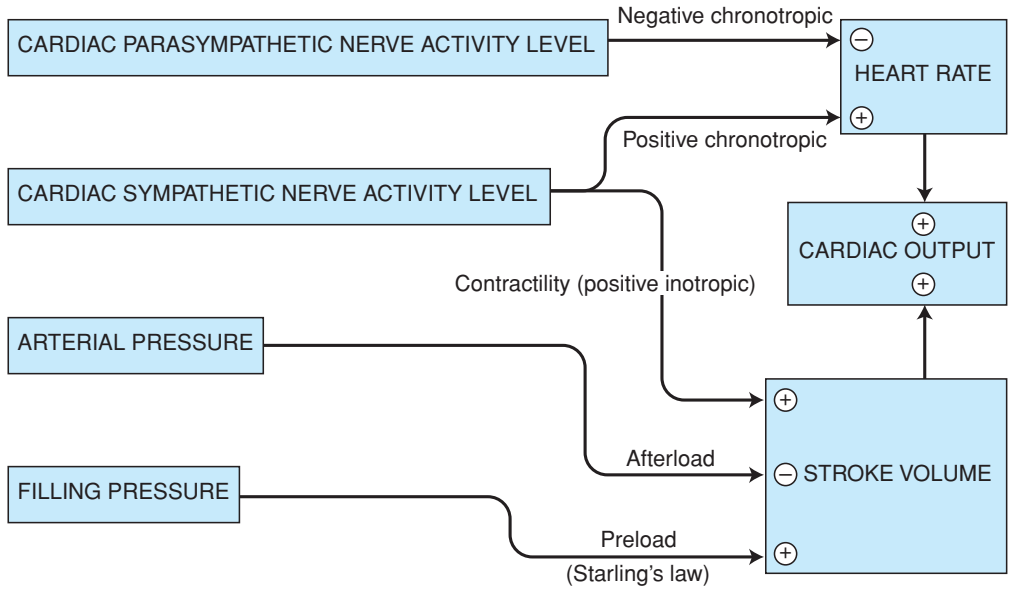

Figure 3–7. Influences on cardiac output.

volume by increasing the contractility of the cardiac muscle. Increased arterial pressure tends to decrease stroke volume by increasing the afterload on cardiac muscle fibers. Increased ventricular filling pressure increases end-diastolic volume, which tends to increase stroke volume through Starling's law.

It is important to recognize at this point that both the heart rate and stroke volume are subject to more than one influence. Thus, the fact that increased contractility tends to increase stroke volume should not be taken to mean that, in the intact cardiovascular system, stroke volume is always high when contractility is high. Following blood loss caused by hemorrhage, for example, stroke volume may be low in spite of a high level of sympathetic nerve activity and increased contractility. The only other possible causes for low stroke volume are high arterial pressure and low cardiac filling pressure. Because arterial pressure is normal or low following hemorrhage, the low stroke volume associated with severe blood loss must be (and is) the result of low cardiac filling pressure.

Cardiac Function Curves

One very useful way to summarize the influences on cardiac function and the interactions between them is by cardiac function curves such as those shown in Figure 3–8.

In this case, cardiac output is treated as the dependent variable and is plotted on the vertical axis in Figure 3–8, while cardiac filling pressure is plotted on the horizontal axis.[3]

[3] Other variables may appear on the axes of these curves. The vertical axis may be designated as stroke volume or stroke work, whereas the horizontal axis may be designated as central venous pressure, right (or left) atrial

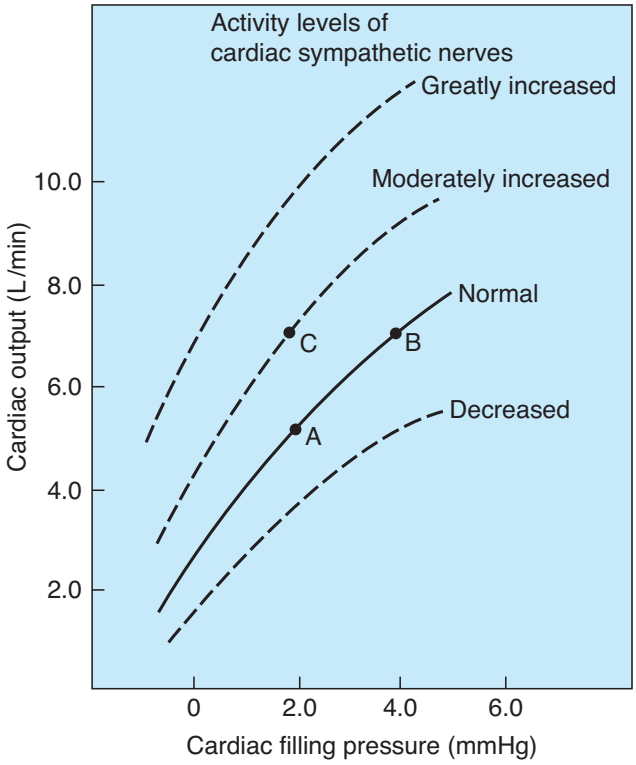

Figure 3–8. Influence of cardiac sympathetic nerves on cardiac function curves.

Different curves are used to show the influence of alterations in cardiac sympathetic nerve activity. Thus, Figure 3–8 shows how the cardiac filling pressure and the activity level of cardiac sympathetic nerves interact to determine cardiac output. When cardiac filling pressure is 2 mmHg and the activity of cardiac sympathetic nerves is normal, the heart will operate at point A and will have a cardiac output of 5 L/min. Each single curve in Figure 3–8 shows how cardiac output would be changed by changes in cardiac filling pressure if cardiac sympathetic nerve activity were held at a fixed level. For example, if cardiac sympathetic nerve activity remained normal, increasing cardiac filling pressure from 2 to 4 mmHg would cause the heart to shift its operation from point A to point B on the cardiac function diagram. In this case, cardiac output would increase from 5 to 7 L/min solely as a result of the increased filling pressure (Starling's law). If, on the other hand, cardiac filling pressure were fixed at 2 mmHg while the activity of cardiac sympathetic nerves was moderately increased from normal, the heart would change from operating at point A to operating at point C. Cardiac output would again increase from 5 to 7 L/min. In this instance, however, cardiac output does not increase through the length-dependent mechanism because cardiac filling pressure did not change. Cardiac output increases at constant filling pressure with an increase in cardiac sympathetic activity for two

pressure, or ventricular end-diastolic volume (or pressure). In all cases, the curves describe the relationship between preload and cardiac function.

reasons. First, increased cardiac sympathetic nerve activity increases the heart rate. Second, but just as importantly, increased sympathetic nerve activity increases stroke volume by increasing cardiac contractility.[4]

Cardiac function graphs thus consolidate knowledge of many mechanisms of cardiac control and are most helpful in describing how the heart interacts with other elements in the cardiovascular system. Furthermore, these graphs reemphasize the important point that a change in cardiac filling pressure alone will have a very potent effect on cardiac output at any level of sympathetic activity.

Summary of Sympathetic Neural Influences on Cardiac Function

Because of its importance in overall control of cardiac function, it is appropriate at this point to summarize the major direct effects that the sympathetic nervous system exerts on electrical and mechanical properties of the cardiac muscle and thus on cardiac pumping ability. These effects are initiated by norepinephrine interaction with β_1-adrenergic receptors on cardiac muscle cells, resulting in a cascade of events involving the G_s activation of adenylate cyclase, formation of cAMP, and activation of protein kinase A with subsequent phosphorylation of many molecules that play key regulatory roles in intracellular processes. These cellular events combine to evoke improvements in pumping capabilities of the heart. These improvements include the following:

1. An increase in the heart rate (positive chronotropic effect) by activating the inward-going sodium i_f current in SA nodal cells;
2. A decrease in cardiac action potential duration by early activation of the delayed i_K current in cardiac myocytes, which minimizes the detrimental effect of high heart rates on diastolic filling time;
3. An increase in the rate of action potential conduction, particularly evident in the AV node (positive dromotropic effect) by altering conductivity of gap junctions;
4. An increase in cardiac contractility (positive inotropic effect) by activating the $i_{Ca^{2+}}$ current and increasing Ca^{2+} release from the sarcoplasmic reticulum, which increases the contractile ability of the cardiac muscle at any given preload; and
5. An increase in the rate of cardiac relaxation (positive lusitropic effect) by increasing Ca^{2+} uptake by the sarcoplasmic reticulum, which also helps minimize the detrimental effect of high heart rates on diastolic filling time.[5,6]

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[4] Decreases in cardiac afterload can also shift the position of the curve upward by allowing more shortening to occur at a given preload. This effect is normally not important because afterload is usually kept constant.

[5] Most catecholamine effects on the heart are a result of increases in sympathetic neural activity. Although circulating catecholamines of adrenal origin can potentially evoke similar effects, their concentrations are normally so low that their contributions are negligible.

[6] All the effects of catecholamines on cardiac muscle can be blocked by specific drugs called β-adrenergic receptor blockers. The drugs may be useful in the treatment of coronary artery disease to thwart increased metabolic demands placed on the heart by activity of sympathetic nerves.

As shown in subsequent chapters, increases in sympathetic activity can have *indirect* influences on cardiac function that are a consequence of sympathetic-induced alterations in arteriolar and venous tone (ie, alterations in afterload and preload, respectively).

CARDIAC ENERGETICS

Energy Sources

In order for the heart to operate properly, it must have an adequate supply of chemical energy in the form of adenosine triphosphate (ATP). The relatively low ATP content of cardiac tissue combined with a relatively high rate of ATP hydrolysis at rest suggests that the myocardial ATP pool will completely turn over every 10 seconds.

The substrates from which ATP is formed by the heart depend partly on which substrates are in the greatest supply at a particular instant. For example, after a high-carbohydrate meal, the heart will take up and metabolize glucose and pyruvate, whereas between meals, the heart can switch to metabolize free fatty acids, triglycerides, and ketones. Unlike the skeletal muscle, the cardiac muscle can utilize lactate as an energy source, which is beneficial during strenuous exercise when skeletal muscles are producing lactate. In addition, the choice of substrate depends on the metabolic phenotype of the cardiac muscle. Fetal and newborn hearts derive most of their ATP from metabolism of glucose and lactate, whereas, within a few weeks of birth, a switch toward fatty acid oxidation occurs so that, by adulthood, 60 to 90% of cardiac ATP is derived from fatty acids. A switch back toward the fetal phenotype accompanies severe heart failure. Glycogen is stored in myocardial cells as a reserve energy supply and can be mobilized via the glycolytic pathway to provide extra substrate under conditions of increased sympathetic stimulation.

The end product of metabolism of glycogen, glucose, fatty acids, triglycerides, pyruvate, and lactate is acetyl CoA, which enters the citric acid (Krebs) cycle in the mitochondria, where, by a process of oxidative phosphorylation, the molecules are degraded to carbon dioxide and water and the energy is converted to ATP. (The student is encouraged to consult a biochemistry textbook for further details of these important metabolic pathways.)

The anaerobic sources of energy in the heart (eg, glycolysis and creatine phosphate) are not adequate to sustain the metabolic demand for more than a few minutes. The heavy (nearly total) reliance of the heart on the aerobic pathways for ATP production is evident by (1) the high number of mitochondria and (2) the presence of high concentrations of the oxygen-binding protein myoglobin within the cardiac muscle cells. Myoglobin can release its oxygen to the mitochondrial cytochrome oxidase system when intracellular oxygen levels are lowered. In these regards, the cardiac muscle resembles "red" skeletal muscle that is adapted for sustained contractile activity as opposed to "white" skeletal muscle that is adapted for high-intensity, short-duration contractile activity.

Determinants of Myocardial Oxygen Consumption

In many pathological situations, such as obstructive coronary artery disease, the oxygen requirements of the myocardial tissue may exceed the capacity of coronary blood flow to deliver oxygen to the heart muscle. It is important to understand what factors determine the energy costs and, therefore, the myocardial oxygen consumption rate because reduction of the oxygen demand may be of significant clinical benefit to the patient.

Because the heart derives its energy almost entirely from aerobic metabolism, myocardial oxygen consumption is directly related to myocardial energy use (ie, ATP splitting). Understanding the determinants of myocardial oxygen consumption essentially means understanding the myocardial processes that require ATP.

The *basal metabolism* of the heart tissue normally accounts for about 25% of myocardial ATP use and therefore myocardial oxygen consumption in a resting individual. Because basal metabolism represents the energy consumed in cellular processes other than contraction (eg, energy-dependent ion pumping), little can be done to reduce it.

The processes associated with *muscle contraction* account for about 75% of myocardial energy use. Primarily, this reflects ATP splitting associated with cross-bridge cycling during the isovolumetric contraction and ejection phases of the cardiac cycle. Some ATP is also used for Ca^{2+} sequestration at the termination of each contraction.

The energy expended during the isovolumetric contraction phase of the cardiac cycle accounts for the largest portion (~50%) of total myocardial oxygen consumption despite the fact that the heart does no external work during this period. The energy needed for isovolumetric contraction depends heavily on the intraventricular pressure that must develop during this time, that is, on the cardiac afterload. *Cardiac afterload* then is a major determinant of myocardial oxygen consumption. Reductions in cardiac afterload can produce clinically significant reductions in myocardial energy requirements and therefore myocardial oxygen consumption.

Energy utilization during isovolumetric contraction is actually more directly related to isometric *wall tension* development than to intraventricular pressure development. Recall that wall tension is related to intraventricular pressure *and* ventricular radius through the law of Laplace ($T = P \times r$). Consequently, reductions in cardiac preload (ie, end-diastolic volume and radius) will also tend to reduce the energy required for isovolumetric contraction.

It is during the ejection phase of the cardiac cycle when the heart actually performs external work and the energy the heart expends during ejection depends on how much *external work* it is doing. In a fluid system, work (force × distance) is equal to pressure (force/distance^2) × volume (distance^3). The external physical work done by the left ventricle in one beat, called *stroke work*, is equal to the area enclosed by the left ventricular pressure–volume loop (see Figure 3–3). Stroke work is increased either by an increase in stroke volume (increased "volume" work) or by an increase in afterload (increased "pressure" work). In terms of ATP utilization and oxygen consumption, increases in the pressure work of the heart are more costly than increases in volume work. Thus, reductions in afterload are especially helpful in reducing the myocardial oxygen requirements for doing external work.

Changes in *myocardial contractility* can have important consequences on the oxygen requirement for basal metabolism, isovolumic wall tension generation, and external work. Heart muscle cells use more energy in rapidly developing a given tension and shortening by a given amount than in doing the same thing more slowly. Also, with increased contractility, more energy is expended in active Ca^{2+} transport. The net result of these influences is often referred to as the "energy wasting" effect of increased contractility.

The *heart rate* is one of the most important determinants of myocardial oxygen consumption because the energy costs per minute must equal the energy cost per beat times the number of beats per minute. In general, it has been found that it is more efficient (less oxygen is required) to achieve a given cardiac output with the low heart rate and high stroke volume than with the high heart rate and low stroke volume. This again appears to be related to the relatively high energy cost of the pressure development phase of the cardiac cycle. The less pressure (wall tension) developed and the less often pressure development occurs, the better.

KEY CONCEPTS

1. *Effective cardiac pumping of blood requires coordinated filling of the chambers, excitation and contraction of the cardiac muscle cells, pressure generation within the chambers, opening and closing of cardiac valves, and one-way movement of blood through the chambers into the aorta or pulmonary artery.*
2. *Except for lower ejection pressures, events of the right side of the heart are identical to those of the left side.*
3. *Heart sounds associated with valve movements and detected on auscultation can be used to identify the beginnings of diastolic and systolic phases of the cardiac cycle.*
4. *The events of a single ventricular cardiac cycle can be displayed as records of electrical, mechanical, pressure, sound or flow changes against time or as a record of volume against pressure.*
5. *Cardiac output is defined as the amount of blood pumped by either of the ventricles per minute and is determined by the product of the heart rate and stroke volume.*
6. *Stroke volume can be altered by changes in ventricular preload (filling), ventricular afterload (arterial pressure), and/or cardiac muscle contractility.*
7. *A cardiac function curve describes the relationship between ventricular filling and cardiac output and can be shifted up (left) or down (right) by changes in sympathetic activity to the heart or by changes in cardiac muscle contractility.*
8. *Energy for cardiac muscle contraction is derived primarily from aerobic metabolic pathways such that cardiac work is tightly related to myocardial oxygen consumption.*

STUDY QUESTIONS

3–1. If pulmonary artery pressure is 24/8 mmHg (systolic/diastolic), what are the respective systolic and diastolic pressures of the right ventricle?

3–2. Because pulmonary artery pressure is so much lower than aortic pressure, the right ventricle has a larger stroke volume than the left ventricle. True or false?

3–3. Which of the following interventions will increase cardiac stroke volume?

a. increased ventricular filling pressure
b. decreased arterial pressure
c. increased activity of cardiac sympathetic nerves
d. increased circulating catecholamine levels

3–4. In which direction will cardiac output change if central venous pressure is lowered while cardiac sympathetic tone is increased?

3–5. Increases in sympathetic neural activity to the heart will result in an increase in stroke volume by causing a decrease in end-systolic volume for any given end-diastolic volume. True or false?

3–6. Four of these conditions exist during the same phase of the cardiac cycle and one does not. Which one is the odd one?

a. The mitral valve is open.
b. The QRS wave of the ECG is occurring.
c. The "v" wave of the jugular venous pulse has just occurred.
d. Ventricular volume is rapidly increasing.
e. Aortic pressure is falling.

3–7. With all other factors equal, myocardial oxygen demands will be increased to the greatest extent by which of the following?

a. increases in the heart rate
b. increases in coronary flow
c. increases in end-diastolic volume
d. decreases in arterial pressure
e. decreases in cardiac contractility

3–8. Sympathetic neural activation of the heart will decrease which of the following?

a. heart rate
b. PR interval on the ECG
c. metabolic demands
d. coronary flow rate
e. cardiac contractility

Measurements of Cardiac Function

4

OBJECTIVES

The student recognizes several techniques of assessing cardiac output and cardiac contractility:

- *Given data, calculates cardiac output using the Fick principle.*
- *Defines ejection fraction and identifies visualization methods used to determine it.*
- *Describes the end-systolic pressure–volume relationship.*

The student understands the physiological basis of the electrocardiogram:

- *States the relationship between electrical events of cardiac excitation and the P, QRS, and T waves, the PR and QT intervals, and the ST segment of the electrocardiogram.*
- *States Einthoven's basic electrocardiographic conventions and, given data, determines the mean electrical axis of the heart.*
- *Describes the standard 12-lead electrocardiogram.*

There are a variety of methods available to assess cardiac function. Some of these are noninvasive (eg, auscultation of the chest to evaluate valve function, electrocardiography to evaluate electrical characteristics, and echocardiography to visualize mechanical pumping action) and others require various types of invasive instrumentation. This chapter provides a brief overview of some of these commonly used clinical tools.

MEASUREMENT OF CARDIAC OUTPUT

Fick principle is one of the most accurate methods of measuring cardiac output, which is discussed in detail in Chapter 6. Briefly, this principle states that the amount of a substance consumed by the tissues, X_{tc}, is equal to what goes in minus what goes out, which is the arterial–venous concentration difference in the substance ($[X]_a - [X]_v$) times the blood flow rate, $\dot{Q}$. This relationship can be algebraically arranged to solve for blood flow:

$$\dot{Q} = \frac{\dot{X}_{tc}}{[X]_a - [X]_v}$$

A common method of determining cardiac output is to use the Fick principle to calculate the collective flow through the systemic organs from (1) the whole body oxygen consumption rate ($\dot{X}_{tc}$), (2) the oxygen concentration in arterial blood ($[X]_a$), and (3) the concentration of oxygen in mixed venous blood ($[X]_v$). Of the values required for this calculation, the oxygen content of mixed venous blood is the most difficult to obtain. Generally, the sample for venous blood oxygen measurement must be taken from venous catheters positioned in the right ventricle or pulmonary artery to ensure that it is a mixed sample of venous blood from all systemic organs.

The calculation of cardiac output from the Fick principle is best illustrated by an example. Suppose that a patient is consuming 250 mL of O_2 per minute when his or her systemic arterial blood contains 200 mL of O_2 per liter and the right ventricular blood contains 150 mL of O_2 per liter. This means that, on the average, each liter of blood loses 50 mL of O_2 as it passes through the systemic organs. In order for 250 mL of O_2 to be consumed per minute, 5 L of blood must pass through the systemic circulation each minute:

$$\dot{Q} = \frac{250 \text{ mL } O_2/\text{min}}{200 - 150 \text{ mL } O_2/\text{L blood}}$$

$$\dot{Q} = 5 \text{ L blood/min}$$

Dye dilution and *thermal dilution* (dilution of heat) are other clinical techniques employed for estimating cardiac output. Usually, a known quantity of indicator (dye or heat) is rapidly injected into the blood as it enters the right side of the heart and appropriate detectors are arranged to continuously record the concentration of the indicator in blood as it leaves the left side of the heart. It is possible to estimate the cardiac output from the quantity of indicator injected and the time record of indicator concentration in the blood that leaves the left side of the heart.

Cardiac index is the cardiac output corrected for the individual's size. For example, the cardiac output of a 50-kg woman will be significantly lower than that of a 90-kg man. It has been found, however, that cardiac output correlates better with body surface area than with body weight. Therefore, it is common to express the cardiac output per square meter of surface area. Under resting conditions, the cardiac index is normally approximately 3 L/min per m^2.

CARDIAC CONTRACTILITY ESTIMATES

Imaging Techniques

It is often important to assess an individual's cardiac function without using major invasive procedures. Advances in several techniques have made it possible to obtain two- and three-dimensional images of the heart throughout the cardiac cycle. Visual or computer-aided analysis of such images provides information useful in clinically evaluating cardiac function. These techniques are especially suited for detecting abnormal operation of cardiac valves or contractile

function in portions of the heart walls. They can also provide estimates of heart chamber volumes at different times in the cardiac cycle that, as described later, are used in a number of ways to assess cardiac function.

Echocardiography is the most widely used of the cardiac imaging techniques currently available. This noninvasive technique is based on the fact that sound waves reflect back toward the source when encountering abrupt changes in the density of the medium through which they travel. A transducer, placed at specified locations on the chest, generates pulses of ultrasonic waves and detects reflected waves that bounce off the cardiac tissue interfaces. The longer the time between the transmission of the wave and the arrival of the reflection, the deeper the structure is in the thorax. Such information can be reconstructed by computer in various ways to produce a continuous image of the heart and its chambers throughout the cardiac cycle.

Cardiac angiography involves the placement of catheters into the right or left ventricle and injection of radiopaque contrast medium during high-speed x-ray filming (cineradiography). *Radionuclide ventriculography* (also known as multigated acquisition scan or MUGA scan) involves the intravenous injection of a radioactive isotope that stays in the vascular space (usually technetium that binds to red blood cells) with measurement of the changes in intensity of radiation detected over the ventricles during the cardiac cycle. A gamma camera is used to obtain images "gated" to different times in the cardiac cycle.

Information derived from the various imaging techniques can be used to evaluate myocardial contractility, a critically important component of cardiac function.

Ejection Fraction

Ejection fraction (EF) is an extremely useful clinical measurement that can be calculated from an echocardiogram. The ejection fraction is defined as the ratio of stroke volume (SV) to end-diastolic volume (EDV):

$$EF = SV/EDV$$

Estimates of end-diastolic and end-systolic volumes can be made from the images and stroke volume calculated. Ejection fraction is commonly expressed as a percentage and normally ranges from 55 to 80% (mean 67%) under resting conditions. Ejection fractions of less than 55% indicate depressed myocardial contractility.

End-Systolic Pressure–Volume Relationship

The end-systolic pressure–volume relationship is useful used clinical technique to assess cardiac contractility. End-systolic volume for a given cardiac cycle is estimated by one of the imaging techniques described previously, while end-systolic pressure for that cardiac cycle can obtained from the arterial pressure record at the point of the closure of the aortic valve (the incisura). Values for several different cardiac cycles may be obtained during infusion of a vasoconstrictor (which increases afterload),

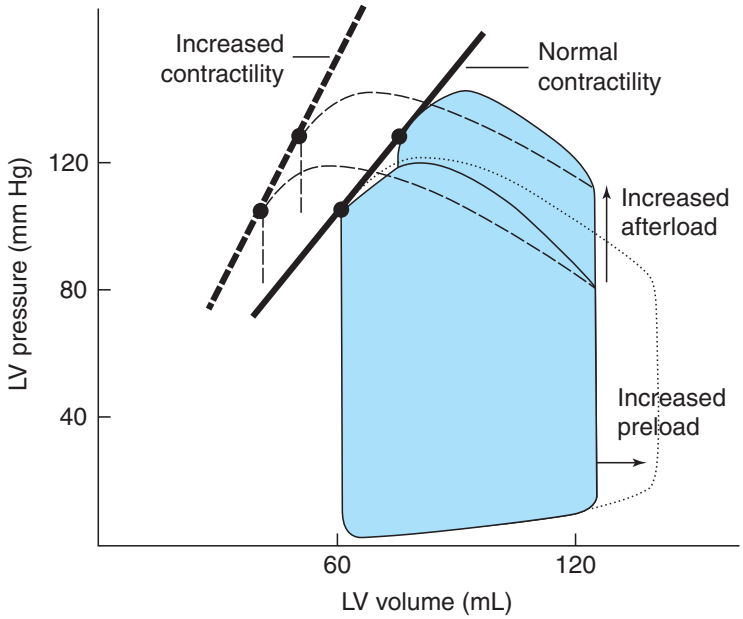

Figure 4–1. The effect of increased contractility on the left ventricular end-systolic pressure–volume relationship.

and the data plotted as in Figure 4–1 in the context of overall ventricular pressure–volume loops. As shown, increases in myocardial contractility are associated with a leftward rotation in the end-systolic pressure–volume relationship. Decreases in contractility (as may be caused by heart disease) are associated with a downward shift of the line, discussed further in Chapter 11. This method of assessing cardiac function is particularly important because it provides an estimate of contractility that is independent of the end-diastolic volume (preload). (Recall from Figure 3–4 and from the pressure–volume loop described by the dotted line in Figure 4–1 that increases in preload cause increases in stroke volume without changing the end-systolic volume. Thus, only alterations in contractility will cause shifts in the end-systolic pressure–volume relationship.)

Note in Figure 4–1 that both the "normal" and "increased contractility" end-systolic pressure–volume lines nearly project to the origin of zero pressure, zero volume. Thus, it is possible to get a reasonable clinical estimate of the slope of the end-systolic pressure–volume relationship (read "myocardial contractility") from a single measurement of end-systolic pressure and volume. This avoids the need to do multiple expensive tests with vasodilator or vasoconstrictor infusions.

MEASUREMENT OF CARDIAC EXCITATION—THE ELECTROCARDIOGRAM

The electrocardiogram is a powerful clinical tool that is used to evaluate cardiac beating rate, rhythm, and conduction characteristics of cardiac tissue. As briefly described in Chapter 2, the electrocardiogram is the result of

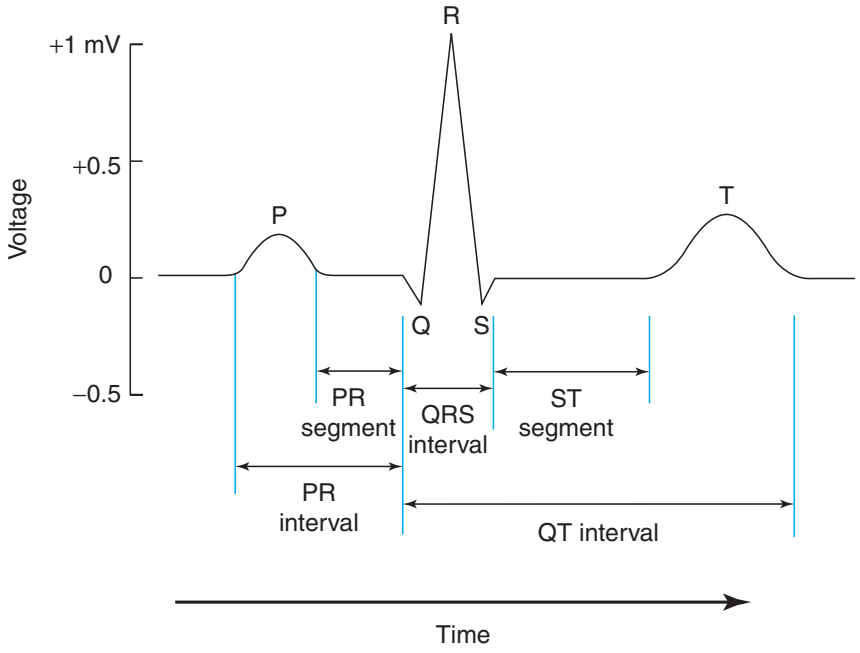

Figure 4–2. Typical electrocardiogram.

currents propagated through the extracellular fluid that are generated by the spread of the wave of excitation throughout the heart. Electrodes placed on the surface of the body record the small potential differences between various recording sites that vary over the time course of the cardiac cycle.

A typical electrocardiographic record is indicated in Figure 4–2. The major features of the electrocardiogram are the P, QRS, and T waves that are caused by atrial depolarization, ventricular depolarization, and ventricular repolarization, respectively. The period from the initiation of the P wave to the beginning of QRS complex is designated as the PR interval and indicates the time it takes for an action potential to spread through the atria and the atrioventricular (AV) node. During the latter portion of the PR interval (PR segment), no voltages are detected on the body surface. This is because atrial muscle cells are depolarized (in the plateau phase of their action potentials), ventricular cells are still resting, and the electrical field setup by the action potential progressing through the small AV node is not intense enough to be detected. The duration of the normal PR interval ranges from 120 to 200 ms. Shortly after the cardiac impulse breaks out of the AV node and into the rapidly conducting Purkinje system, all the ventricular muscle cells depolarize within a very short period and cause the QRS complex. The R wave is the largest event in the electrocardiogram because ventricular muscle cells are so numerous and because they depolarize nearly in unison. The normal QRS complex lasts between 60 and 100 ms. (The repolarization of atrial cells is also occurring during the period in which ventricular depolarization generates the QRS complex on the electrocardiogram, see Figure 2–5. Atrial repolarization is not evident on the electrocardiogram because it is a poorly synchronized event in a relatively small mass of heart tissue and is

completely overshadowed by the major electrical events occurring in the ventricles at this time.)

The QRS complex is followed by the *ST segment.* Normally, no electrical potentials are measured on the body surface during the ST segment because no rapid changes in membrane potential are occurring in any of the cells of the heart; atrial cells have already returned to the resting phase, whereas ventricular muscle cells are in the plateau phase of their action potentials. (Myocardial injury or inadequate blood flow, however, can produce elevations or depressions in the ST segment.) When ventricular cells begin to repolarize, a voltage once again appears on the body surface and is measured as the T wave of the electrocardiogram. The T wave is broader and not as large as the R wave because ventricular repolarization is less synchronous than depolarization. At the conclusion of the T wave, all the cells in the heart are in the resting state. The *QT interval* roughly approximates the duration of the ventricular myocyte depolarization and thus the period of ventricular systole. At a normal heart rate of 60 beats per minute, the QT interval is normally less than 380 ms. No body surface potential is measured until the next impulse is generated by the sinoatrial (SA) node.

It should be recognized that the operation of the specialized conduction system is a primary factor in determining the normal electrocardiographic pattern. For example, the AV nodal transmission time determines the PR interval. Also, the effectiveness of the Purkinje system in synchronizing ventricular depolarization is reflected in the large magnitude and short duration of the QRS complex. It should also be noted that nearly every heart muscle cell is inherently capable of rhythmicity and that all cardiac cells are electrically interconnected through gap junctions. Thus, a functional heart rhythm can and often does occur without the involvement of part or all of the specialized conduction system. Such a situation is, however, abnormal, and the existence of abnormal conduction pathways would produce an abnormal electrocardiogram.

Basic Electrocardiographic Conventions

Recording electrocardiograms is a routine diagnostic procedure, which is standardized by universal application of certain conventions. The conventions for recording and analysis of electrocardiograms from the three standard bipolar limb leads are briefly described here.

Recording electrodes are placed on both arms and the left leg—usually at the wrists and ankle. The appendages are assumed to act merely as extensions of the recording system, and voltage measurements are assumed to be made between points that form an equilateral triangle over the thorax, as shown in Figure 4–3. This conceptualization is called *Einthoven's triangle* in honor of the Dutch physiologist who devised it at the turn of the century. Any single electrocardiographic trace is a recording of the voltage difference measured between any two vertices of Einthoven's triangle. An example of the lead II electrocardiogram measured between the right arm and the left leg has already been shown in Figure 4–2. Similarly, lead I and lead III electrocardiograms represent voltage measurements taken along the other

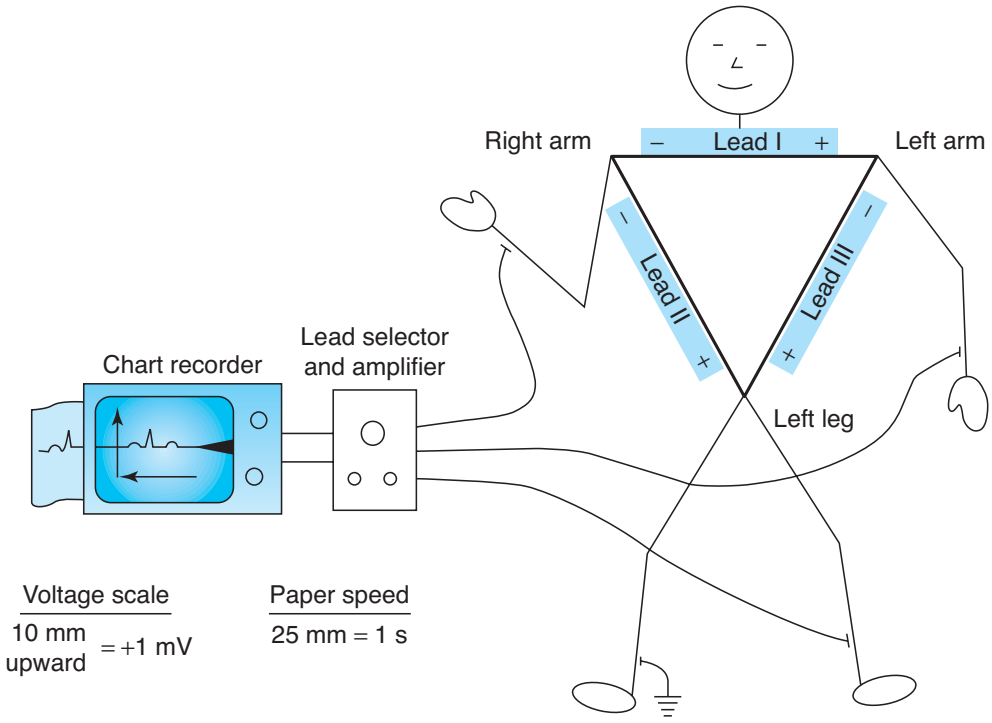

Figure 4–3. Einthoven's electrocardiographic conventions.

two sides of Einthoven's triangle, as indicated in Figure 4–3. The "+" and "–" symbols in Figure 4–3 indicate polarity conventions that have been universally adopted. For example, an upward deflection in a lead II electrocardiogram (as normally occurs during the P, R, and T waves) indicates that an electrical polarity exists at that instant between the left leg and the right shoulder electrodes, with the left leg electrode being positive. Conversely, a downward deflection in a lead II record indicates that a polarity exists between the electrodes at that instant, with the left leg electrode being negative. Similar polarity conventions have been established for lead I and lead III recordings and are indicated by the "+" and "–" symbols in Figure 4–3. In addition, electrocardiographic recording equipment is often standardized so that a 1-cm deflection on the vertical axis always represents a potential difference of 1 mV, and that 25 mm on the horizontal axis of any electrocardiographic record represents 1 second. Most electrocardiographic records contain calibration signals so that abnormal rates and wave amplitudes can be easily detected.

As shown in the next chapter, many cardiac electrical abnormalities can be detected in recordings from a single electrocardiographic lead. However, certain clinically useful information can be derived only by combining the information obtained from two electrocardiographic leads. To understand these more complex electrocardiographic analyses, a close examination of how voltages appear on the body surface as a result of the cardiac electrical activity must be done.

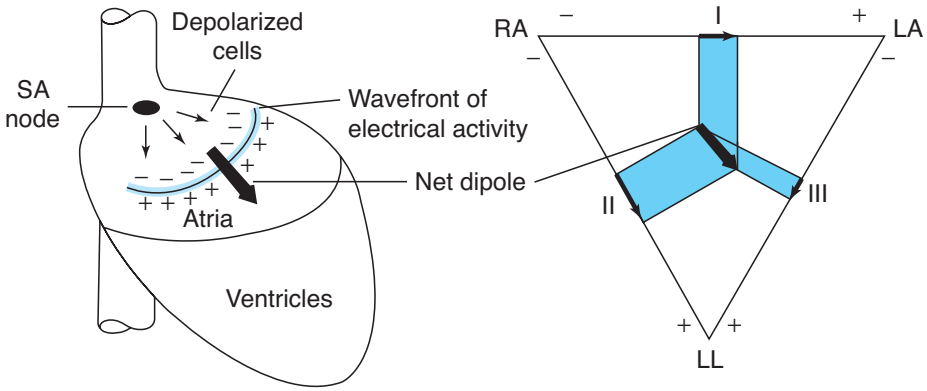

Figure 4–4. Net cardiac dipole during atrial depolarization and its components on the limb leads.

CARDIAC DIPOLES AND ELECTROCARDIOGRAPHIC RECORDS

Einthoven's conceptualization of how cardiac electrical activity causes potential differences on the surface of the body is illustrated in Figure 4–4. In this example, the heart is shown at one instant in the atrial depolarization phase. The cardiac impulse, after having arisen in the SA node, is spreading as a wavefront of depolarization through the atrial tissue. At each point along this wavefront of electrical activity, a small charge separation exists in the extracellular fluid between polarized membranes (positive outside) and depolarized membranes (negative outside). Thus, the wavefront may be thought of as a series of individual *electrical dipoles* (regions of charge separation). Each individual dipole is oriented in the direction of local wavefront movement. The large, black arrow in Figure 4–4 represents the total *net* dipole created by the summed contributions of all the individual dipoles distributed along the wavefront of atrial depolarization. The salty extracellular fluid acts as an excellent conductor, allowing these instantaneous net dipoles, generated on the surface of the heart muscle to be recorded by electrodes on the surface of the body.

The net dipole that exists at any instant is oriented (ie, points) in the general direction of wavefront movement at that instant. The magnitude or strength of the dipole (represented here by the arrow length) is determined by (1) how extensive the wavefront is (ie, how many cells are simultaneously depolarizing at the instant in question) and (2) the consistency of orientation between individual dipoles at different points in the wavefront (dipoles with the same orientation reinforce each other; dipoles with opposite orientation cancel each other).

The net dipole in the example in Figure 4–4 causes the lower-left portion of the body to be generally positive with respect to the upper-right portion. This particular dipole will cause positive voltages to exist on all three of the electrocardiogram limb leads. As shown in the right half of Figure 4–4, this can be deduced from Einthoven's triangle by observing that the net dipole has some component that points in the positive direction of leads I, II, and III. As illustrated in Figure 4–4, the component

that a cardiac dipole has on a given electrocardiogram lead is found by drawing perpendicular lines from the appropriate side of Einthoven's triangle to the tip and tail of the dipole. (It may be helpful to think of the component on each lead as the "shadow" cast by the dipole on that lead as a result of a "sun" located far beyond the corner of Einthoven's triangle that is opposite the lead.) Note that the dipole in this example is most parallel to lead II and therefore has a large component in the lead II direction. Thus, it will create a larger voltage on lead II than on lead I or III. This dipole has a rather small component on lead III because it is oriented nearly perpendicular to lead III.

The limb lead configuration may be thought of as a way to view the heart's electrical activity from three different perspectives (or axes). The vector representing the heart's instantaneous dipole strength and orientation is the object under observation, and its appearance depends on the position from which it is viewed. The instantaneous voltage measured on the axis of lead I, for example, indicates how the dipole being generated by the heart's electrical activity at that instant appears when viewed from directly above. A cardiac dipole that is oriented horizontally appears large on lead I, whereas a vertically oriented cardiac dipole, however large, produces no voltage on lead I. Thus, it is necessary to have views from two directions to establish the magnitude and orientation of the heart's dipole. A vertically oriented dipole would be invisible on lead I but would be readily apparent if viewed from the perspective of lead II or lead III.

It is important to recognize that the example in Figure 4–4 pertains only to one instant during atrial depolarization. The net cardiac dipole continually changes in magnitude and orientation during the course of atrial depolarization. The nature of these changes will determine the shape of the P wave on each of the electrocardiogram leads.

The P wave terminates when the wave of depolarization, as illustrated in Figure 4–4, reaches the nonmuscular border between the atria and the ventricles and the number of individual dipoles becomes very small. At this time, the cardiac impulse is still being slowly transmitted toward the ventricles through the AV node. However, the electrical activity in the AV node involves so few cells that it generates no detectable net cardiac dipole. Thus, no voltages are measured on the surface of the body for a brief period following the P wave. A net cardiac dipole reappears only when the depolarization completes its passage through the AV node, enters the Purkinje system, and begins its rapid passage over the ventricular muscle cells. Because the Purkinje fibers initially pass through the intraventricular septum and to the endocardial layers at the apex of the ventricles, ventricular depolarization occurs first in these areas and then proceeds outward and upward through the ventricular myocardium.

Ventricular Depolarization and the QRS Complex

It is the rapid and large changes in the magnitude and direction of the net cardiac dipole that occur during ventricular depolarization that cause the QRS complex of the electrocardiogram. The normal process is illustrated in Figure 4–5. The

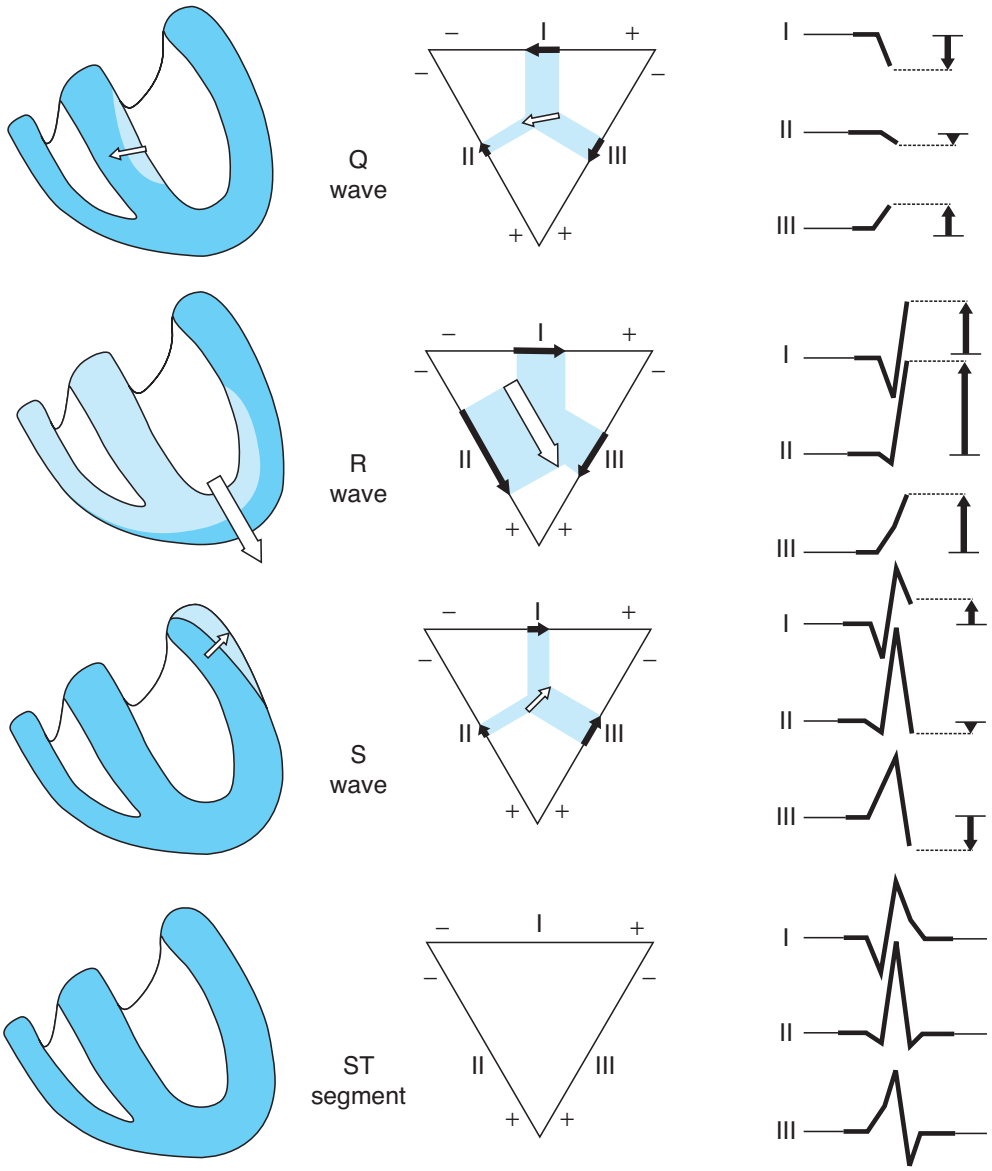

Figure 4–5. Ventricular depolarization and the generation of the QRS complex.

initial ventricular depolarization usually occurs on the left side of the intraventricular septum as illustrated in the upper panel of the figure. Analysis of the cardiac dipole formed by this initial ventricular depolarization with the aid of Einthoven's triangle shows that this dipole has a negative component on lead I, a small negative component on lead II, and a positive component on lead III. The upper right panel shows the actual deflections on each of the electrocardiographic limb leads that will be produced by this dipole. Note that it is possible for a given cardiac dipole to produce opposite deflections on different leads. For example, in Figure 4–5, Q waves appear on leads I and II but not on lead III.

The second row of panels in Figure 4–5 shows the ventricles during the instant in ventricular depolarization when the number of individual dipoles is greatest and/or their orientation is most similar. This phase generates the large net cardiac dipole, which is responsible for the R wave of the electrocardiogram. In Figure 4–5, this net cardiac dipole is nearly parallel to lead II. As indicated, such a dipole produces large positive R waves on all three limb leads.

The third row in Figure 4–5 shows the situation near the end of the spread of depolarization through the ventricles and indicates how the small net cardiac dipole present at this time produces the S wave. Note that an S wave does not necessarily appear on all electrocardiogram leads (as in lead I of this example).

The bottom row in Figure 4–5 shows that during the ST segment, all ventricular muscle cells are in a depolarized state. There are no waves of electrical activity moving through the heart tissue. Consequently, no net cardiac dipole exists at this time and no voltage differences exist between points on the body surface. All electrocardiographic traces will be flat at the *isoelectric* (zero voltage) level.

Ventricular Repolarization and the T Wave

As illustrated in Figure 4–2, the T wave is normally positive on lead II as is the R wave. This indicates that the net cardiac dipole generated during ventricular repolarization is oriented in the same general direction as that which exists during ventricular depolarization. This may be somewhat surprising. However, recall from Figure 2–5 that the *last ventricular cells to depolarize are the first to repolarize*. The reasons for this are not well understood, but the result is that the wavefront of electrical activity during ventricular repolarization tends to retrace, in *reverse direction*, the course followed during ventricular depolarization. Therefore, the dipole formed during repolarization has the *same* polarity as that during depolarization. This reversed wavefront propagation pathway during ventricular repolarization results in a positive T wave recorded, for example, on lead II. The T wave is broader and smaller than the R wave because the repolarization of ventricular muscle cells is less well synchronized than is their depolarization.

MEAN ELECTRICAL AXIS AND AXIS DEVIATIONS

The orientation of the cardiac dipole during the most intense phase of ventricular depolarization (ie, at the instant the R wave reaches its peak) is called the *mean electrical axis* of the heart. It is used clinically as an indicator of whether ventricular depolarization is proceeding over normal pathways. The mean electrical axis is reported in degrees according to the convention indicated in Figure 4–6. (Note that the downward direction corresponds to *plus* 90 degrees in this polar coordinate system.) As indicated, a mean electrical axis that lies anywhere in the patient's lower left-hand quadrant is considered normal. A *left axis deviation* exists when the mean electrical axis falls in the patient's upper left-hand quadrant and may indicate a physical displacement of the heart to the left, left ventricular hypertrophy, or loss of electrical activity in the right ventricle. A *right axis deviation*

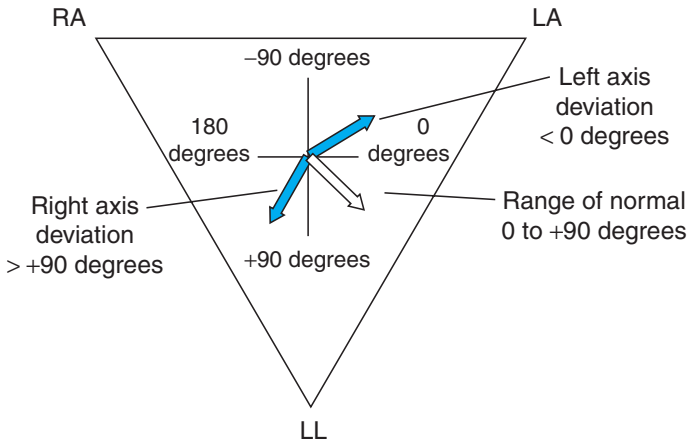

Figure 4–6. Mean electrical axis and axis deviations.

exists when the mean electrical axis falls in the patient's lower right-hand quadrant and may indicate a physical displacement of the heart to the right, right ventricular hypertrophy, or loss of electrical activity in the left ventricle.

The mean electrical axis of the heart can be determined from the electrocardiogram. The process involves determining what single net dipole orientation will produce the R-wave amplitudes recorded on any two leads. For example, if the R waves on leads II and III are both positive (upright) and of equal magnitude, the mean electrical axis must be +90 degrees. As should be obvious, in this case, the amplitude of the R wave on lead I will be zero.[1] Alternatively, one can scan the electrocardiographic records for the lead tracing with the largest R waves and then deduce that the mean electrical axis must be nearly parallel to that lead. In Figure 4–5, for example, the largest R wave occurs on lead II. Lead II has an orientation of +60 degrees, which is very close to the actual mean electrical axis in this example.

Another analysis technique called *vectorcardiography* is based on continuously following the magnitude and orientation of the heart's dipole throughout the cardiac cycle. A typical vectorcardiogram is illustrated in Figure 4–7 and is a graphical record of the dipole amplitude in the *x* and *y* directions throughout a single cardiac cycle. If one imagines the heart's electrical dipole as a vector with its tail always positioned at the center of Einthoven's triangle, then the vectorcardiogram can be thought of as a complete record of all the various positions that the head of the dipole assumes during the course of one cardiac cycle. A vectorcardiogram starts from an isoelectric diastolic point and traces three loops during each cardiac

[1] An accurate, albeit tedious, way to determine the mean electrical axis is to follow these steps: (1) determine the algebraic sum of the R- and S-wave amplitude on each of the two leads, (2) plot these magnitudes as components on the appropriate sides of Einthoven's equilateral triangle according to the standardized polarity conventions, (3) project perpendicular lines from the heads and tails of these components into the interior of the triangle to find the position of the head and tail of the cardiac dipole, which produced the R waves, and (4) measure the angular orientation of this dipole.

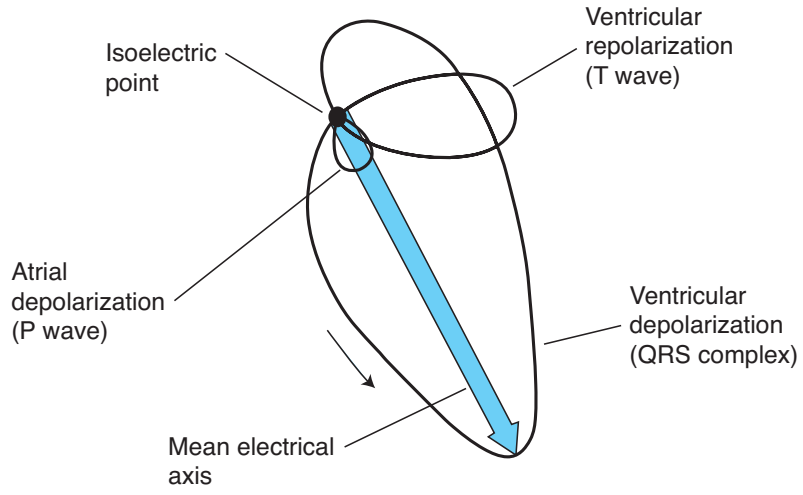

Figure 4–7. Typical vectorcardiogram.

cycle. The first small loop is caused by atrial depolarization, the second large loop is caused by ventricular depolarization, and the final intermediate-sized loop is caused by ventricular repolarization. The mean electrical axis of the ventricle is immediately apparent in a vectorcardiographic record as the orientation of the largest deviation from the isoelectric point during ventricular depolarization. Analogous "mean axes" can similarly be defined for the P wave and T wave but are not commonly used.

THE STANDARD 12-LEAD ELECTROCARDIOGRAM

The standard clinical electrocardiogram involves voltage measurements recorded from 12 different leads. Three of these are the bipolar limb leads I, II, and III, which have already been discussed. The other 9 leads are unipolar leads. Three of these leads are generated by using the limb electrodes. Two of the electrodes are electrically connected to form an *indifferent electrode*, while the third limb electrode is made the positive pole of the pair. Recordings made from these electrodes are called *augmented unipolar limb leads.* The voltage record obtained between the electrode on the right arm and the indifferent electrode is called a lead aVR electrocardiogram. Similarly, lead aVL is recorded from the electrode on the left arm, and lead aVF is recorded from the electrode on the left leg.

The standard limb leads (I, II, and III) and the augmented unipolar limb leads (aVR, aVL, and aVF) record the electrical activity of the heart as it appears from six different "perspectives," all in the frontal plane. As shown in Figure 4–8A, the axes for leads I, II, and III are those of the sides of Einthoven's triangle, while those for aVR, aVL, and aVF are specified by lines drawn from the center of Einthoven's triangle to each of its vertices. As indicated in Figure 4–8B, these six limb leads can be thought of as a hexaxial reference system for observing the cardiac vectors in the frontal plane.

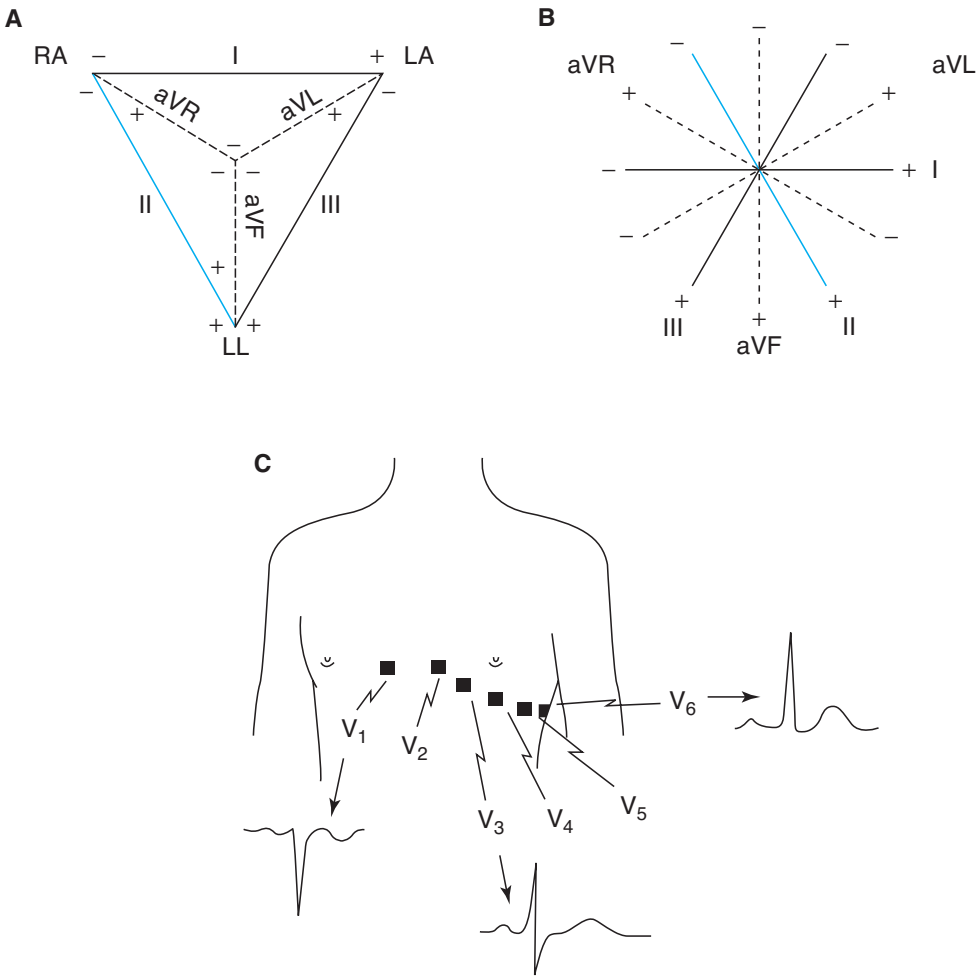

Figure 4–8. The standard 12-lead electrocardiogram. (**A** and **B**) Leads in the frontal plane. (**C**) Electrode positions for precordial leads in the transverse plane.

The other six leads of the standard 12-lead electrocardiogram are also unipolar leads that "look" at the electrical vector projections in the transverse plane. These potentials are obtained by placing an additional (*exploring*) electrode in six specified positions on the chest wall as shown in Figure 4–8C. The indifferent electrode in this case is formed by electrically connecting the limb electrodes. These leads are identified as *precordial* or *chest* leads and are designated as V1 through V6. As shown in this figure, when the positive electrode is placed in position 1 and the wave of ventricular excitation sweeps away from it, the resultant deflection will be downward. When the electrode is in position 6 and the wave of ventricular excitation sweeps toward it, the deflection will be upward.

In summary, the electrocardiogram is a powerful tool for evaluating cardiac excitation characteristics. It must be recognized, however, that the ECG does not provide direct evidence of mechanical pumping effectiveness. For example, a leaky valve will have no direct electrocardiographic consequences but may adversely influence pumping ability of the heart.

KEY CONCEPTS

1. *A variety of methods are available for measuring various aspects of cardiac mechanical function. These methods are based on the Fick principle, dye-dilution techniques, and various imaging techniques including echocardiography.*
2. *The ejection fraction (stroke volume/end-diastolic volume) is a very useful index of cardiac contractility.*
3. *The electrocardiogram is a record of the voltage changes that occur on the surface of the body as a result of the propagation of the action potential through the heart during a cardiac cycle.*
4. *There are standardized conventions used for recording electrocardiograms.*
5. *The magnitude and direction of the net dipole formed by the wavefront of the action potential at any instant in time can be deduced from the magnitude and orientation of the electrocardiographic deflections.*
6. *The mean electrical axis describes the orientation of the net dipole at the instant of maximum wavefront propagation during ventricular depolarization and normally falls between 0 and +90 degrees on a polar coordinate system.*
7. *The standard 12-lead electrocardiogram is widely used to evaluate cardiac electrical activity and consists of a combination of bipolar and unipolar records from limb electrodes and chest electrodes.*

STUDY QUESTIONS

4–1. *Given the following information, calculate cardiac output:*

Systemic arterial blood oxygen concentration, $[O_2]_{SA} = 200$ mL/L
Pulmonary arterial blood oxygen concentration, $[O_2]_{PA} = 140$ mL/L
Total body oxygen consumption, $VO_2 = 600$ mL/min

4–2. *If left ventricular end-diastolic volume is 150 mL and end-systolic volume is 50 mL, what is the ejection fraction? Is this "normal" for a resting adult?*

4–3. *A decrease in atrioventricular nodal conduction velocity will*

a. *decrease the heart rate*
b. *increase P-wave amplitude*
c. *increase the PR interval*
d. *widen the QRS complex*
e. *increase the ST-segment duration*

4–4. The P wave on lead aVR of the normal electrocardiogram will be

a. an upward deflection
b. a downward deflection
c. not detectable
d. highly variable

4–5. If the R wave is upright and equally large on leads I and aVF, what is the mean electrical axis of the heart? Is it within normal range? Which lead(s) will have the smallest R wave amplitude?

4–6. What is the definition of cardiac "ejection fraction"?

a. stroke volume expressed as a percent of cardiac output
b. the ratio of the end-systolic volume to the end-diastolic volume
c. the ratio of the end-diastolic volume to the end-systolic volume
d. the ratio of stroke volume to the end-diastolic volume
e. the ratio of the time spent in systole to the time spent in diastole

4–7. Electrocardiograms give information about all of the following except

a. atrial beating rate
b. site of pacemaker origination
c. pathway of ventricular activation
d. rate of AV nodal conduction
e. amplitude of the ventricular action potential

4–8. If something slows the conduction pathway of the action potential through the ventricular muscle, which of the following alterations would you most likely see on the ECG?

a. absence of P waves
b. prolongation of the PR interval
c. prolongation of the QRS interval
d. shortening of the QT interval
e. elevation of the ST segment

Cardiac Abnormalities 5

OBJECTIVES

The student, through understanding normal cardiac function, diagnoses and appreciates the consequences of common cardiac abnormalities:

- *Detects common cardiac arrhythmias from the electrocardiogram, identifies their physiological bases, and describes their physiological consequences.*
- *Lists four common valvular abnormalities for the left side of the heart and describes the alterations in intracardiac and arterial pressures, flow patterns, and heart sounds that accompany them.*

Recall that effective, efficient ventricular pumping action depends on proper cardiac function in five basic aspects. This chapter focuses on the abnormalities in three of these aspects: (1) abnormal cardiac excitation and rhythmicity, (2) valvular stenosis (inadequate valve opening), and (3) valvular insufficiency (incomplete valve closure). Discussion of abnormalities in myocardial force production and cardiac filling is presented in Chapter 11. The material presented here is an introduction to the more common cardiac electrical and valvular dysfunctions, with an emphasis on the primary physiological consequences of these abnormal situations.

ELECTRICAL ABNORMALITIES AND ARRHYTHMIAS

Many cardiac excitation problems can be diagnosed from the information in a single lead of an electrocardiogram. The lead II electrocardiogram traces at the top of Figure 5–1 and 5–2 are identified as normal sinus rhythms based on the following characteristics: (1) the frequency of QRS complexes is approximately 1 per second, indicating a normal beating rate; (2) the shape of the QRS complex is normal for lead II and its duration is less than 120 ms, indicating rapid depolarization of the ventricles via normal conduction pathways; (3) each QRS complex is preceded by a P wave of proper configuration, indicating sinoatrial (SA) nodal origin of the excitation; (4) the PR interval is less than 200 ms, indicating proper conduction delay of the impulse propagation through the atrioventricular (AV) node; (5) the QT interval is less than half of the R-to-R interval, indicating normal

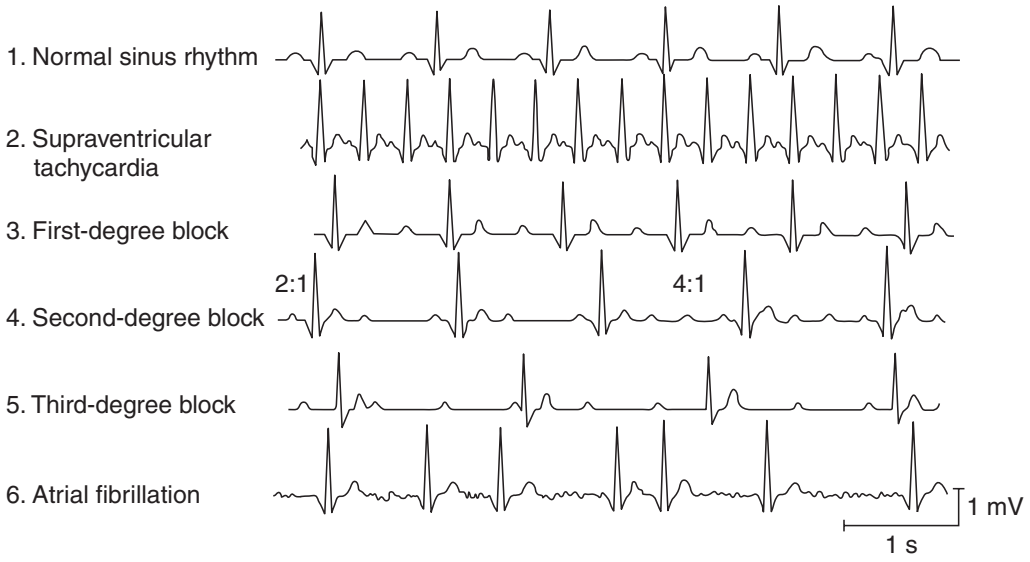

Figure 5–1. Supraventricular arrhythmias.

ventricular repolarization; and (6) there are no extra P waves, indicating that no AV nodal conduction block is present. The subsequent electrocardiographic tracings in Figures 5–1 and 5–2 represent irregularities commonly found in clinical practice. Examination of each of these traces with the above characteristics in mind will aid in the differential diagnosis.

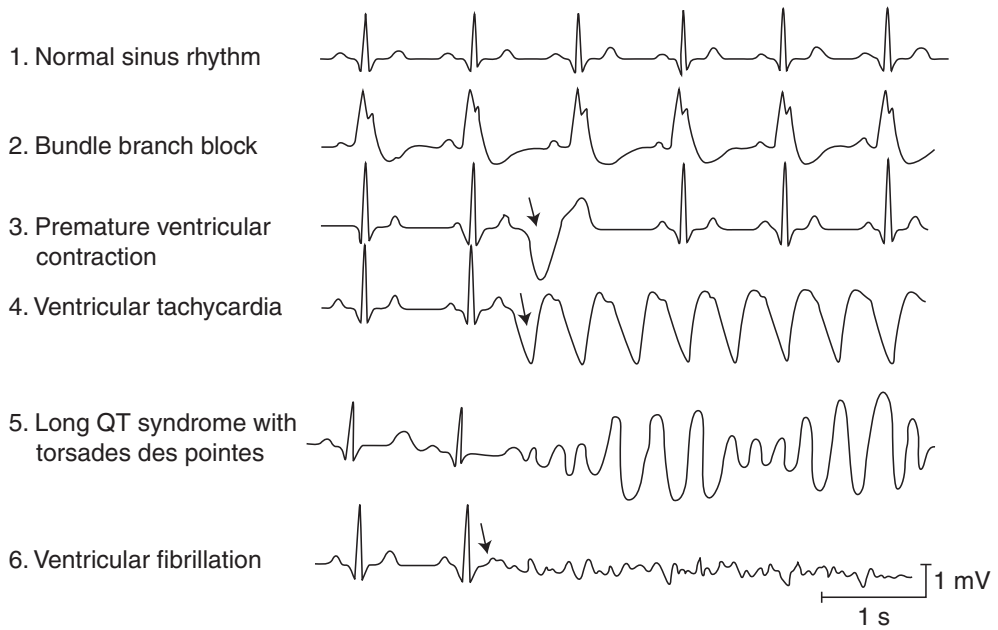

Figure 5–2. Ventricular arrhythmias.

2 The physiological consequences of abnormal excitation and conduction in the heart depend on whether the electrical abnormality evokes a *tachycardia*, which will limit the time for cardiac filling between beats; evokes a *bradycardia*, which is inadequate to support sufficient cardiac output; or decreases the coordination of myocyte contraction, which will reduce stroke volume.

Supraventricular Abnormalities

3 Traces 2 through 6 below the normal trace in Figure 5–1 represent typical supraventricular arrhythmias (ie, originating in the atria or AV node). *Supraventricular tachycardia* (shown in trace 2 in Figure 5–1 and sometimes called *paroxysmal atrial tachycardia*) occurs when the atria are abnormally excited and drive the ventricles at a very rapid rate. These paroxysms begin abruptly, last for a few minutes to a few hours, and then, just as abruptly, disappear and the heart rate reverts to normal. QRS complexes appear normal (albeit frequent) with simple paroxysmal atrial tachycardia because the ventricular conduction pathways operate normally. The P and T waves may be superimposed because of the high heart rate. Low blood pressure and dizziness may accompany bouts of this arrhythmia because the extremely high heart rate does not allow sufficient diastolic time for ventricular filling.

4 There are two mechanisms that may account for supraventricular tachycardia. First, an atrial region, usually outside the SA node, may become irritable (perhaps because of local interruption in blood flow) and begin to fire rapidly to take over the pacemaker function. Such an abnormal pacemaker region is called an *ectopic focus.* Alternatively, atrial conduction may become altered so that a single wave of excitation does not die out but continually travels around some abnormal atrial conduction loop. In this case, the continual activity in the conduction loop may drive the atria and AV node at a very high frequency. This self-sustaining process is called a *reentry phenomenon* and is illustrated in Figure 5–3. This situation

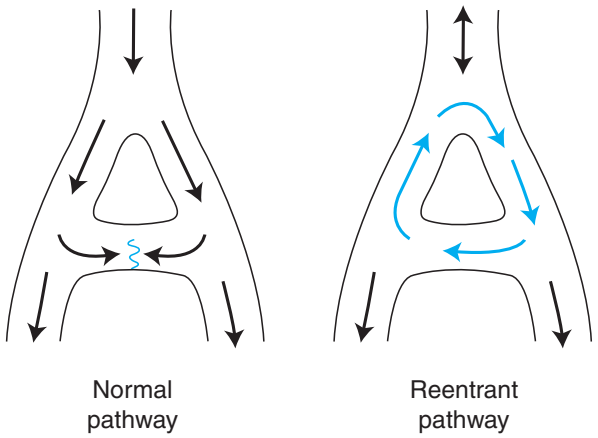

Figure 5–3. Normal and reentrant (circus) cardiac excitation pathways.

may develop as a result of abnormal repolarization and altered refractory periods in local areas of the myocardium. *Atrial flutter* is a special form of tachycardia of atrial origin in which a large reentrant pathway drives the atria at very fast rates (250 to 300 beats per minute) and normal refractory periods of AV nodal tissue are overwhelmed. Thus, ventricular rate is often some fixed ratio of the atrial rate (2:1, 4:1) with frequencies often 150 to 220 beats per minute. The electrocardiogram often shows a sawtooth pattern of merged P waves with intermittent normal QRS complexes.

Conduction blocks occur at the AV node and generally represent impaired conduction through this tissue. In a *first-degree heart block* (trace 3 in Figure 5–1), the only electrical abnormality is unusually slow conduction through the AV node. This condition is detected by an abnormally long PR interval (>0.2 second). Otherwise, the electrocardiogram may be completely normal. At normal heart rates, the physiological effects of the first-degree block are inconsequential. The danger, however, is that the slow conduction may deteriorate to an actual interruption of conduction.

A *second-degree heart block* (trace 4 in Figure 5–1) is said to exist when some but not all atrial impulses are transmitted through the AV node to the ventricle. Impulses are blocked in the AV node if the cells of the region are still in a refractory period from a previous excitation. The situation is aggravated by high atrial rates and slower than normal conduction through the AV nodal region. In the second-degree block, some but not all P waves are accompanied by corresponding QRS complexes and T waves. Atrial rate is often faster than ventricular rate by a certain ratio (eg, 2:1, 3:1, and 4:1). This condition may not represent a serious clinical problem as long as the ventricular rate is adequate to meet the pumping needs.

In a *third-degree heart block* (trace 5 in Figure 5–1), no impulses are transmitted through the AV node. In this event, some area in the ventricles—often in the common bundle or bundle branches near the exit of the AV node—assumes the pacemaker role for the ventricular tissue. Atrial rate and ventricular rate are completely independent, and P waves and QRS complexes are totally dissociated in the electrocardiogram. Ventricular rate is likely to be slower than normal (bradycardia) and sometimes is slow enough to impair cardiac output.

Atrial fibrillation (trace 6 in Figure 5–1) is characterized by a complete loss of the normally close synchrony of the excitation and resting phases between individual atrial cells. Cells in different areas of the atria depolarize, repolarize, and are excited again randomly. Consequently, no P waves appear in the electrocardiogram although there may be rapid, irregular, small waves apparent throughout diastole. The ventricular rate is often very irregular in atrial fibrillation because impulses enter the AV node from the atria at unpredictable times. Fibrillation is a self-sustaining process. The mechanisms behind it are not well understood, but impulses are thought to progress repeatedly around irregular conduction pathways (sometimes called circus pathways, which imply a reentry phenomenon as described earlier and in Figure 5–3). However, because atrial contraction usually plays a negligible role in

ventricular filling, atrial fibrillation may be well tolerated by most patients as long as ventricular rate is sufficient to maintain the cardiac output.[1]

Ventricular Abnormalities

Traces 2 through 6 below the normal trace in Figure 5–2 show typical ventricular electrical abnormalities. Conduction blocks called *bundle branch blocks* or *hemiblocks* (trace 2 in Figure 5–2) can occur in either of the branches of the Purkinje system of the intraventricular septum often as a result of a myocardial infarction. Ventricular depolarization is less synchronous than normal in the half of the heart with the nonfunctional Purkinje system. This results in a widening of the QRS complex (>0.12 second) because a longer time is required for ventricular depolarization to be completed. The direct physiological effects of bundle branch blocks are usually inconsequential.

Premature ventricular contractions (PVCs) (trace 3 in Figure 5–2) are caused by action potentials initiated by and propagated away from an ectopic focus in the ventricle. As a result, the ventricle depolarizes and contracts before it normally would. A PVC is often followed by a missed beat (called a *compensatory pause*) because the ventricular cells are still refractory when the next normal impulse emerges from the SA node. The highly abnormal ventricular depolarization pattern of a PVC produces the large-amplitude, long-duration deflections on the electrocardiogram. The shapes of the electrocardiographic records of these extra beats are highly variable and depend on the ectopic site of their origin and the depolarization pathways involved. The volume of blood ejected by the premature beat itself is smaller than normal, whereas the stroke volume of the beat following the compensatory pause is larger than normal. This is partly due to the differences in filling times and partly to an inherent phenomenon of the cardiac muscle called *postextrasystolic potentiation.* Single PVCs occur occasionally in most individuals and, although sometimes alarming to the individual experiencing them, are not dangerous. Frequent occurrence of PVCs, however, may be a signal of possible myocardial damage or perfusion problems.

Ventricular tachycardia (trace 4 in Figure 5–2) occurs when the ventricles are driven at high rates, usually by impulses originating from a ventricular ectopic focus. Ventricular tachycardia is a very serious condition. Not only is diastolic filling time limited by the rapid rate, but the abnormal excitation pathways make ventricular contraction less synchronous and therefore less effective than normal. In addition, ventricular tachycardia often precedes ventricular fibrillation.

Prolonged QT intervals (the left side of trace 5 in Figure 5–2) are a result of delayed ventricular myocyte repolarization, which may be due to inappropriate opening of

[1] The real danger with atrial fibrillation lies in the tendency for blood to form clots in the atria in the absence of the normal vigorous coordinated atrial contraction. These clots can fragment and move out of the heart to lodge in small arteries throughout the systemic circulation. These emboli can have devastating effects on critical organ function. Consequently, anticoagulant therapy is usually prescribed for patients in atrial fibrillation.

sodium channels or prolonged closure of potassium channels during the action potential plateau phase. Although the normal QT interval varies with heart rate, it is normally less than 40% of the cardiac cycle length (except at very high heart rates). Long QT syndrome is identified when the QT interval is greater than 50% of the cycle duration. It may be genetic in origin (mutations influencing various ion channels involved with cardiac excitability), may be acquired from several electrolyte disturbances (low blood levels of Ca^{2+}, Mg^{2+}, or K^{+}), or may be induced by several pharmacological agents (including some antiarrhythmic drugs). The prolongation of the myocyte refractory period, which accompanies the long QT syndrome, extends the vulnerable period during which extra stimuli can evoke tachycardia or fibrillation. Patients with long QT syndrome are predisposed to a particularly dangerous type of ventricular tachycardia called *torsades de pointes* ("twisting of points" as shown in the right side of trace 5 in Figure 5–2). This differs from the ordinary ventricular tachycardia in that the ventricular electrical complexes cyclically vary in amplitude around the baseline and can deteriorate rapidly into ventricular fibrillation.

In *ventricular fibrillation* (trace 6 in Figure 5–2), various areas of the ventricle are excited and contract asynchronously. The mechanisms are similar to those in atrial fibrillation. The ventricle is especially susceptible to fibrillation whenever a premature excitation occurs at the end of the T wave of the previous excitation, that is, when most ventricular cells are in the "hyperexcitable" or "vulnerable" period of their electrical cycle. In addition, because some cells are repolarized and some are still refractory, circus pathways can be triggered easily at this time. Since no pumping action occurs with ventricular fibrillation, the situation is fatal unless quickly corrected by *cardiac conversion*. During conversion, the artificial application of large currents to the entire heart (via paddle electrodes applied across the chest) may be effective in depolarizing all heart cells simultaneously and thus allowing a normal excitation pathway to be reestablished.

VALVULAR ABNORMALITIES

Pumping action of the heart is impaired when the valves do not function properly. Abnormal heart sounds, which usually accompany cardiac valvular defects, are called *murmurs.* These sounds are caused by abnormal pressure gradients and turbulent blood flow patterns that occur during the cardiac cycle. A number of techniques, ranging from simple auscultation (listening to the heart sounds) to echocardiography or cardiac catheterization, are used to obtain information about the nature and extent of these valvular malfunctions.

In general, when a valve does not open fully (ie, is stenotic), the chamber upstream of the valve has to develop more pressure during its systolic phase to achieve a given flow through the valve. This increase in "pressure" work will induce hypertrophy of cardiac muscle cells and thickening of the walls of that chamber. When a valve does not close completely (ie, is insufficient), the regurgitant blood flow represents an additional volume that must be ejected in order to get sufficient forward flow

out of the ventricle into the tissues. This increase in "volume" work often leads to chamber dilation but not to an increase in wall thickness.[2]

A second generality about valve abnormalities is that whenever there is an elevation in the atrial pressure as a result of AV valve stenosis or regurgitation, this will result in higher pressures in the upstream capillary beds. If capillary hydrostatic pressures are elevated, tissue edema will ensue with consequences on the function of those upstream organs.

A brief overview of four of the common valve defects influencing left ventricular function is given in Figure 5–4. Note that similar stenotic and regurgitant abnormalities can occur in right ventricular valves with similar consequences on right ventricular function.

Aortic Stenosis

Some characteristics of aortic stenosis are shown in Figure 5–4A. Normally, the aortic valve opens widely and offers a pathway of very low resistance through which blood leaves the left ventricle. If this opening is narrowed (stenotic), resistance to flow through the valve increases. A significant pressure difference between the left ventricle and the aorta may be required to eject blood through a stenotic aortic valve. As shown in Figure 5–4A, intraventricular pressures may rise to very high levels during systole while aortic pressure rises more slowly than normal to a systolic value that is subnormal. Pulse pressure is usually low with aortic stenosis. High intraventricular pressure development is a strong stimulus for cardiac muscle cell hypertrophy, and an increase in left ventricular muscle mass invariably accompanies aortic stenosis. This tends to produce a leftward deviation of the electrical axis. (The mean electrical axis will fall in the upper right-hand quadrant in Figure 4–6.) Blood being ejected through the narrowed orifice may reach very high velocities, and turbulent flow may occur as blood enters the aorta. This abnormal turbulent flow can be heard as a *systolic* (or ejection) *murmur* with a properly placed stethoscope. The primary physiological consequence of aortic stenosis is a high ventricular afterload that is caused by restriction of the outflow tract. This imposes an increased pressure workload on the left ventricle.

Mitral Stenosis

Some characteristics of mitral stenosis are shown in Figure 5–4B. A pressure difference of more than a few millimeters of mercury across the mitral valve during diastole is distinctly abnormal and indicates that this valve is stenotic. The high resistance mandates an elevated pressure difference to achieve normal flow across the valve ($\dot{Q} = \Delta P/R$). Consequently, as shown in Figure 5–4B, left atrial pressure is elevated with mitral stenosis. The high left atrial workload may induce

[2] A useful analogy is to compare the hypertrophied skeletal muscles of the weightlifter (doing isometric or pressure work) to the nonhypertrophied but well-toned skeletal muscles of the long-distance runner (doing isotonic or shortening work).

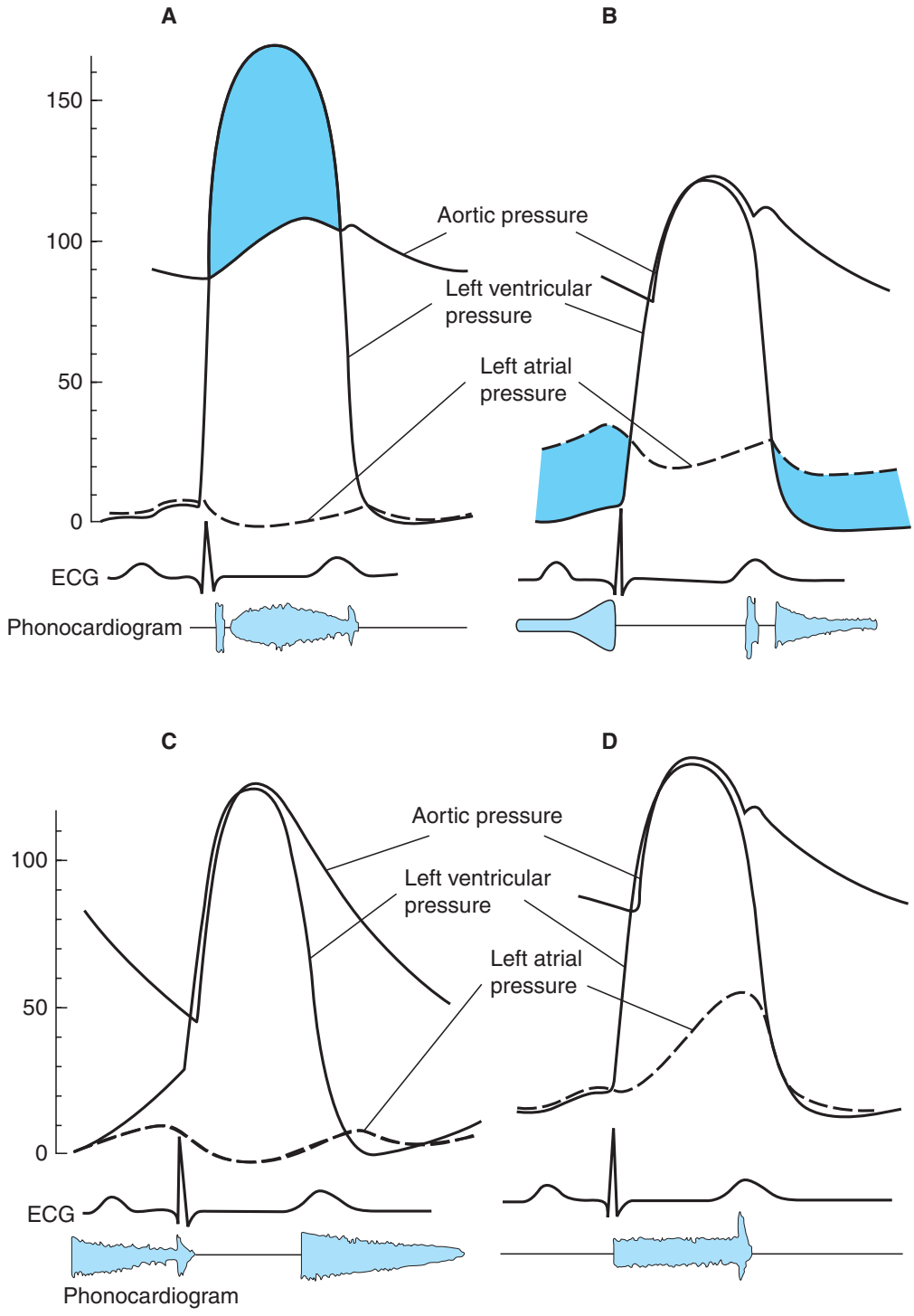

Figure 5–4. Common valvular abnormalities: (**A**) aortic stenosis, (**B**) mitral stenosis, (**C**) aortic regurgitation (insufficiency), and (**D**) mitral insufficiency.

hypertrophy of the left atrial muscle. Elevated left atrial pressure is reflected back into the pulmonary bed and, if high enough, causes pulmonary congestion and "shortness of breath." A *diastolic murmur* associated with turbulent flow through the stenotic mitral valve can often be heard. The primary physiological consequences of mitral stenosis are elevations in left atrial pressure and pulmonary capillary pressure. The latter can cause pulmonary edema and interference with normal gas exchange in the lungs (leading to shortness of breath).

Aortic Insufficiency

Typical characteristics of aortic regurgitation (insufficiency, incompetence) are shown in Figure 5–4C. When the leaflets of the aortic valve do not provide an adequate seal, blood regurgitates from the aorta back into the left ventricle during the diastolic period. Aortic pressure falls faster and further than normal during diastole, which causes a low diastolic pressure and a large pulse pressure. In addition, ventricular end-diastolic volume and pressure are higher than normal because of the extra blood that reenters the chamber through the incompetent aortic valve during diastole. Turbulent flow of the blood reentering the left ventricle during early diastole produces a characteristic diastolic murmur. Often the aortic valve is altered so that it is both stenotic and insufficient. In these instances, both a systolic and a diastolic murmurs are present. The primary physiological consequences of aortic insufficiency are a reduction in forward flow out to the tissues (if the insufficiency is severe) and an increase in the volume workload of the left ventricle.

Mitral Regurgitation

Typical characteristics of mitral regurgitation (insufficiency, incompetence) are shown in Figure 5–4D. When the mitral valve is insufficient, some blood regurgitates from the left ventricle into the left atrium during systole. A systolic murmur may accompany this abnormal flow pattern. Left atrial pressure is raised to abnormally high levels, and left ventricular end-diastolic volume and pressure increase. Mitral valve *prolapse* is a common form of mitral insufficiency in which the valve leaflets evert into the left atrium during systole. The primary physiological consequences of mitral regurgitation are somewhat similar to aortic insufficiency in that forward flow out of the left ventricle into the aorta may be compromised (if the insufficiency is severe) and there is an increase in the volume workload of the left ventricle. In addition, the elevated left atrial pressure can also lead to pulmonary effects with shortness of breath.

KEY CONCEPTS

Cardiac arrhythmias can often be detected and diagnosed from a single electrocardiographic lead.

2. *Physiological consequences of abnormal excitation and conduction in the heart depend on whether the electrical abnormality limits the time for adequate cardiac filling or decreases the coordination of myocyte contractions resulting in inadequate pressure development and ejection.*

3. *Supraventricular arrhythmias are a result of abnormal action potential initiation at the SA node or altered propagation characteristics through the atrial tissue and the AV node.*

4. *Tachycardias may originate either in the atria or in the ventricles and are a result of increased pacemaker automaticity or of continuously circling pathways setting up a reentrant circuit.*

5. *Abnormal conduction through the AV node results in conduction blocks.*

6. *Abnormal conduction pathways in the Purkinje system or in the ventricular tissue result in significant QRS alterations.*

7. *Ventricular tachycardia and ventricular fibrillation represent severe abnormalities that are incompatible with effective cardiac pumping.*

8. *Failure of cardiac valves to open fully (stenosis) can result in elevated upstream chamber pressure and abnormal pressure gradients, congestion in upstream vascular beds, chamber wall hypertrophy, turbulent forward flow across the valve, and murmurs during systole or diastole.*

9. *Failure of cardiac valves to close completely (insufficiency, incompetence, regurgitation) can result in large stroke volumes, abnormal pressure pulses, congestion in upstream vascular beds, turbulent backward flow across the valve, and murmurs during systole or diastole.*

STUDY QUESTIONS

5–1. *Which of the following arrhythmias might result in a reduced stroke volume?*
   a. *paroxysmal atrial tachycardia*
   b. *ventricular tachycardia*
   c. *atrial fibrillation*
   d. *ventricular fibrillation*
   e. *third-degree heart block*

5–2. *Describe the primary pressure abnormalities associated with*
   a. *aortic stenosis*
   b. *mitral stenosis*

5–3. You notice an abnormally large pulsation of your patient's jugular vein, which occurs at about the same time as heart sound, S_1. What is your diagnosis?

5–4. What alteration in jugular venous pulsations might accompany third-degree heart block?

5–5. Given the following data, calculate the resistance to flow across this stenotic valve.

Aortic pressures (systolic/diastolic) = 150/100 mmHg
Left ventricular pressures (systolic/diastolic) = 150/2 mmHg
Left atrial pressures (systolic/diastolic) = 50/32 mmHg
Heart rate = 60 beats per minute
Stroke volume = 50 mL/beat

a. *3.0 L/min*
b. *6.0 L/min*
c. *100 mmHg*
d. *30 mmHg/L per minute*
e. *10 mmHg/L per minute*

5–6. Your 75-year-old male patient is alert with complaints of general fatigue. His heart rate = 90 beats per minute and arterial pressure = 180/50 mmHg. A diastolic murmur is present. There are no ECG abnormalities identified and mean electrical axis = 10 degrees. Cardiac catheterization indicates that LV pressure = 180/20 mmHg and left atrial pressure = 10/3 mmHg (as peak systolic/end-diastolic). Which of the following is most consistent with these findings?

a. *aortic stenosis*
b. *aortic insufficiency*
c. *mitral stenosis*
d. *mitral insufficiency*
e. *right ventricular hypertrophy*

5–7. Evaluation of your patient's electrocardiogram shows that P waves occur at a regular rate of 90 per minute and QRS complexes occur at a regular rate of 37 per minute. Which of the following is the most likely diagnosis?

a. *supraventricular tachycardia*
b. *first-degree heart block*
c. *second-degree heart block*
d. *third-degree heart block*
e. *bundle branch block*

The Peripheral Vascular System 6

OBJECTIVES

The student understands the basic principles of cardiovascular transport and its role in maintaining homeostasis:

- *Defines convective transport and diffusion and lists the factors that determine the rate of each.*
- *Given data, uses the Fick principle to calculate the rate of removal of a solute from blood as it passes through an organ.*
- *Describes how capillary wall permeability to a solute is related to the size and lipid solubility of the solute.*
- *Lists the factors that influence transcapillary fluid movement and, given data, predicts the direction of transcapillary fluid movement.*
- *Describes the lymphatic vessel system and its role in preventing fluid accumulation in the interstitial space.*

The student understands the physical factors that regulate blood flow through and blood volume in the various components of the vasculature:

- *Given data, calculates the vascular resistances of networks of vessels arranged in parallel and in series.*
- *Describes differences in the blood flow velocity in the various segments and how these differences are related to their total cross-sectional area.*
- *Describes laminar and turbulent flow patterns and the origin of flow sounds in the cardiovascular system.*
- *Identifies the approximate percentage of the total blood volume that is contained in the various vascular segments in the systemic circulation.*
- *Defines peripheral venous pool and central venous pool.*
- *Describes the pressure changes that occur as blood flows through a vascular bed and relates them to the vascular resistance of the various vascular segments.*
- *States how the resistance of each consecutive vascular segment contributes to an organ's overall vascular resistance and, given data, calculates the overall resistance.*
- *Defines total peripheral resistance (systemic vascular resistance) and states the relationship between it and the vascular resistance of each systemic organ.*
- *Defines vascular compliance and states how the volume–pressure curves for arteries and veins differ.*
- *Predicts what will happen to venous volume when venous smooth muscle contracts or when venous transmural pressure increases.*

- *Describes the role of arterial compliance in storing energy for blood circulation.*
- *Describes the auscultation technique for determining arterial systolic and diastolic pressures.*
- *Identifies the physical bases of the Korotkoff sounds.*
- *Indicates the relationship between arterial pressure, cardiac output, and total peripheral resistance and predicts how arterial pressure will be altered when cardiac output and/or total peripheral resistance changes.*
- *Given arterial systolic and diastolic pressures, estimates mean arterial pressure.*
- *Indicates the relationship between pulse pressure, stroke volume, and arterial compliance and predicts how pulse pressure will be changed by changes in stroke volume, or arterial compliance.*
- *Describes how arterial compliance changes with age and how this affects arterial pulse pressure.*

Recall from Chapter 1 that the primary job of the cardiovascular system is to maintain "homeostasis" within a body that contains billions of closely spaced individual cells. Homeostasis implies that each and every cell in the body is continually bathed in a local environment of constant composition that is optimal for cell function. In essence, the peripheral vascular system is a sophisticated irrigation system. Blood flow is continually delivering nutrients to and removing waste products from the local interstitial environment throughout the body each and every minute, as required.

The heart supplies the pumping power required to create flow through the system. Because of the heart's action, pressure at the inlet (the aorta) of the vascular network is higher than that at its outlets (the vena cavae). Everywhere within the vascular system, blood always flows passively "downhill" from higher pressure to lower pressure according to well-known physical rules. Like water flowing downhill, blood seeks to travel along the path of least resistance. Consequently, the peripheral vascular system changes the resistance of its various pathways to direct blood flow to where it is needed.

To appreciate the elegant design of our peripheral vascular system, it is essential to understand the physical constraints within which it must operate. This chapter begins with a description of the mechanisms responsible for the transport of dissolved substances through the vascular system and the movement of these substances and fluid from capillaries to and from the interstitial space. Next, the basic equation for flow through a single vessel ($\dot{Q} = \Delta P/R$, presented in Chapter 1) is applied to the complex network of branching vessels that actually exist in the cardiovascular system. Then, the consequences of the elastic (balloon-like) properties of the large-diameter arteries and veins on overall cardiovascular system operation are considered. Finally, the principles behind the routine clinical measurement of arterial blood pressure are presented along with the conclusions about overall cardiovascular function that can be made from the information.

CARDIOVASCULAR TRANSPORT

The Fick Principle

Substances are carried between organs within the cardiovascular system by the process of *convective transport*, the simple process of being swept along with the flow of the blood in which they are contained. The rate at which a substance (X) is transported by this process depends solely on the concentration of the substance in the blood and the blood flow rate.

$$\text{Transport rate} = \text{flow rate} \times \text{concentration}$$

or

$$\dot{X} = \dot{Q}[\text{X}]$$

where $\dot{X}$ = rate of transport of X (mass/time)
$\dot{Q}$ = blood flow rate (volume/time)
[X] = concentration of X in blood (mass/volume)

It is evident from the preceding equation that only two methods are available for altering the rate at which a substance is carried to an organ: (1) a change in the blood flow rate through the organ or (2) a change in the arterial blood concentration of the substance. The preceding equation might be used, for example, to calculate how much oxygen is carried to a certain skeletal muscle each minute. Note, however, that this calculation would not indicate whether the muscle actually used the oxygen carried to it.

One can extend the convective transport principle to determine a tissue's rate of utilization (or production) of a substance by simultaneously considering the transport rate of the substance to *and from* the tissue. The relationship that results is referred to as the *Fick principle* (Adolf Fick, a German physician, 1829–1901) and may be formally stated as follows:

$$\dot{X}_{\text{tc}} = \dot{Q}([\text{X}]_a - [\text{X}]_v)$$

where $\dot{X}_{\text{tc}}$ = transcapillary efflux rate of X (mass/time)
$\dot{Q}$ = blood flow rate (volume/time)
$[\text{X}]_{a,v}$ = arterial and venous concentrations of X

The Fick principle essentially says that the amount of a substance that goes into an organ in a given period ($\dot{Q}[\text{X}]_a$) minus the amount that comes out ($\dot{Q}[\text{X}]_v$) must equal the tissue utilization rate of that substance. (If the tissue is producing substance X, then the above equation will yield a negative utilization rate.)

Recall that one method for determining cardiac output described in Chapter 3 used the Fick principle to calculate the blood flow rate through the systemic circulation. In that case, the known variables included the systemic tissue oxygen

consumption rate and the concentrations of oxygen in arterial blood and mixed venous blood, and the above equation was rearranged to solve for the blood flow rate ($\dot{Q}$).

Transcapillary Solute Diffusion

Capillaries act as efficient exchange sites where most substances cross the capillary walls simply by *passively diffusing* from regions of high concentration to regions of low concentration.[1] As in any diffusion situation, there are four factors that determine the diffusion rate of a substance between the blood and the interstitial fluid: (1) the concentration difference, (2) the surface area for exchange, (3) the diffusion distance, and (4) the permeability of the capillary wall to the diffusing substance.[2]

Capillary beds allow huge amounts of materials to enter and leave blood because they maximize the area across which exchange can occur while minimizing the distance over which the diffusing substances must travel. Capillaries are extremely fine vessels with a *lumen* (inside) diameter of approximately 5 μm, a wall thickness of approximately 1 μm, and an average length of perhaps 0.5 mm. (For comparison, a human hair is roughly 100 μm in diameter.) Capillaries are distributed in incredible numbers in organs and communicate intimately with all regions of the interstitial space. It is estimated that there are approximately 10^{10} capillaries in the systemic organs with a collective surface area of approximately 100 m^2. That is roughly the area of one player's side of a single tennis court. Recall from Chapter 1 that no cell is more than approximately 10 μm (less than 1/10th the thickness of paper) from a capillary. Diffusion is a tremendously powerful mechanism for material exchange when operating over such a short distance and through such a large area. We are far from being able to duplicate—in an artificial lung or kidney, for example—the favorable geometry for diffusional exchange that exists in our own tissues.

As illustrated in Figure 6–1, the capillary wall itself consists of only a single thickness of endothelial cells joined to form a tube. The ease with which a particular solute crosses the capillary wall is expressed in a parameter called its capillary *permeability*. Permeability takes into account all the factors (diffusion coefficient, diffusion distance, and surface area)—except concentration difference—that affect the rate at which a solute crosses the capillary wall.

Careful experimental studies on how rapidly different substances cross capillary walls indicate that two fundamentally distinct pathways exist for transcapillary exchange. Lipid-soluble substances, such as the gases—oxygen and carbon dioxide,

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[1] Evidence indicates that the capillary endothelial cells can metabolize or produce certain substances. In these special cases, the capillary wall cannot be considered as a passive barrier between the intravascular and interstitial compartments.

[2] These factors are combined in an equation (Fick's first law of diffusion), which describes the rate of diffusion ($\dot{X}_d$) of a substance X across a barrier: $\dot{X}_d = DA\,\Delta[X]/\Delta L$, $\Delta P_1 = \dot{Q}R_1$, where D, A, $\Delta[X]$, and ΔL represent the diffusion coefficient, surface area, concentration difference, and diffusion distance, respectively.

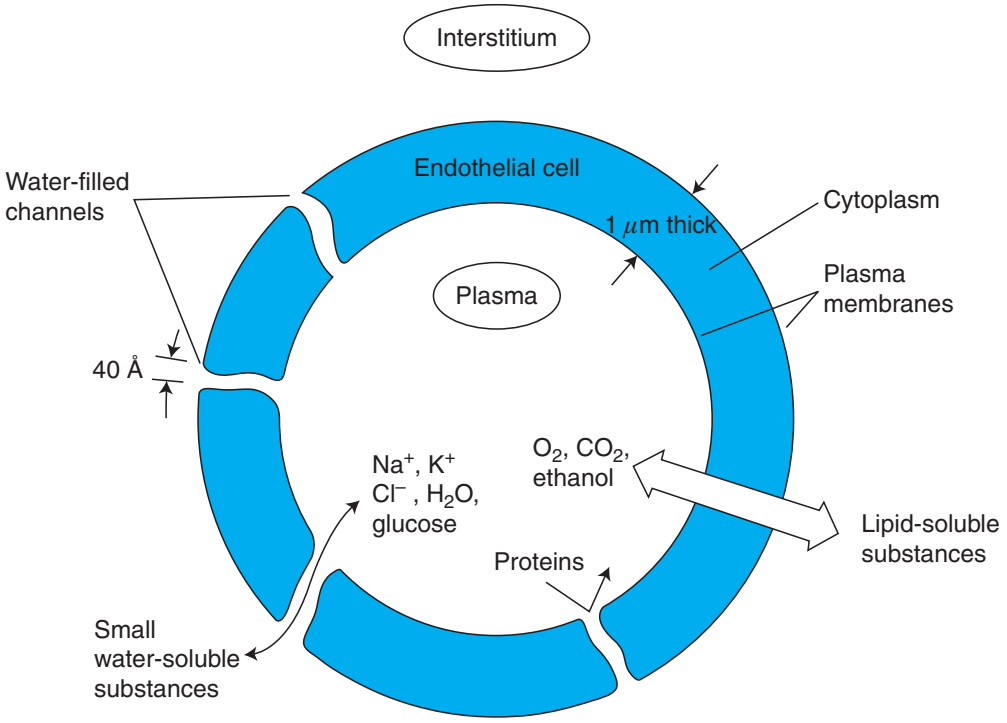

Figure 6–1. Pathways for transcapillary solute diffusion.

cross the capillary wall easily. Because the lipid endothelial cell plasma membranes are not a significant diffusion barrier for lipid-soluble substances, transcapillary movement of these substances can occur through the entire capillary surface area.

The capillary permeability to small polar particles such as sodium and potassium ions is about 10,000-fold less than that for oxygen. Nevertheless, the capillary permeability to small ions is several orders of magnitude higher than the permeability that would be expected if the ions were forced to move through the lipid plasma membranes. It is therefore postulated that capillaries are somehow perforated at intervals with water-filled channels or *pores.*[3] Calculations from diffusion data indicate that the collective cross-sectional area of the pores relative to the total capillary surface area varies greatly between capillaries in different organs. Brain capillaries appear to be very tight (have few pores), whereas capillaries in the kidney and fluid-producing glands are much more leaky. On the average, however, pores constitute only a very small fraction of total capillary surface area—perhaps 0.01%. This area is, nevertheless, sufficient to allow very rapid equilibration of small water-soluble substances between the plasma and interstitial fluids of most organs. Thus, the concentrations of inorganic ions measured in a plasma sample can be taken to indicate their concentrations throughout the entire extracellular space.

[3] Pores, as such, are not readily apparent in electron micrographs of capillary endothelial cells. Most believe the pores are really clefts in the junctions between endothelial cells.

An effective maximum diameter of about 40 Å has been assigned to individual pores because substances with molecular diameters larger than this essentially do not cross capillary walls.[4] Thus, albumin and other proteins in the plasma are normally confined to the plasma space.[5]

Endothelial Cells

In addition to forming capillaries, a layer of endothelial cells lines the entire cardiovascular system—including the heart chambers and valves. Because of their ubiquitous and intimate contact with blood, endothelial cells have evolved to serve many functions other than acting as a barrier to transcapillary solute and water exchange. For example, endothelial cell membranes contain specific enzymes that convert some circulating hormones from inactive to active forms. Endothelial cells are also intimately involved in producing substances that lead to blood clot formation and the stemming of bleeding in the event of tissue injury. Moreover, and as discussed in the next chapter, the endothelial cells lining muscular vessels such as arterioles can produce vasoactive substances that act on the smooth muscle cells that surround them to influence arteriolar diameter.

Transcapillary Fluid Movement

In addition to providing a diffusion pathway for polar molecules, the water-filled channels that traverse capillary walls permit fluid flow through the capillary wall. Net shifts of fluid between the capillary and interstitial compartments are important for a host of physiological functions, including the maintenance of circulating blood volume, intestinal fluid absorption, tissue edema formation, and saliva, sweat, and urine production. Net fluid movement out of capillaries is referred to as *filtration*, and fluid movement into capillaries is called *reabsorption.*

Fluid flows through transcapillary channels in response to pressure differences between the interstitial and intracapillary fluids according to the basic flow equation. However, both *hydrostatic* and *osmotic pressures* influence transcapillary fluid movement. How hydrostatic pressure provides the driving force for causing blood flow along vessels has been discussed previously. The hydrostatic pressure inside capillaries, P_c, is about 25 mmHg and is the driving force that causes blood to return to the right side of the heart from the capillaries of systemic organs. In addition, however, the 25-mmHg hydrostatic intracapillary pressure tends to cause fluid to flow through the transcapillary pores into the interstitium where the hydrostatic pressure (P_i) is near 0 mmHg. Thus, there is normally a large hydrostatic pressure difference favoring fluid filtration across the capillary wall. Our entire plasma volume would

[4] The precise mechanism responsible for this size selectivity remains controversial. It may stem from the actual physical dimensions of the "pores," or it may represent the filtering properties of a fiber matrix that either covers or fills the pores.

[5] In reality, macromolecules do cross capillary walls ever so slowly by a pinocytotic mechanism sometimes referred to as the "large pore" system. Even with this special system, the capillary protein permeability is still about 1000-fold less than either sodium or glucose permeability.

soon be in the interstitium if there were not some counteracting force tending to draw fluid into the capillaries. The balancing force is an osmotic pressure that arises from the fact that plasma has a higher protein concentration than does interstitial fluid.

Recall that water always tends to move from regions of low to regions of high total solute concentration in establishing osmotic equilibrium. Also, recall that osmotic forces are quantitatively expressed in terms of osmotic pressure. The osmotic pressure of a given solution is defined as the hydrostatic pressure necessary to prevent osmotic water movement into the test solution when it is exposed to pure water across a membrane permeable only to water. The total osmotic pressure of a solution is proportional to the total number of solute particles in the solution. Plasma, for example, has a total osmotic pressure of approximately 5000 mmHg—nearly all of which is attributable to dissolved mineral salts such as NaCl and KCl. As discussed, the capillary permeability to small ions is quite high. Their concentrations in plasma and interstitial fluid are very nearly equal and, consequently, they do not affect transcapillary fluid movement.

There is however a small but important difference in the osmotic pressures of plasma and interstitial fluid that is due to the presence of albumin and other proteins in the plasma, which are normally absent from the interstitial fluid. A special term, *oncotic pressure*, is used to denote the portion of a solution's total osmotic pressure that is due to particles that do not move freely across capillaries.[6] Because of the plasma proteins, the oncotic pressure of plasma (π_c) is approximately 25 mmHg. Because of the absence of proteins, the oncotic pressure of the interstitial fluid (π_i) is near 0 mmHg. Thus, there is normally a large osmotic force for fluid reabsorption into capillaries. The forces that influence transcapillary fluid movement are summarized in the left side of Figure 6–2.

The relationship among the factors that influence transcapillary fluid movement, known as the *Starling hypothesis*,[7] can be expressed by the equation:

$$\text{Net filtration rate} = K[(P_c - P_i) - (\pi_c - \pi_i)]$$

where P_c = the hydrostatic pressure of intracapillary fluid
π_c = the oncotic pressure of intracapillary fluid
P_i and π_i = the same quantities for interstitial fluid
K = a constant expressing how readily fluid can move across capillaries (essentially the reciprocal of the resistance to fluid flow through the capillary wall)

Fluid balance within a tissue (the absence of net transcapillary water movement) occurs when the bracketed term in this equation is zero. This equilibrium may be upset by alterations in any of the four pressure terms. The pressure imbalances

[6] This osmotic force is also called "colloid osmotic pressure."
[7] After the British physiologist Ernest Starling (1866–1927).

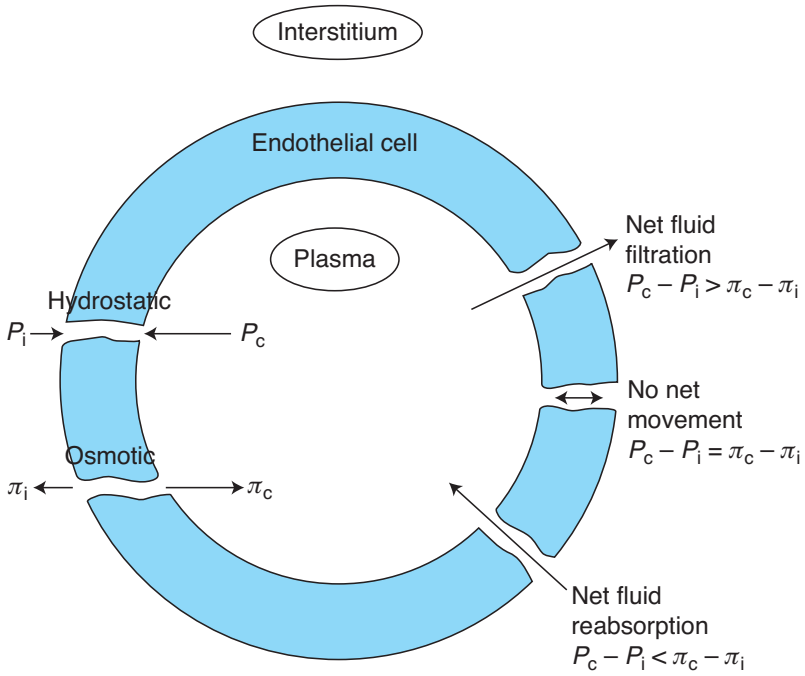

Figure 6–2. Factors influencing transcapillary fluid movement.

that cause capillary filtration and reabsorption are indicated in the right side of Figure 6–2.

In most tissues, rapid net filtration of fluid is abnormal and causes tissue swelling as a result of excess fluid in the interstitial space (edema). For example, a substance called *histamine* is often released in damaged tissue. One of the actions of histamine is to increase capillary permeability to the extent that proteins leak into the interstitium. Net filtration and edema accompany histamine release, in part, because the oncotic pressure difference ($\pi_c - \pi_i$) is reduced below normal.

Transcapillary fluid filtration is not always detrimental. Indeed, fluid-producing organs such as salivary glands and kidneys utilize high intracapillary hydrostatic pressure to produce continual net filtration. Moreover, in certain abnormal situations, such as severe loss of blood volume through hemorrhage, the net fluid reabsorption accompanying diminished intracapillary hydrostatic pressure helps restore the volume of circulating fluid.

Lymphatic System

Despite the extremely low capillary permeability to proteins, these molecules as well as other large particles such as long-chain fatty acids and bacteria find their way into the interstitial space. If such particles are allowed to accumulate in the interstitial space, filtration forces will ultimately exceed reabsorption forces and edema will result. The lymphatic system represents a pathway by which large molecules reenter the circulating blood.

The lymphatic system begins in the tissues with blind-end lymphatic capillaries that are roughly equivalent in size to but less numerous than regular capillaries. These capillaries are very porous and easily collect large particles accompanied by interstitial fluid. This fluid, called *lymph*, moves through the converging lymphatic vessels, is filtered through lymph nodes where bacteria and particulate matter are removed, and reenters the circulatory system near the point where the blood enters the right side of the heart.

Flow of lymph from the tissues toward the entry point into the circulatory system is promoted by two factors: (1) increases in tissue interstitial pressure (due to fluid accumulation or to movement of surrounding tissue) and (2) contractions of the lymphatic vessels themselves. Valves located in these vessels also prevent backward flow.

Roughly 2.5 L of lymphatic fluid enters the cardiovascular system each day. In the steady state, this indicates a total body *net* transcapillary fluid filtration rate of 2.5 L per day. When compared with the total amount of blood that circulates each day (approximately 7000 L), this may seem like an insignificant amount of net capillary fluid leakage. However, lymphatic blockage is a very serious problem and is accompanied by severe swelling. Thus, the lymphatics play a critical role in keeping the interstitial protein concentration low and in removing excess capillary filtrate from the tissues.

BASIC VASCULAR FUNCTION

Resistance and Flow in Networks of Vessels

In Chapter 1, it was asserted that the basic flow equation ($\dot{Q} = \Delta P/R$) may be applied to networks of tubes as well as to individual tubes. The reason is that any network of resistances, however complex, can always be reduced to a single "equivalent" resistor that relates the total flow through the network to the pressure difference across the network. Of course, one way of finding the overall resistance of a network is to perform an experiment to see how much flow goes through it for a given pressure difference between its inlet and outlet. Another approach to finding the overall resistance of a network is to calculate it from knowledge of the resistances of the individual elements in the network and how they are connected. To do so, one needs to apply the parallel and series resistance formulas presented below. These formulas may look familiar because they are analogous to those by which networks of electrical resistances are analyzed with Ohm's law ($I = V/R$).

When vessels with individual resistances $R_1, R_2, \ldots, R_n$ are connected in series, the overall resistance of the network is given by the following formula:

$$R_s = R_1 + R_2 + \cdots + R_n$$

Figure 6–3A shows an example of three vessels connected *in series* between some region where the pressure is P_i and another region with a lower pressure P_o, so that the total pressure difference across the network, ΔP, is equal to $P_i - P_o$. By the

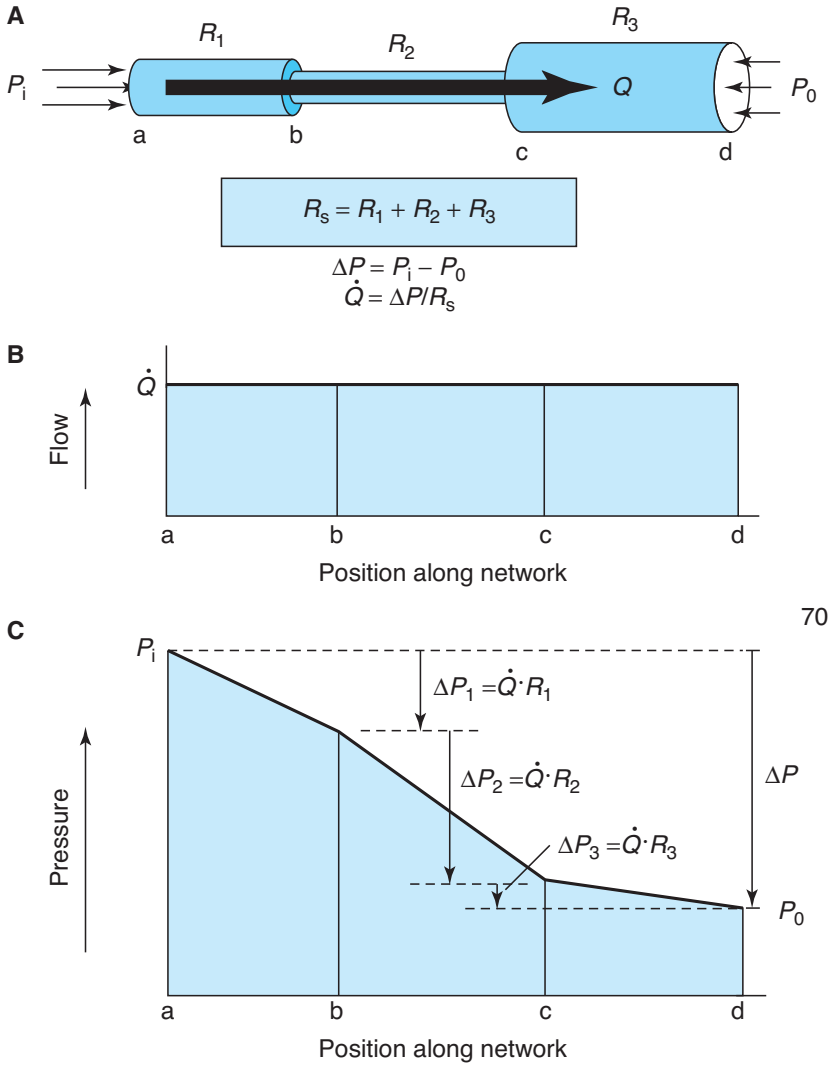

Figure 6–3. Series resistance network.

series resistance equation, the total resistance across this network (R_s) is equal to $R_1 + R_2 + R_3$. By the basic flow equation, the flow through the network ($\dot{Q}$) is equal to $\Delta P/R_s$. It should be intuitively obvious that $\dot{Q}$ is the flow (volume/time) through each of the elements in the series as indicated in Figure 6–3B. (Fluid particles may move with different velocities, distance/time, in different elements of a series network, but the volume that passes through each element in a minute must be identical.)

As shown in Figure 6–3C, a portion of the total pressure drop across the network occurs within each element of the series. The pressure drop across any element in the series can be calculated by applying the basic flow equation to that element, for example, $\Delta P_1 = \dot{Q}R_1$. Note that the largest portion of the overall pressure drop will occur across the element in the series with the largest resistance to flow (R_2 in Figure 6–3).

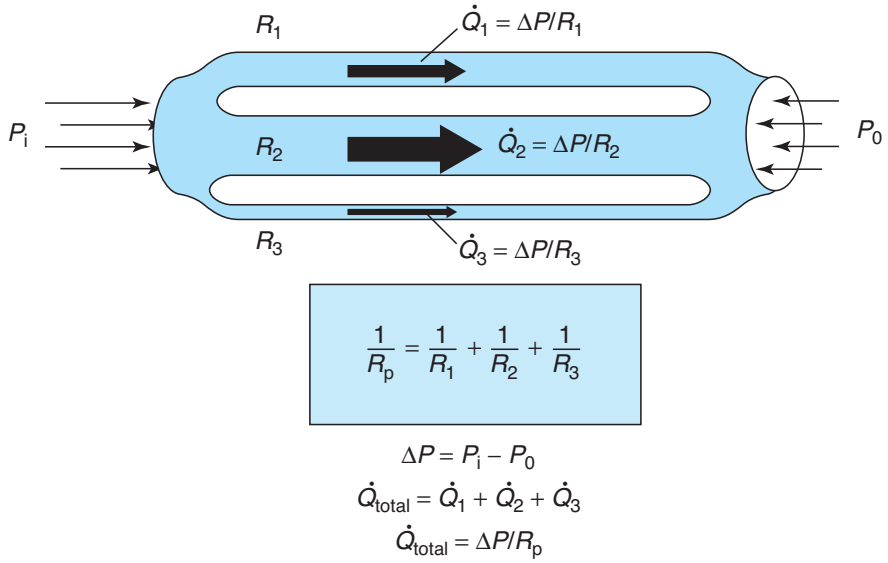

Figure 6–4. Parallel resistance network.

As indicated in Figure 6–4, when several tubes with individual resistances R_1, $R_2, \ldots, R_n$ are brought together to form a *parallel* network of vessels, one can calculate a single overall resistance for the parallel network R_p according to the following formula:

$$\frac{1}{R_p} = \frac{1}{R_1} + \frac{1}{R_2} + \cdots + \frac{1}{R_n}$$

The total flow through a parallel network is determined by $\Delta P/R_p$. As the preceding equation implies, the overall resistance of any parallel network will always be less than that of any of the elements in the network. (In the special case where the individual elements that form the network have identical resistances R_x, the overall resistance of the network is equal to the resistance of an individual element divided by the number of n of parallel elements in the network: $R_p = R_x/n$.) In general, the more parallel elements that occur in the network, the lower the overall resistance of the network. Thus, for example, a capillary bed that consists of many individual capillary vessels in parallel can have a very low overall resistance to flow even though the resistance of a single capillary is relatively high.

As indicated in Figure 6–4, the basic flow equation may be applied to any single element in the network or to the network as a whole. For example, the flow through only the first element of the network ($\dot{Q}_1$) is given by $\dot{Q}_1 = \Delta P/R_1$, whereas the flow through the entire parallel network is given by $\dot{Q}_p = \Delta P/R_p$.

The series and parallel resistance equations may be used alternately to analyze resistance networks of great complexity. For example, any or all the series resistances shown in Figure 6–3 could actually represent the calculated overall resistance of many vessels arranged in parallel.

Peripheral Blood Flow Velocities

It is important to make the distinction between blood flow (volume/time) and blood flow velocity (distance/time) in the peripheral vascular system. Consider the analogy of a stream whose water moves with greater velocity through shallow rapids than it does through an adjacent deep pool. The volume of water passing through the pool in a day (volume/time = flow), however, must equal that passing through the rapids in the same day. In such a series arrangement, the flow is the same at all points along the channel but the flow velocity varies inversely with the local cross-sectional area. The situation is the same in the peripheral vasculature, where blood flows most rapidly in the region with the smallest total cross-sectional area (the aorta) and most slowly in the region with the largest total cross-sectional area (the capillary beds). Regardless of the differences in velocity, when the cardiac output (flow into the aorta) is 5 L/min, the flow through the systemic capillaries (or arterioles, or venules) is also 5 L/min. The changes in flow velocity that occur as blood passes through the peripheral vascular system are shown in the top trace in Figure 6–5. These are a

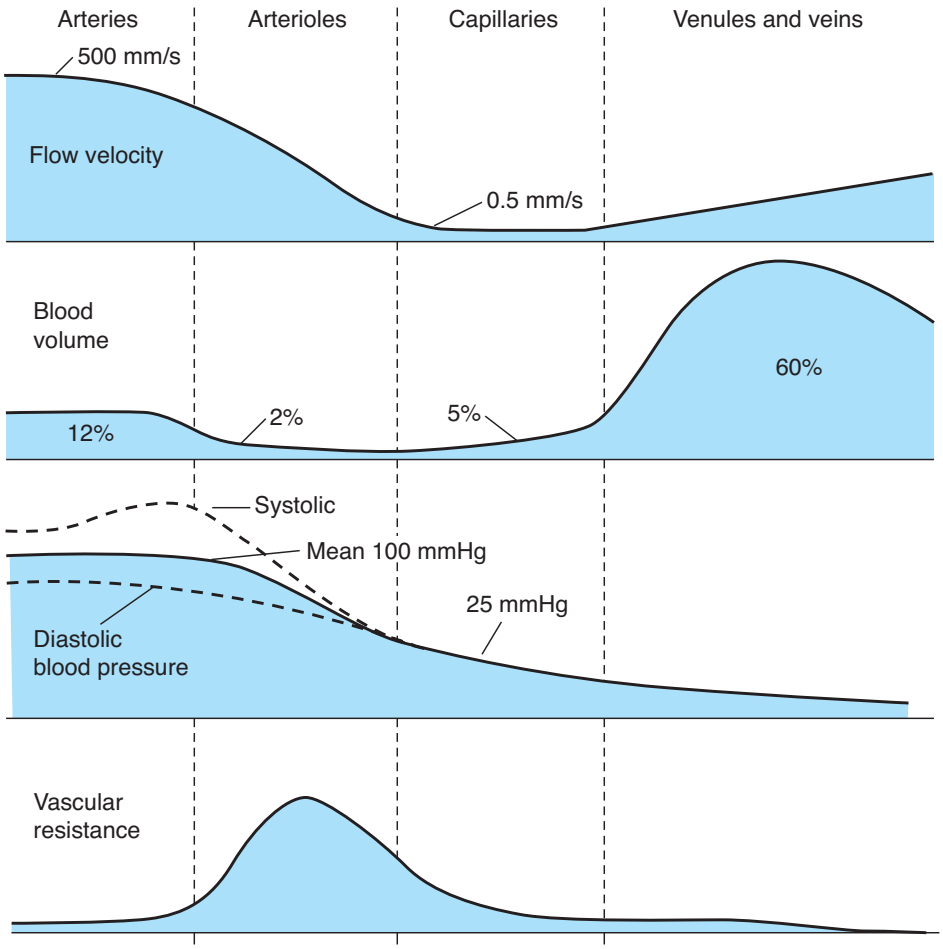

Figure 6–5. Flow velocities, blood volumes, blood pressures, and vascular resistances in the peripheral vasculature from aorta to right atrium.

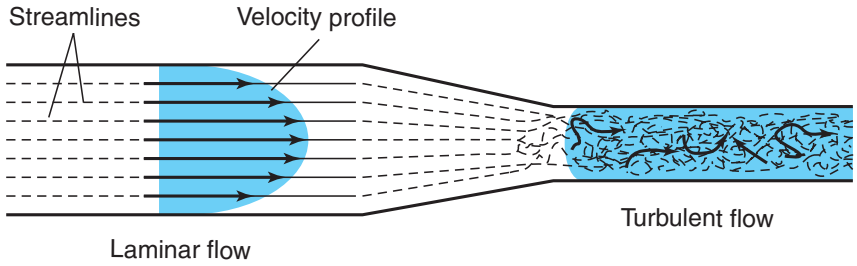

Figure 6–6. Laminar and turbulent flow patterns.

direct consequence of the variations in total cross-sectional area that were indicated in Figure 1–8.

5 The important consequence of this slow flow through the capillaries is that it allows sufficient time for adequate solute and fluid exchange between the vascular and interstitial compartments.

Blood normally flows through all vessels in the cardiovascular system in an orderly streamlined manner called *laminar flow.* With laminar flow, there is a parabolic velocity profile across the tube as shown in the left side of Figure 6–6. Velocity is fastest along the central axis of the tube and falls to zero at the wall. The concentric layers of fluid with different velocities slip smoothly over one another. Little mixing occurs between fluid layers so that individual particles move in straight streamlines parallel to the axis of the flow. Laminar flow is very efficient because little energy is wasted on anything but producing forward fluid motion.

Because blood is a viscous fluid, its movement through a vessel exerts a *shear stress* on the walls of the vessel. This is a force that wants to drag the inside surface (the endothelial cell layer) of the vessel along with the flow. With laminar flow, the shear stress on the wall of a vessel is proportional to the rate of flow through it.[8] The endothelial cells that line a vessel are able to sense (and possibly respond to) changes in the rate of blood flow through the vessel by detecting changes in the shear stress on them. Shear stress may also be an important factor in certain pathological situations. For example, atherosclerotic plaques tend to form preferentially near branches off large arteries where, for complex hemodynamic reasons beyond the scope of this text, high shear stresses exist.

6 When blood is forced to move with too high a velocity through a narrow opening, the normal laminar flow pattern may break down into the *turbulent flow* pattern shown in the right side of Figure 6–6.[9] With turbulent flow, there is much internal mixing and friction. When the flow within a vessel is turbulent, the vessel's resistance to flow is significantly higher than that predicted from the Poiseuille equation given in Chapter 1. Turbulent flow also generates sound,

[8] With pure laminar flow of a homogeneous fluid in a uniform smooth round tube, the shear stress (force/surface area σ_s) on the wall is a function of fluid viscosity (η), flow (volume/time, $\dot{Q}$), and the inside radius of the tube (r_i) as follows: $\sigma_s = 4\eta\dot{Q}/\pi r_i^3$.

[9] Turbulence occurs when a parameter called the *Reynolds number* (R_e) exceeds a value of 2000. $R_e = 4\rho Q/\pi\eta d_i$, where ρ = fluid density, $\dot{Q}$ = flow (volume/time), η = fluid viscosity, and d_i = inside diameter.

which can be heard with the aid of a stethoscope. Cardiac murmurs, for example, are manifestations of turbulent flow patterns generated by cardiac valve abnormalities. Detection of sounds from peripheral arteries (bruits) is abnormal and usually indicates significant pathological reduction of a large vessel's cross-sectional area.

Peripheral Blood Volumes

The second trace in Figure 6–5 shows the approximate percentage of the total circulating blood volume that is contained in the different vascular regions of the systemic organs at any instant of time. (Approximately 20% of the total volume is contained in the pulmonary system and the heart chambers and is not accounted for in this figure.)

Note that most of the circulating blood is contained within the veins of the systemic organs. This diffuse but large blood reservoir is often referred to as the *peripheral venous pool.* A second but smaller reservoir of venous blood, called the *central venous pool*, is contained in the great veins of the thorax and the right atrium. When peripheral veins constrict, blood is displaced from the peripheral venous pool and enters the central pool. An increase in the central venous volume, and thus pressure, enhances cardiac filling, which in turn augments stroke volume according to the Frank–Starling law of the heart. This is an extremely important mechanism of cardiovascular regulation and is discussed in greater detail in Chapter 8.

Peripheral Blood Pressures

Blood pressure decreases in the consecutive segments with the pattern shown in the third trace in Figure 6–5. Recall from Figure 3–1 that aortic pressure fluctuates between a systolic value and a diastolic value with each heartbeat, and the same is true throughout the arterial system. (For complex hemodynamic reasons, the difference between systolic and diastolic pressures actually increases with the distance from the heart in the large arteries.[10]) The average pressure in the arch of the aorta, however, is about 100 mmHg, and this *mean arterial pressure* falls by only a small amount within the arterial system.

A large pressure drop occurs in the arterioles, where the pulsatile nature of the pressure also nearly disappears. The average capillary pressure is approximately 25 mmHg. Pressure continues to decrease in the venules and veins as blood

[10] A rigorous analysis of the dynamics of pulsatile fluid flow in tapered, branching, elastic tubes is required to explain such behavior. Pressure does not increase simultaneously throughout the arterial system with the onset of cardiac ejection. Rather, the pressure increase begins at the root of the aorta and travels outward from there. When this rapidly moving pressure wave encounters obstacles such as vessel bifurcations, reflected waves are generated, which travel back toward the heart. These reflected waves can summate with and reinforce the oncoming wave in a manner somewhat analogous to the progressive cresting of surface waves as they impinge on a beach.

returns to the right heart. The central venous pressure (which is the filling pressure for the right side of the heart) is normally very close to 0 mmHg.

Peripheral Vascular Resistances

The bottom trace in Figure 6–5 indicates the relative resistance to flow that exists in each of the consecutive vascular regions. Recall from Chapter 1 that resistance, pressure difference, and flow are related by the basic flow equation $\dot{Q} = \Delta P/R$. Because the flow ($\dot{Q}$) must be the same through each of the consecutive regions indicated in Figure 6–5, the pressure drop that occurs across each of these regions is a direct reflection of the resistance to flow within that region (see Figure 6–3). Thus, the large pressure drop occurring as blood moves through arterioles indicates that arterioles present a large resistance to flow. The mean pressure drops little in arteries because they have little resistance to flow. Similarly, the modest pressure drop that exists across capillaries is a reflection of the fact that the capillary bed has a modest resistance to flow when compared with that of the arteriolar bed. (Recall from Figure 6–4 that the capillary bed can have a low resistance to flow because it is a parallel network of a very large number of individual capillaries.)

Blood flow through many individual organs can vary over a 10-fold or greater range. Because mean arterial pressure is a relatively stable cardiovascular variable, large changes in an organ's blood flow are achieved by changes in its overall vascular resistance to blood flow. The consecutive vascular segments are arranged in series within an organ, and the overall vascular resistance of the organ must equal the sum of the resistances of its consecutive vascular segments:

$$R_{\text{organ}} = R_{\text{arteries}} + R_{\text{arterioles}} + R_{\text{capillaries}} + R_{\text{venules}} + R_{\text{veins}}$$

Because arterioles have such a large vascular resistance in comparison to the other vascular segments, the overall vascular resistance of any organ is determined to a very large extent by the resistance of its arterioles. Arteriolar resistance is, of course, strongly influenced by arteriolar radius (R is proportional to $1/r^4$). Thus, the blood flow through an organ is primarily regulated by adjustments in the internal diameter of arterioles caused by contraction or relaxation of their muscular arteriolar walls.

When the arterioles of an organ change diameter, not only does the flow to the organ change but the manner in which the pressures drop within the organ is also modified. The effects of arteriolar dilation and constriction on the pressure profile within a vascular bed are illustrated in Figure 6–7. Arteriolar constriction causes a greater pressure drop across the arterioles, and this tends to increase the arterial pressure while it decreases the pressure in capillaries and veins. (The arterioles function somewhat like a dam; closing a dam's gates decreases the flow while increasing the level of the reservoir behind it and decreasing the level of its outflow stream.) Conversely, increased organ blood flow caused by arteriolar dilation is accompanied by decreased arterial pressure and increased capillary pressure. Because of the changes in capillary hydrostatic pressure, arteriolar constriction

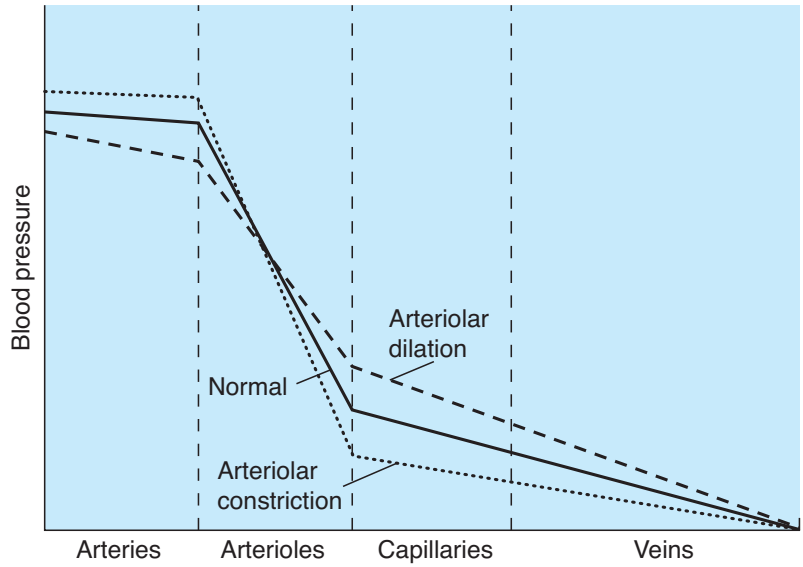

Figure 6–7. Effect of changes in arteriolar resistance on vascular pressures.

tends to cause transcapillary fluid reabsorption whereas arteriolar dilation tends to promote transcapillary fluid filtration.

Total Peripheral Resistance

The overall resistance to flow through the entire systemic circulation is called the *total peripheral resistance.* Because the systemic organs are generally arranged in parallel (Figure 1–2), the vascular resistance of each organ contributes to the total peripheral resistance according to the following parallel resistance equation:

$$\frac{1}{\text{TPR}} = \frac{1}{R_{\text{organ}_1}} + \frac{1}{R_{\text{organ}_2}} + \cdots + \frac{1}{R_{\text{organ}_n}}$$

As discussed later in this chapter, the total peripheral resistance is an important determinant of arterial blood pressure.

Elastic Properties of Arteries and Veins

As indicated earlier, arteries and veins contribute only a small portion to the overall resistance to flow through a vascular bed. Therefore, changes in their diameters have no significant effect on the blood flow through systemic organs. The elastic behavior of arteries and veins is however very important to overall cardiovascular function because they can act as reservoirs and substantial amounts of blood can be stored in them. Arteries or veins behave more like balloons with one pressure throughout rather than as resistive pipes with a flow-related pressure difference from end to end. Thus, think of an "arterial compartment" and a "venous compartment," each with

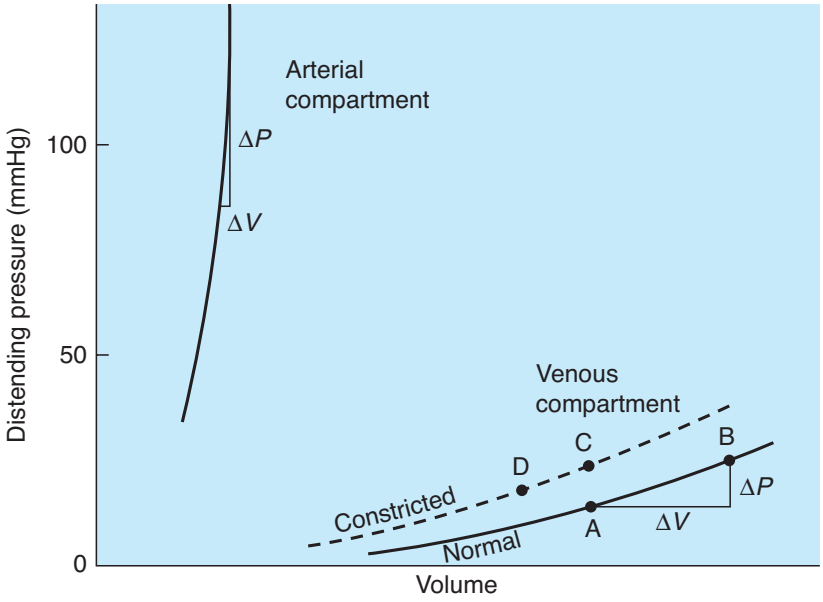

Figure 6–8. Volume–pressure curves of arterial and venous compartments.

an internal pressure that is related to the volume of blood within it at any instant and how elastic (stretchy) its walls are.

The elastic nature of a vascular region is characterized by a parameter called *compliance* (C) that describes how much its volume changes (ΔV) in response to a given change in distending pressure (ΔP): $C = \Delta V/\Delta P$. Distending pressure is the difference between the internal and external pressures on the vascular walls.

The volume–pressure curves for the systemic arterial and venous compartments are shown in Figure 6–8. It is immediately apparent from the disparate slopes of the curves in this figure that the elastic properties of arteries and veins are very different. For the arterial compartment, the $\Delta V/\Delta P$ measured near a normal operating pressure of 100 mmHg indicates a compliance of about 2 mL/mmHg. By contrast, the venous pool has a compliance of over 100 mL/mmHg near its normal operating pressure of 5 to 10 mmHg.

Because veins are so compliant, even small changes in peripheral venous pressure can cause a significant amount of the circulating blood volume to shift into or out of the peripheral venous pool. Standing upright, for example, increases venous pressure in the lower extremities and promotes blood accumulation (pooling) in these vessels as might be represented by a shift from point A to point B in Figure 6–8. Fortunately, this process can be counteracted by active venous constriction. The dashed line in Figure 6–8 shows the venous volume–pressure relationship that exists when veins are constricted by activation of venous smooth muscle. In constricted veins, volume may be normal (point C) or even below normal (point D) despite higher than normal venous pressure. Peripheral venous constriction tends to increase peripheral venous pressure and shift blood out of the peripheral venous compartment.

The elasticity of arteries allows them to act as a reservoir on a beat-to-beat basis. Arteries play an important role in converting the pulsatile flow output of the heart into a steady flow through the vascular beds of systemic organs. During the early rapid phase of cardiac ejection, the arterial volume increases because blood is entering the aorta more rapidly than it is passing into systemic arterioles. Thus, part of the work the heart does in ejecting blood goes to stretching the elastic walls of arteries. Toward the end of systole and throughout diastole, arterial volume decreases because the flow out of arteries exceeds flow into the aorta. Previously stretched arterial walls recoil to shorter lengths and in the process give up their stored potential energy. This reconverted energy is what actually does the work of propelling blood through the peripheral vascular beds during diastole. If the arteries were rigid tubes that could not store energy by expanding elastically, arterial pressure would fall immediately to zero with the termination of each cardiac ejection.

MEASUREMENT OF ARTERIAL PRESSURE

Recall that the systemic arterial pressure fluctuates with each heart cycle between a diastolic value (P_D) and a higher systolic value (P_S). Obtaining estimates of an individual's systolic and diastolic pressures is one of the most routine diagnostic techniques available to the physician. The basic principles of the *auscultation* technique used to measure blood pressure are described here with the aid of Figure 6–9.

An inflatable cuff is wrapped around the upper arm, and a device, such as a mercury manometer, is attached to monitor the pressure within the cuff. The cuff is initially inflated with air to a pressure (≃175 to 200 mmHg) that is well above

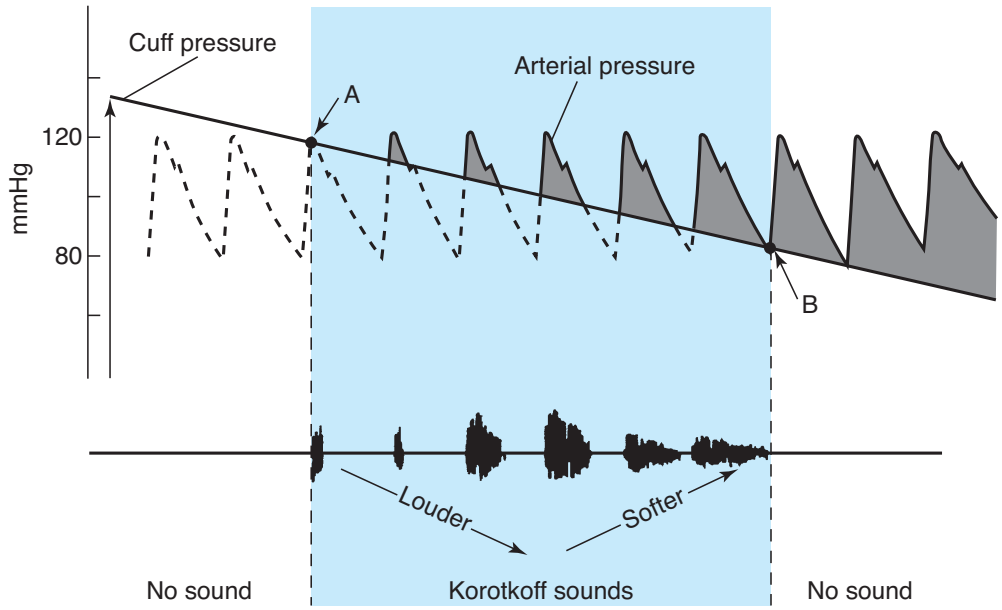

Figure 6–9. Blood pressure measurement by auscultation. Point **A** indicates systolic pressure and point **B** indicates diastolic pressure.

normal systolic values. This pressure is transmitted from the flexible cuff into the upper arm tissues, where it causes all blood vessels to collapse. No blood flows into (or out of) the forearm as long as the cuff pressure is higher than the systolic arterial pressure. After the initial inflation, air is allowed to gradually "bleed" from the cuff so that the pressure within it falls slowly and steadily through the range of arterial pressure fluctuations. The moment the cuff pressure falls below the peak systolic arterial pressure, some blood is able to pass through the arteries beneath the cuff during the systolic phase of the cycle. This flow is intermittent and occurs only over a brief period of each heart cycle. Moreover, because it occurs through partially collapsed vessels beneath the cuff, the flow is turbulent rather than laminar. The intermittent periods of flow beneath the cuff produce tapping sounds, which can be detected with a stethoscope placed over the radial artery at the elbow. As indicated in Figure 6–9, sounds of varying character, known collectively as *Korotkoff sounds*, are heard whenever the cuff pressure is between the systolic and diastolic aortic pressures.

Because there is no blood flow and thus no sound when cuff pressure is higher than systolic arterial pressure, *the highest cuff pressure at which tapping sounds are heard is taken as the systolic arterial pressure.* When the cuff pressure falls below the diastolic pressure, blood flows through the vessels beneath the cuff without periodic interruption and again no sound is detected over the radial artery. *The cuff pressure at which the sounds become muffled or disappear is taken as the diastolic arterial pressure.* The Korotkoff sounds are more distinct when the cuff pressure is near the systolic arterial pressure than when it is near the diastolic pressure. Thus, consistency in determining diastolic pressure by auscultation requires concentration and experience.

DETERMINANTS OF ARTERIAL PRESSURE

Mean Arterial Pressure

Mean arterial pressure is a critically important cardiovascular variable because it is the average effective pressure that drives blood through the systemic organs. One of the most fundamental equations of cardiovascular physiology is that which indicates how mean arterial pressure ($\bar{P}_A$) is related to cardiac output (CO) and total peripheral resistance (TPR):

$$\bar{P}_A = CO \times TPR$$

This equation is simply a rearrangement of the basic flow equation ($\dot{Q} = \Delta P/R$) applied to the entire systemic circulation with the single assumption that central venous pressure is approximately zero so that $\Delta P = \bar{P}_A$. Note that mean arterial pressure is influenced both by the heart (via cardiac output) and by the peripheral vasculature (via total peripheral resistance). *All changes in mean arterial pressure result from changes in either cardiac output or total peripheral resistance.*

Calculating the true value of mean arterial pressure requires mathematically averaging the arterial pressure waveform over one or more complete heart cycles. Most often, however, we know from auscultation only the systolic and diastolic pressures, yet wish to make some estimate of the mean arterial pressure. Mean arterial pressure necessarily falls between the systolic and diastolic pressures. A useful rule of thumb is that mean arterial pressure ($\bar{P}_A$) is approximately equal to diastolic pressure (P_D) plus one-third of the difference between systolic and diastolic pressures ($P_S - P_D$):

$$\bar{P}_A \simeq P_D + \frac{1}{3}(P_S - P_D)$$

Arterial Pulse Pressure

The *arterial pulse pressure* (P_p) is defined simply as systolic pressure minus diastolic pressure:

$$P_p = P_S - P_D$$

To be able to use pulse pressure to deduce something about how the cardiovascular system is operating, one must do more than just define it. It is important to understand what *determines* pulse pressure; that is, what causes it to be what it is and what can cause it to change. In a previous section of this chapter, there was a brief discussion about how, as a consequence of the compliance of the arterial vessels, arterial pressure increases as arterial blood volume is expanded during cardiac ejection. The magnitude of the pressure increase (ΔP) caused by an increase in arterial volume depends on how large the volume change (ΔV) is and on how compliant (C_A) the arterial compartment is: $\Delta P = \Delta V/C_A$. If, for the moment, the fact that some blood leaves the arterial compartment *during* cardiac ejection is neglected, then the increase in arterial volume during each heartbeat is equal to the stroke volume (SV).

Thus, pulse pressure is, to a first approximation, equal to stroke volume divided by arterial compliance:

$$P_p \simeq \frac{SV}{C_A}$$

Arterial pulse pressure is approximately 40 mmHg in a normal resting young adult because stroke volume is approximately 80 mL and arterial compliance is approximately 2 mL/mmHg. Pulse pressure tends to increase with age in adults because of a decrease in arterial compliance ("hardening of the arteries"). Arterial volume–pressure curves for a 20-year-old and a 70-year-old are shown in Figure 6–10. The decrease in arterial compliance with age is indicated by the steeper curve for the 70-year-old (more ΔP for a given ΔV) than for the 20-year-old. Thus, a 70-year-old will necessarily have a larger pulse pressure for a given stroke volume than a 20-year-old. As indicated in Figure 6–10, the decrease in arterial compliance

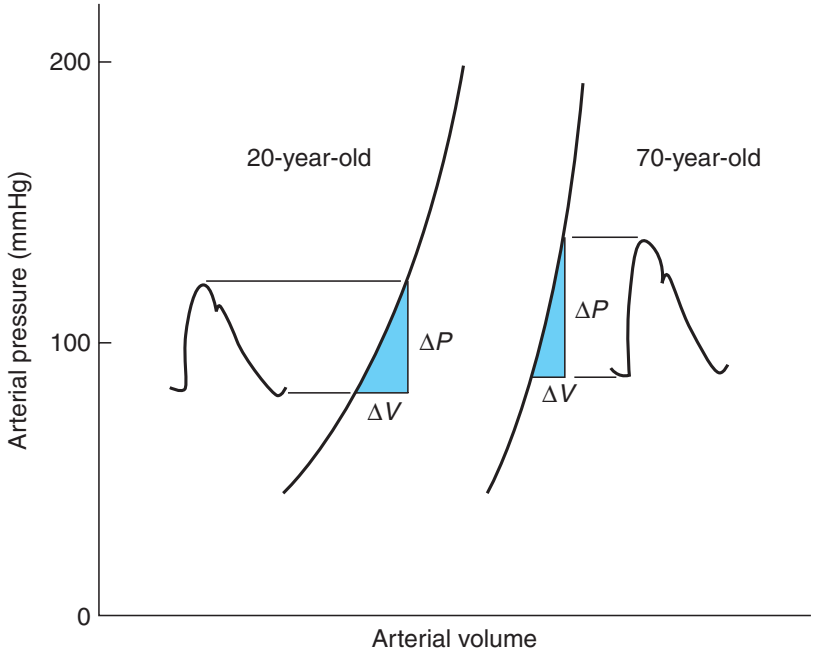

Figure 6–10. Observed effects of aging on the pressure-volume relationship of arteries. Also indicated are normal age-related changes in stroke volume (ΔV) and arterial pressures.

is sufficient to cause increased pulse pressure even though stroke volume tends to decrease with age.

Figure 6–10 also illustrates the fact that arterial blood volume and mean arterial pressure tend to increase with age. The increase in *mean* arterial pressure is *not* caused by the decreased arterial compliance because compliance changes do not directly influence either cardiac output or total peripheral resistance, which are the *sole determinants* of $\overline{P}_A$. Mean arterial pressure tends to increase with age because of an age-dependent increase in total peripheral resistance, which is controlled primarily by arterioles, not arteries.

Arterial compliance also decreases with increasing mean arterial pressure as evidenced by the curvature of the volume–pressure relationships shown in Figure 6–10. Otherwise, arterial compliance is a relatively stable parameter. Thus, most acute changes in arterial pulse pressure are the result of changes in stroke volume.

The preceding equation for pulse pressure is a much-simplified description of some very complex hemodynamic processes. It correctly identifies stroke volume and arterial compliance as the major determinants of arterial pulse pressure but is based on the assumption that no blood leaves the aorta during systolic ejection. Obviously, this is not strictly correct. Furthermore, close examination of Figure 3–1 will reveal that peak systolic pressure is reached even before cardiac ejection is complete. It is therefore not surprising that several factors other than arterial compliance and stroke volume have minor influences on pulse pressure. For example, because the arteries have viscous properties as well as elastic characteristics, faster cardiac ejection

caused by increased myocardial contractility tends to increase pulse pressure somewhat even if stroke volume remains constant. Changes in total peripheral resistance, however, have *little or no effect on pulse pressure*, because a change in total peripheral resistance causes parallel changes in both systolic and diastolic pressures.

A common misconception in cardiovascular physiology is that the systolic pressure alone or the diastolic pressure alone indicates the status of a specific cardiovascular variable. For example, high diastolic pressure is often taken to indicate high total peripheral resistance. This is not necessarily so because high diastolic pressure can exist with normal (or even reduced) total peripheral resistance if the heart rate and cardiac output are high. Both systolic and diastolic pressures are influenced by the heart rate, stroke volume, total peripheral resistance, and C_A.[11] The student should not attempt to interpret systolic and diastolic pressure values independently. Interpretation is much more straightforward when the focus is on mean arterial pressure ($\overline{P}_A = CO \times TPR$) and arterial pulse pressure ($P_p \simeq SV/C_A$). (See study question 6–14.)

KEY CONCEPTS

1. *Within the cardiovascular system, convection is used to transport substances between capillary beds and diffusion is used to transport substances between blood and tissue.*
2. *Water may move out of (filtration) or into (reabsorption) capillaries depending on the net balance of hydrostatic and osmotic forces across capillary walls.*
3. *Plasma proteins are responsible for the major osmotic force across capillary walls.*
4. *Lymphatic vessels serve to remove excess filtrate from tissues and keep interstitial protein concentration low.*
5. *The velocity of blood flow is inversely proportional to the total cross-sectional area of the vascular segment and is slowest in capillaries.*

[11] The equations presented in this and preceding chapters can be solved simultaneously to show that

$$P_S \simeq SV \times HR \times TPR + \frac{2}{3}\frac{SV}{C_A}$$

$$P_D \simeq SV \times HR \times TPR - \frac{1}{3}\frac{SV}{C_A}$$

6. *Turbulent blood flow is abnormal and makes noise (murmurs and bruits).*

7. *Veins contain most of the total blood volume.*

8. *Arterioles contribute most to the resistance to flow through organs.*

9. *Arteriolar constriction tends to reduce flow through an organ, reduce capillary hydrostatic pressure, and promote transcapillary fluid reabsorption within the organ.*

10. *Venous constriction is important for cardiac filling and the ability to cope with blood loss.*

11. *Because arteries are elastic, the intermittent flow from the heart is converted to continuous flow through capillaries.*

12. *Mean systemic arterial pressure is determined by the product of cardiac output and total peripheral resistance.*

13. *Changes in arterial pulse pressure reflect changes in stroke volume and/or the compliance of the arterial space.*

STUDY QUESTIONS

6–1. Determine the rate of glucose uptake by an exercising skeletal muscle ($\dot{G}_m$) from the following data:

Arterial blood glucose concentration, $[G]_a = 50$ mg/100 mL
Muscle venous blood glucose concentration, $[G]_V = 30$ mg/100 mL
Blood flow, $\dot{Q} = 60$ mL/min

6–2. Determine the direction of transcapillary fluid movement ($\dot{F}$) within a tissue, given the following data:

Capillary hydrostatic pressure, $P_c = 28$ mmHg
Plasma oncotic pressure, $\pi_c = 24$ mmHg
Tissue hydrostatic pressure, $P_i = -4$ mmHg
Tissue oncotic pressure, $\pi_i = 0$ mmHg

6–3. Which of the following conditions favor edema formation?

a. *lymphatic blockage*
b. *thrombophlebitis (venous clot)*

c. *decreased plasma protein concentration*
d. *greatly increased capillary pore size*

6–4. *Assume that three vessels with identical dimensions are combined into a network of one vessel followed by a parallel combination of the other two and that a pressure (P_i) is applied to the inlet of the first vessel while a lower pressure (P_o) exists at the outlet of the parallel pair.*
a. *Find the overall resistance of the network (R_n) if the resistance of each vessel is equal to R_e.*
b. *Is the pressure (P_j) at the central junction of the network closer to P_i or P_o?*
c. *Use the basic flow equation to derive an equation that relates the pressure drop across the input vessel ($P_i - P_j$) to the total pressure drop across the network ($P_i - P_o$).*

6–5. *Given the following data, calculate an individual's total peripheral resistance (TPR):*

Mean arterial pressure, $\bar{P}_A = 100$ mmHg
Central venous pressure, $P_{CV} = 0$ mmHg
Cardiac output, CO = 6 L/min

6–6. *The TPR to blood flow is greater than the resistance to flow through any of the systemic organs. True or false?*

6–7. *Other factors being equal, a decrease in the renal vascular resistance will increase TPR. True or false?*

6–8. *Constriction of arterioles in an organ promotes reabsorption of interstitial fluid from that organ. True or false?*

6–9. *Chronic elevation of arterial pressure requires that either cardiac output or TPR (or both) be chronically elevated. True or false?*

6–10. *Whenever cardiac output is increased, mean arterial pressure must also be increased. True or false?*

6–11. *Acute increases in arterial pulse pressure usually result from increases in stroke volume. True or false?*

6–12. *An increase in TPR increases diastolic pressure (P_D) more than systolic pressure (P_S). True or false?*

6–13. *Estimate the mean arterial pressure when the measured arterial pressure is 110/70 mmHg.*

6–14. *At rest the patient has a pulse rate of 70 beats per minute and an arterial blood pressure of 119/80 mmHg. During exercise on a treadmill, pulse rate is 140 beats per minute and blood pressure is 135/90 mmHg. Use this information to estimate the exercise-related changes in the following variables:*
a. *stroke volume*
b. *cardiac output*
c. *total peripheral resistance (TPR)*

6–15. *Which of the following is consistent with a normal mean arterial pressure but an abnormally high arterial pulse pressure?*
a. *low stroke volume*
b. *high heart rate*
c. *decreased total peripheral resistance*
d. *increased arterial stiffness*
e. *aortic valve stenosis*

6–16. Which of the following substances is likely to move most easily across a skeletal muscle capillary wall?

a. potassium
b. glucose
c. oxygen
d. water
e. albumin

6–17. In which of the following vessels do red cells move with the fastest speed (distance/time)?

a. arteries
b. arterioles
c. capillaries
d. venules
e. veins