Cardiac Physiology

INTRODUCTION

Within about three weeks after conception, the heart of the developing embryo starts to function. Scientists believe it is the first organ to become functional. At this time the human embryo is only a few millimeters long. The circulatory system has three basic components:

1. The heart serves as the pump that imparts pressure to the blood to establish the pressure gradient needed for blood to flow to the tissues. Like all liquids, blood flows down a pressure gradient from an area of higher pressure to an area of lower pressure. This chapter focuses on cardiac physiology (cardia means "heart").

2. The blood vessels serve as the passageways through which blood is directed and distributed from the heart to all parts of the body and subsequently returned to the heart.

3. Blood is the transport medium within which materials being transported long distances in the body (such as O_2, CO_2, nutrients, wastes, electrolytes, and hormones) are dissolved or suspended.

Blood travels continuously through the circulatory system to and from the heart through two separate vascular (blood vessel) loops, both originating and terminating at the heart (Figure 9-1). The pulmonary circulation consists of a closed loop of vessels carrying blood between the heart and lungs (pulmo means "lung). The systemic circulation is a circuit of vessels carrying blood between the heart and other body systems.

ANATOMY OF THE HEART

The heart is a hollow, muscular organ about the size of a clenched fist. It lies in the thoracic (chest) cavity about midline between the sternum (breastbone) anteriorly and the vertebrae (backbone) posteriorly. Place your hand over your heart. People usually put their hand on the left side of the chest, even though the heart is actually in the middle of the chest. The heart has a broad base at the top and tapers to a pointed tip, the apex, at the bottom. It is situated at an angle under the sternum so that its base lies predominantly to the right and the apex to the left of the sternum.

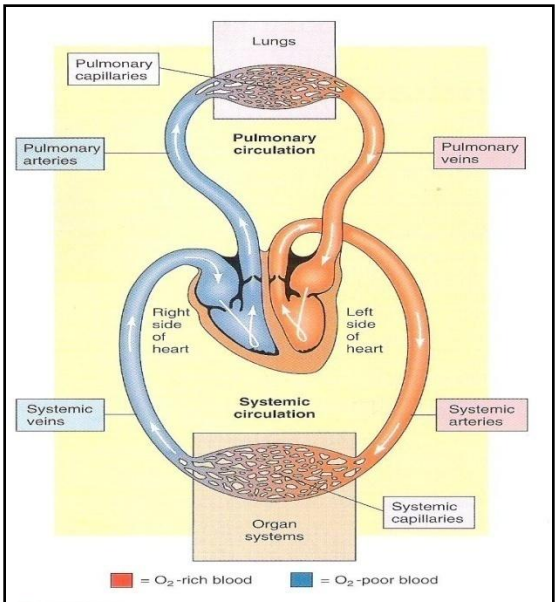


FIGURE 9-1

Pulmonary and systemic circulation in relation to the heart. The circulatory system consists of two separate vascular loops: the pulmonary circulation, which carries blood between the heart and lungs; and the systemic circulation, which carries blood between the heart and organ systems.

The heart's position between two bony structures, the sternum and vertebrae, makes it possible to manually drive blood out of the heart when it is pumping effectively, by rhythmically depressing the sternum. This maneuver compresses the heart between the sternum and vertebrae so that blood is squeezed out into the blood vessels, maintaining blood flow to the tissues. Often this external cardiac compression, which is part of cardiopulmonary resuscitation (CPR), serves as a lifesaving measure until appropriate therapy can restore the heart to normal function.

The heart is a dual pump

Even though anatomically the heart is a single organ, the right and left sides of the heart function as two separate pumps. The heart is divided into right and left halves and has four chambers, an upper and a lower chamber within each half (Figure 9-2a). The upper chambers, the atria (singular, atrium), receive blood returning to the heart and transfer it to the lower chambers, the ventricles, which pump blood from the heart. The vessels that return blood from the tissues to the atria are veins, and those that carry blood away from the ventricles to the tissues are arteries. The two halves of the heart are separated by the septum, a continuous muscular partition that prevents mixture of blood from the two sides of the heart. This separation is extremely important, because the right half of the heart is receiving and pumping O_2-poor blood, whereas the left side of the heart receives and pumps O_2-rich blood.

THE COMPLETE CIRCUIT OF BLOOD FLOW

Let us look at how the heart functions as a dual pump, by tracing a drop of blood through one complete circuit (Figure 9-2a and b). Blood returning from the systemic circulation enters the right atrium via two large veins, the venae cavae, one returning blood from above and the other returning blood from below heart level. The drop of blood entering the right atrium has returned from the body tissues, where O_2 has been taken from it and CO_2 has been added to it. This partially deoxygenated blood flows from the right atrium into the right ventricle, which pumps it out through the pulmonary artery, which immediately forms two branches, one going to each of the two lungs. Thus the right side of the heart receives blood from the systemic circulation and pumps it into the pulmonary circulation.

Within the lungs, the drop of blood loses its extra CO_2 and picks up a fresh supply of O_2 before being returned to the left atrium via the pulmonary veins coming from both lungs. This O_2-rich blood returning to the left atrium subsequently flows into the left ventricle, the pumping chamber that propels the blood to all body systems except the lungs; that is, the left side of the heart receives blood from the pulmonary circulation and pumps it into the systemic circulation. The single large artery carrying blood away from the left ventricle is the aorta. Major arteries branch from the aorta to supply the various organs of the body.

In contrast to the pulmonary circulation, in which all the blood flows through the lungs, the systemic circulation may be viewed as a series of parallel pathways. Part of the blood pumped out by the left ventricle goes to the muscles, part to the kidneys, part to the brain, and so on. Thus the output of the left ventricle is distributed so that each part of the body receives a fresh blood supply; the same arterial blood does not pass from organ to organ. Tissue cells within the organ take O_2 from the blood and use it to oxidize nutrients for energy production; in the

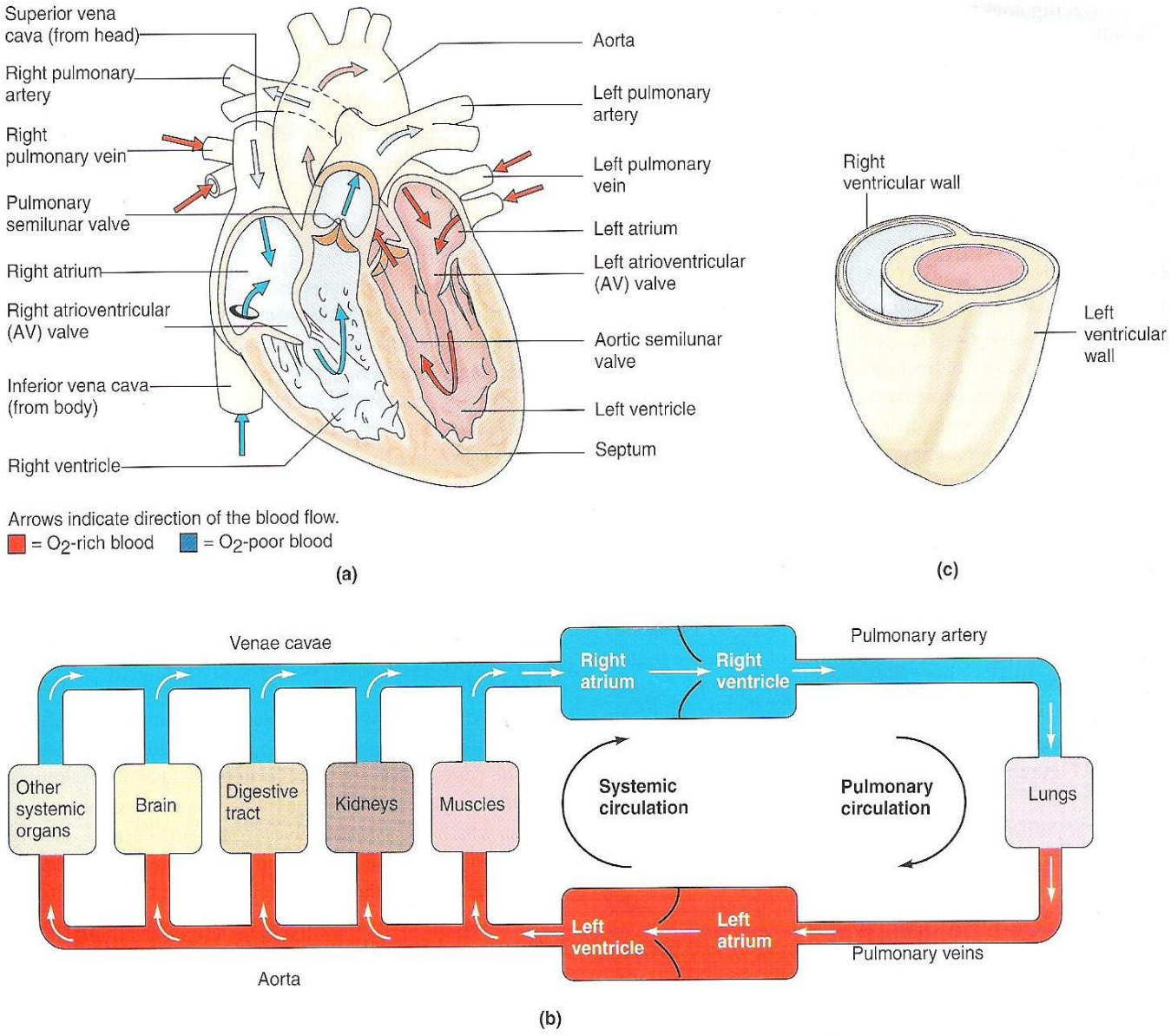


FIGURE 9-2

Blood flow through and pump action of the heart. (a) Blood flow through the heart. (b) Dual pump action of the heart. The right side of the heart receives O_2-poor blood from the systemic circulation and pumps it into the pulmonary circulation. The left side of the heart receives O_2-rich blood from the pulmonary circulation and pumps it into the systemic circulation. Note the parallel pathways of blood flow through the systemic organs. (The relative volume of blood flowing through each organ is not drawn to scale.) (c) Comparison of the thickness of the right and left ventricular walls. Note that the left ventricular wall is much thicker than the right wall.

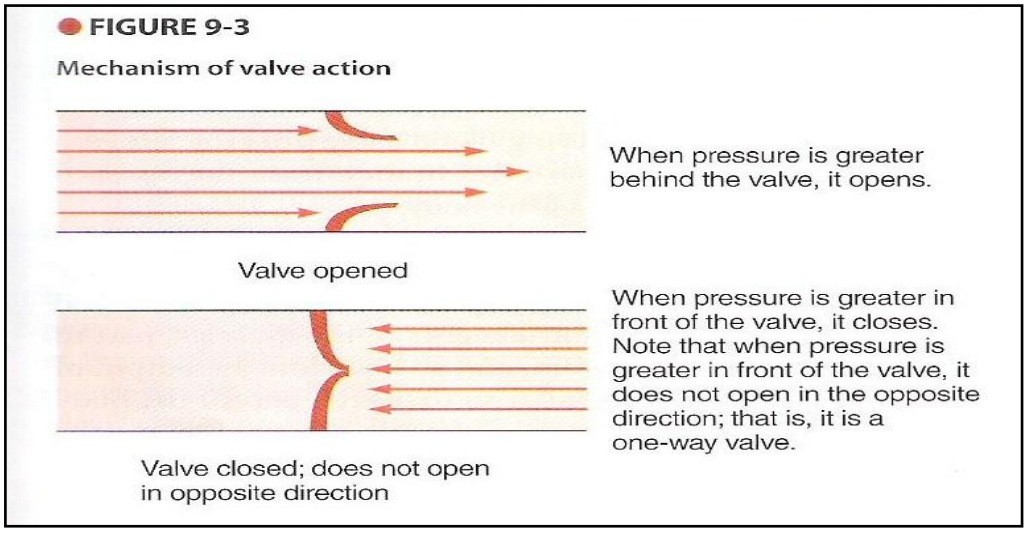
process, the tissue cells form CO_2 as a waste product that is added to the blood. The drop of blood, now partially depleted of O_2 content and increased in CO_2 content, returns to the right side of the heart, which once again will pump it to the lungs. One circuit is complete.

COMPARISON OF THE RIGHT AND LEFT PUMPS

Both sides of the heart simultaneously pump equal amounts of blood. The volume of O_2-poor blood being pumped to the lungs by the right side of the heart soon becomes the same volume of O_2-rich blood being delivered to the tissues by the left side of the heart. The pulmonary circulation is a low-pressure, low-resistance system, whereas the systemic circulation is a high-pressure, high-resistance system. Pressure is the force exerted on the vessel walls by the blood pumped into the vessels by the heart. Resistance is the opposition to blood flow, largely caused by friction between the flowing blood and the vessel wall. Even though the right and left sides of the heart pump the same amount of blood, the left side performs more work, because it pumps an equal volume of blood at a higher pressure into a higher-resistance and longer system. Accordingly, the heart muscle on the left side is much thicker than the muscle on the right side, making the left side a stronger pump (Figure 9-2c).

Heart valves

Blood flows through the heart in one fixed direction from veins to atria to ventricles to arteries. The presence of 4 one-way heart valves ensures this unidirectional flow of blood. The valves are positioned so that they open and close passively because of pressure differences (Figure 9-3).

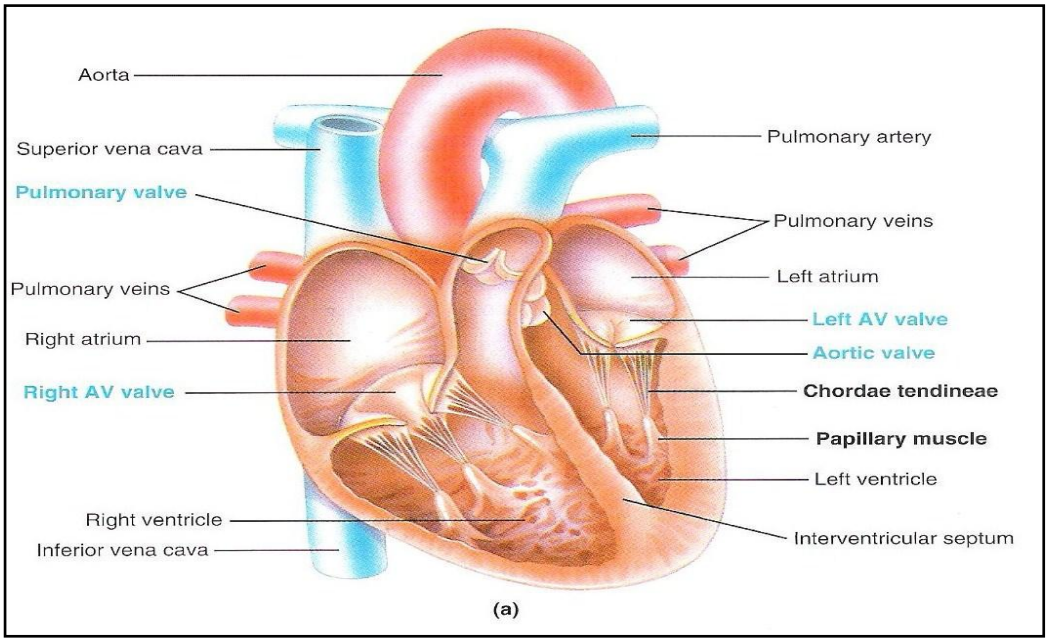


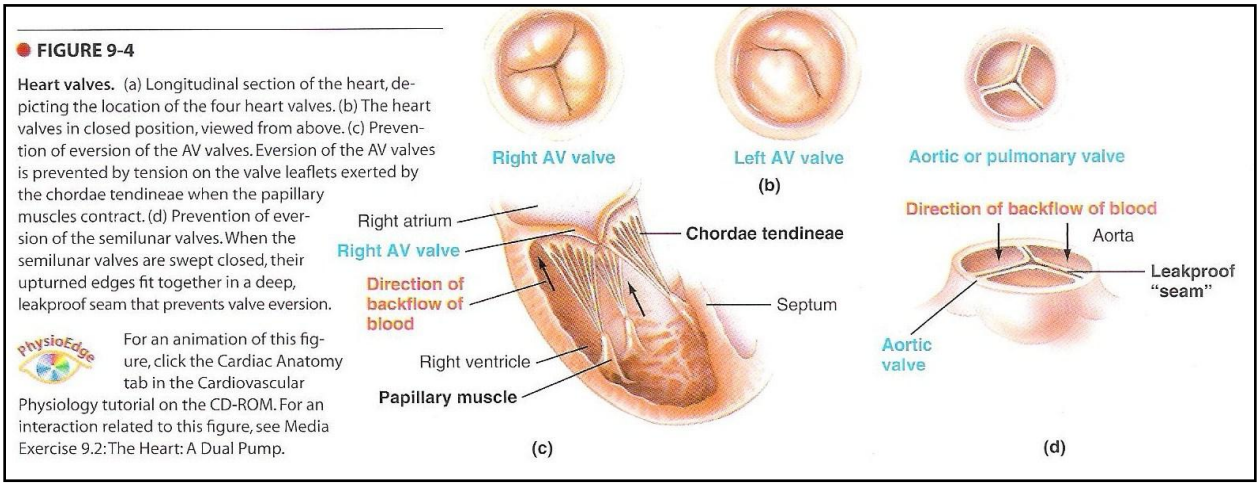
AV VALVES BETWEEN THE ATRIA AND VENTRICLES

Two of the heart valves, the right and left atrioventricular (AV) valves, are positioned between the atrium and the ventricle on the right and left sides, respectively (Figure 9-4a). These valves let blood flow from the atria into the ventricles during ventricular filling (when atrial pressure exceeds ventricular pressure) but prevent the backflow of blood from the ventricles into the atria during ventricular emptying (when ventricular pressure greatly exceeds atrial pressure). The

right AV valve is also called the tricuspid valve (tri means "three"), because it consists of three cusps or leaflets (Figure 9-4b). Likewise, the left AV valve, which has two cusps, is often called the bicuspid valve (bi means "two").

The edges of the AV valve leaflets are fastened by tough, thin, fibrous cords of tendinous-type tissue, the chordae tendineae, which prevent the valves from being everted. That is, the chordae tendineae prevent the AV valve from being forced by the high ventricular pressure to open in the opposite direction into the atria. These cords extend from the edges of each cusp and attach to small, nipple-shaped papillary muscles, which protrude from the inner surface of the ventricular walls (papilla means "nipple"). When the ventricles contract, the papillary muscles also contract, pulling downward on the chordae tendineae. This pulling exerts tension on the closed AV valve cusps to hold them in position, much like tethering ropes hold down a hot-air balloon. This action helps keep the valve tightly sealed in the face of a strong backward pressure gradient (e Figure 9-4c).





SEMILUNAR VALVES

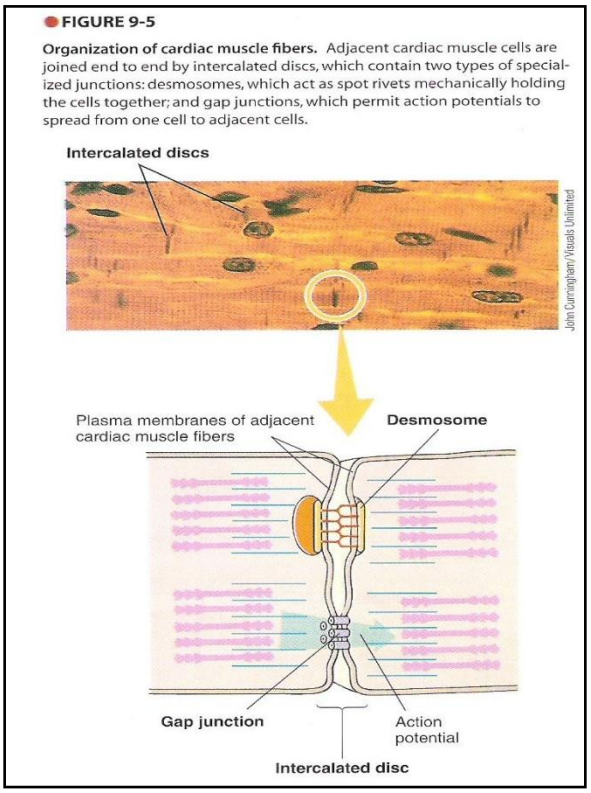
The two remaining heart valves, the aortic and pulmonary valves, lie at the juncture where the major arteries leave the ventricles (Figure 9-4a). They are known as semilunar valves because they have three cusps, each resembling a shallow half-moan-shaped pocket (semi means "half"; lunar means "moon") (Figure 9-4b). These valves are forced open when the left and right ventricular pressures exceed the pressure in the aorta and pulmonary artery, respectively, during ventricular contraction and emptying. Closure results when the ventricles relax and ventricular pressures fall below the aortic and pulmonary artery pressures. The closed valves prevent blood from flowing from the arteries back into the ventricles from which it has just been pumped.

The heart walls

The heart wall has three distinct layers:

- A thin inner layer, the endothelium, a unique type of epithelial tissue that lines the entire circulatory system
- A middle layer, the myocardium, which is composed of cardiac muscle and constitutes the bulk of the heart wall (myo means "muscle"; cardia means "heart")
- A thin external membrane, the epicardium that covers the heart (epi mans "on")

Cardiac muscle fibers



The individual cardiac muscle cells interconnect to form branching fibers, with adjacent cells joined end to end at specialized structures called intercalated discs. Inside an intercalated disc are two types of membrane junctions: desmosomes and gap junctions (Figure 9-5). A desmosome is a type of adhering junction that attaches firmly adjacent cells, mechanically holding them together. Desmosomes are particularly abundant in tissues, such as the heart, that are subject to a lot of mechanical stress. Furthermore, at intervals along the intercalated disc, the opposing membranes approach each other very closely to form gap junctions, which are areas of low electrical resistance that let action potentials spread from one cardiac cell to adjacent cells. Some cardiac-muscle cells can generate action potentials without any nervous stimulation. When one of the cardiac cells spontaneously undergoes an action potential, the electrical impulse spreads to all the other cells that are joined by gap junctions in the surrounding muscle mass, so they become excited and contract as a single unit or functional syncytium. The

atria and the ventricles each form a functional syncytium and contract as separate units. The synchronous contraction of the muscle cells that make up the walls of each of these chambers produces the force needed to eject the enclosed blood.

No gap junctions join the atrial and ventricular contractile cells, and furthermore, the atria and ventricles are separated by electrically nonconductive fibrous tissue that surrounds and supports the valves. However, an important, specialized conduction system facilitates and coordinates transmission of electrical excitation from the atria to the ventricles to ensure synchronization between atrial and ventricular pumping. Because of both the syncytial nature of cardiac muscle and the conduction system between the atria and ventricles, an impulse spontaneously generated in one part of the heart spreads throughout the entire heart.

ELECTRICAL ACTIVITY OF THE HEART

Contraction of cardiac muscle cells to eject blood is triggered by action potentials sweeping across the muscle cell membranes. The heart contracts, or beats, rhythmically as a result of action potentials that it generates by itself, a property called **autorhythmicity** (auto means "self"). There are two specialized types of cardiac muscle cells:

1. **Contractile cells**, which are 99% of the cardiac muscle cells, do the mechanical work of pumping. These working cells normally do not initiate their own action potentials.
2. In contrast, the small but extremely important remainder of the cardiac cells, the **autorhythmic cells**, do not contract but instead are specialized for initiating and conducting the action potentials responsible for contraction of the working cells.

Cardiac autorhythmic cells

In contrast to nerve and skeletal muscle cells, in which the membrane remains at constant resting potential unless the cell is stimulated, the cardiac autorhythmic cells do not have a resting potential. Instead, they display pacemaker activity; that is, their membrane potential slowly depolarizes, or drifts, between action potentials until threshold is reached, at which time the membrane fires or has an action potential. An autorhythmic cell membrane's slow drift to threshold is called the pacemaker potential (Figure 9-6). This slow depolarization results from built-in, complex changes in passive ion movement across the membrane between action potentials. Through repeated cycles of drift and fire, these autorhythmic cells cyclically initiate action potentials, which then spread throughout the heart to trigger rhythmic beating without any nervous stimulation.

The sinoatrial node is the normal pacemaker of the heart

The specialized noncontractile cardiac cells capable of autorhythmicity lie in the following specific sites (Figure 9-7):

1. The sinoatrial node (SA node), a small, specialized region in the right atrial wall near the opening of the superior vena cava.
2. The atrioventricular node (AV node), a small bundle of specialized cardiac muscle cells

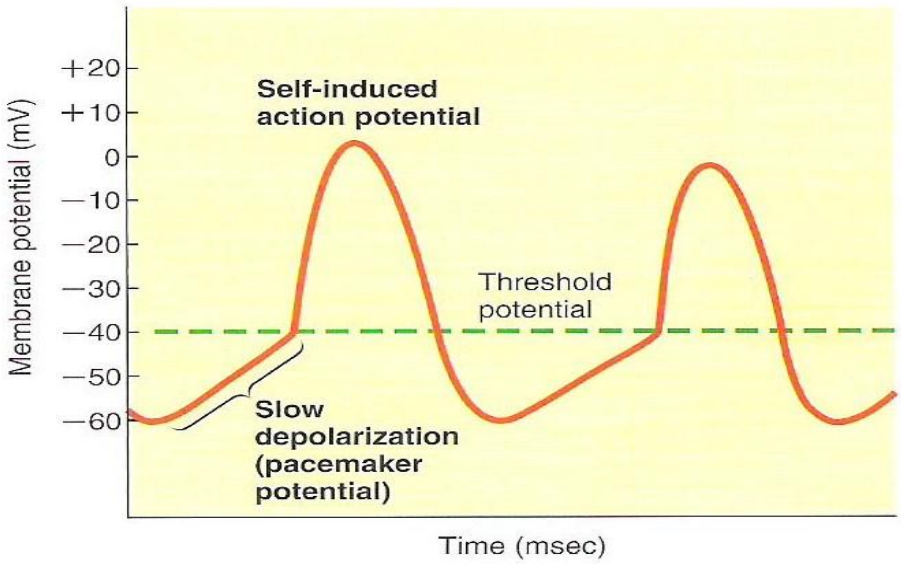


FIGURE 9-6

Pacemaker activity of cardiac autorhythmic cells

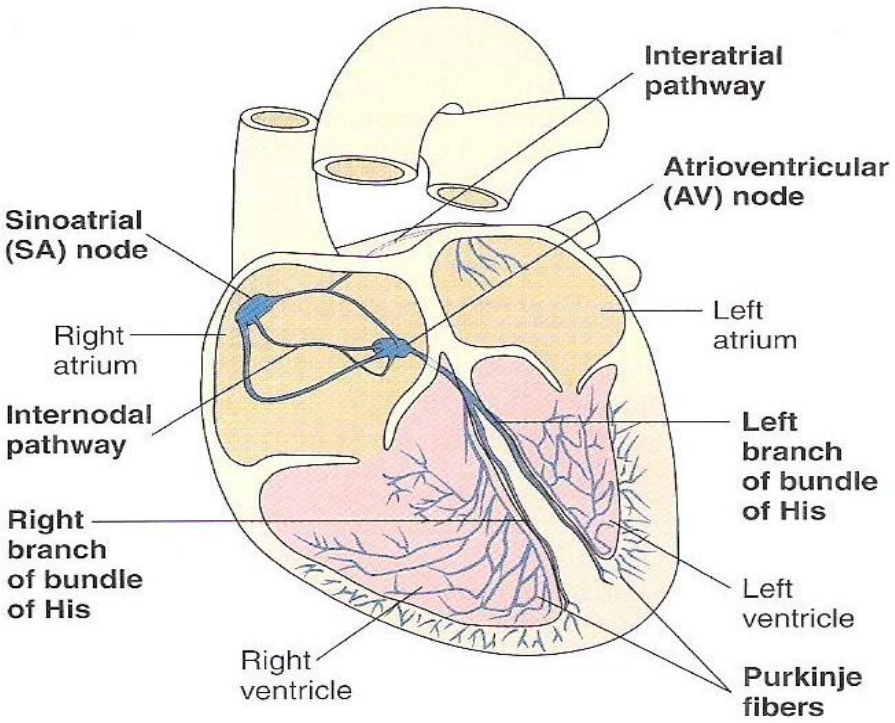


FIGURE 9-7

Specialized conduction system of the heart

located at the base of the right atrium near the septum, just above the junction of the atria and ventricles.

3. The bundle of His (atrioventricular bundle), a tract of specialized cells that originates at the AV node and enters the interventricular septum. Here, it divides to form the right and left bundle branches that travel down the septum, curve around the tip of the ventricular chambers, and travel back toward the atria along the outer walls.
4. Purkinje fibers, small terminal fibers that extend from the bundle of His and spread throughout the ventricular myocardium much like small twigs of a tree branch.

NORMAL PACEMAKER ACTIVITY

Because these various autorhythmic cells have different rates of slow depolarization to threshold, the rates at which they are normally capable of generating action potentials also differ (Table 9-1). The heart cells with the fastest rate of action potential initiation are localized in the SA node. Once an action potential occurs in any cardiac muscle cell, it is propagated throughout the rest of the myocardium via gap junctions and the specialized conduction system. Therefore, the SA node, which normally has the fastest rate of autorhythmicity, at 70 to 80 action potentials per minute, drives the rest of the heart at this rate and thus is known as the **pacemaker** of the heart. That is, the entire heart becomes excited, triggering the contractile cells to contract and the heart to beat at the pace or rate set by SA node autorhythmicity, normally at 70 to 80 beats per minute. The other autorhythmic tissues cannot assume their own naturally slower rates, because they are activated by action potentials originating in the SA node before they can reach threshold at their own, slower rhythm.

TABLE 9-1

Normal Rate of Action Potential Discharge in Autorhythmic Tissues of the Heart

TISSUE	ACTION POTENTIALS PER MINUTE*
SA node (normal pacemaker)	70–80
AV node	40–60
Bundle of His and Purkinje fibers	20–40

ABNORMAL PACEMAKER ACTIVITY

If for some reason the fastest engine breaks down (SA node damage), the next fastest engine (AV node) over and the entire train travels at 50 mph; that is, if the SA node becomes nonfunctional, the AV node assumes pacemaker activity (Figure 9-8b). The non-SA nodal autorhythmic tissues are latent pacemakers that can take over, although at a lower rate, if the normal pacemaker fails.

If impulse conduction becomes blocked between the atria and the ventricles, the atria continue at the typical rate of 70 beats per minute, and the ventricular tissue, not being driven by the faster

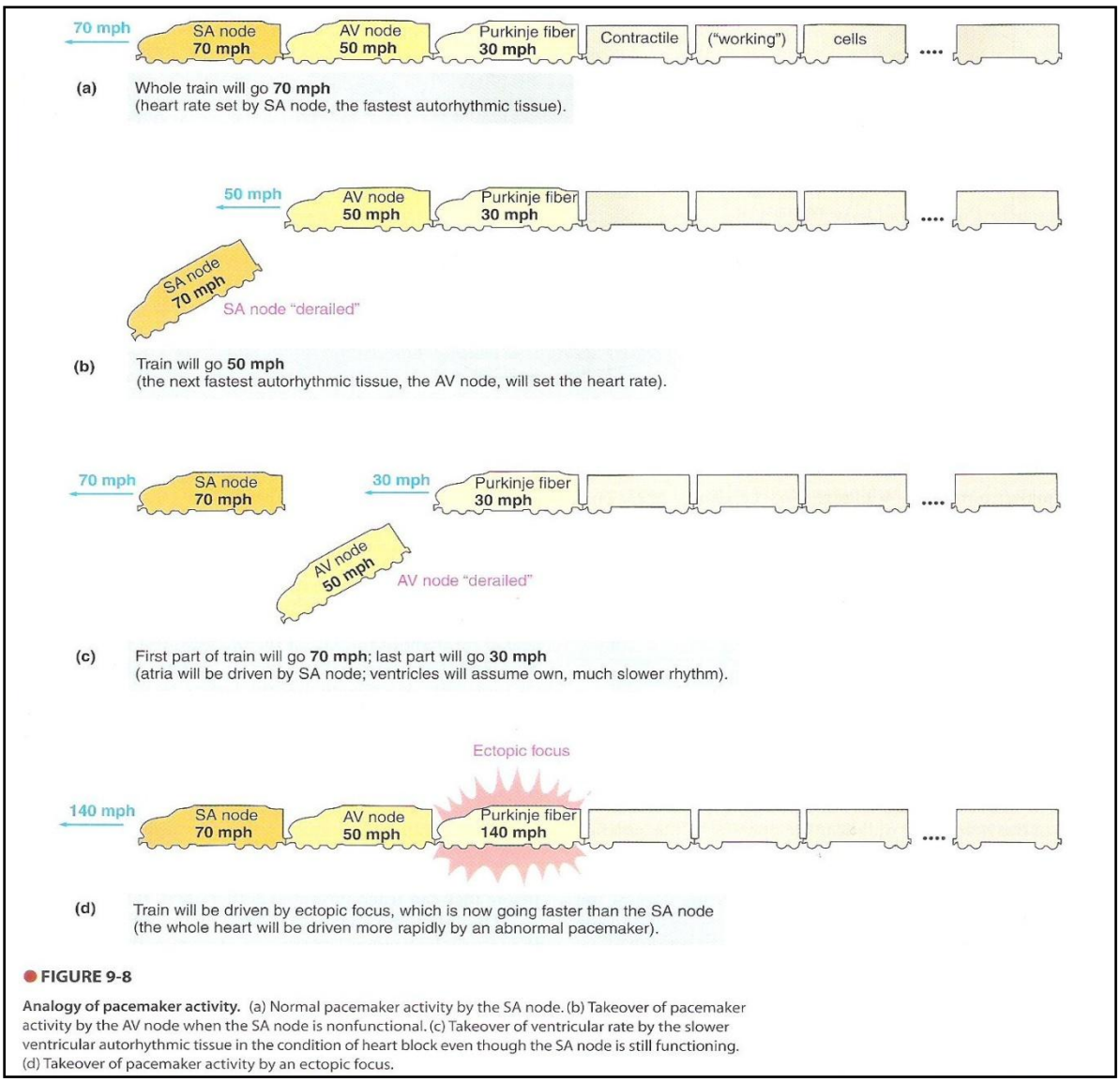


FIGURE 9-8

Analogy of pacemaker activity. (a) Normal pacemaker activity by the SA node. (b) Takeover of pacemaker activity by the AV node when the SA node is nonfunctional. (c) Takeover of ventricular rate by the slower ventricular autorhythmic tissue in the condition of heart block even though the SA node is still functioning. (d) Takeover of pacemaker activity by an ectopic focus.

SA nodal rate, assumes its own much slower autorhythmic rate of about 30 beats per minute, initiated by the ventricular autorhythmic cells (Purkinje fibers). This complete heart block occurs when the conducting tissue between the atria and ventricles is damaged and becomes non-functional. A ventricular rate of 30 beats per minute will support only a very sedentary existence; in fact, the patient usually becomes comatose. When a person has an abnormally low heart rate, as in SA node failure or heart block, an **artificial pacemaker** can be used. Such an implanted device rhythmically generates impulses that spread throughout the heart to drive both the atria and ventricles at the typical rate of 70 beats per minute.

Occasionally an area of the heart, such as a Purkinje fiber, becomes overly excitable and depolarizes more rapidly than the SA node. This abnormally excitable area, an ectopic focus, initiates a premature action potential that spreads throughout the rest of the heart before the SA node can initiate a normal action potential (ectopic means "out of place"). An occasional abnormal impulse from a ventricular ectopic focus produces a **premature ventricular contraction (PVC).** If the ectopic focus continues to discharge at its more rapid rate, pacemaker

activity shifts from the SA node to the ectopic focus. The heart rate abruptly becomes greatly accelerated and continues this rapid rate for a variable time period until the ectopic focus returns to normal. Such overly irritable areas may be associated with organic heart disease, but more frequently they occur in response to anxiety, lack of sleep, or excess caffeine, nicotine, or alcohol consumption.

Coordination of cardiac excitation

Once initiated in the SA node, an action potential spreads throughout the rest of the heart. For efficient cardiac function, the spread of excitation should satisfy three criteria:

1. Atrial excitation and contraction should be complete before the onset of ventricular contraction. Complete ventricular filling requires that atrial contraction precede ventricular contraction. During cardiac relaxation, the AV valves are open, so that venous blood entering the atria continues to flow directly into the ventricles. Almost 80% of ventricular filling occurs by this means before atrial contraction. When the atria do contract, more blood is squeezed into the ventricles to complete ventricular filling. Ventricular contraction then occurs to eject blood from the heart into the arteries. To ensure complete filling of the ventricles-to obtain the remaining 20% of ventricular filling that occurs during atrial contraction -the atria must become excited and contract before ventricular excitation and contraction.

2. Excitation of cardiac muscle fibers should be coordinated to ensure that each heart chamber contracts as a unit to pump efficiently. If the muscle fibers in a heart chamber became excited and contracted randomly rather than contracting simultaneously in a coordinated fashion, they would be unable to eject blood. A smooth, uniform ventricular contraction is essential to squeeze out the blood. Random, uncoordinated excitation and contraction of the cardiac cells is known as **fibrillation**. Fibrillation of the ventricles is much more serious than atrial fibrillation. Ventricular fibrillation rapidly causes death, because the heart cannot pump blood into the arteries. This condition can often be corrected by **electrical defibrillation**, in which a very strong electrical current is applied on the chest wall.

3. The pair of atria and pair of ventricles should be functionally coordinated so that both members of the pair contract simultaneously. This coordination permits synchronized pumping of blood into the pulmonary and systemic circulation.

The normal spread of cardiac excitation is carefully orchestrated to ensure that these criteria are met and the heart functions efficiently, as follows (Figure 9-9).

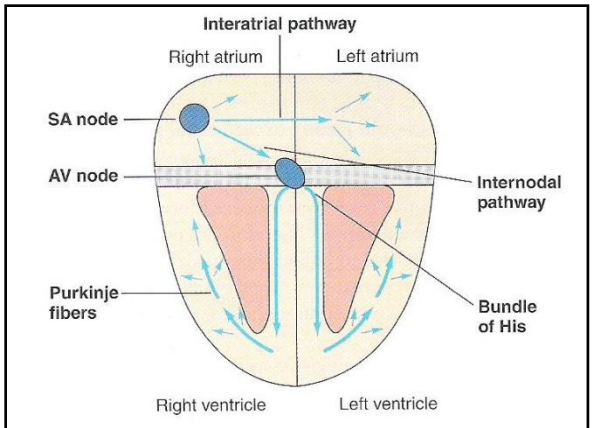


FIGURE 9-9

Spread of cardiac excitation. An action potential initiated at the SA node first spreads throughout both atria. Its spread is facilitated by two specialized atrial conduction pathways, the interatrial and internodal pathways. The AV node is the only point where an action potential can spread from the atria to the ventricles. From the AV node, the action potential spreads rapidly throughout the ventricles, hastened by a specialized ventricular conduction system consisting of the bundle of His and Purkinje fibers.

ATRIAL EXCITATION

An action potential originating in the SA node first spreads throughout both atria, primarily from cell to cell via gap junctions.

- The **interatrial pathway** extends from the SA node within the right atrium to the left atrium. Because this pathway rapidly transmits the action potential from the SA node to the pathway's termination in the left atrium, a wave of excitation can spread across the gap junctions throughout the left atrium at the same time excitation is similarly spreading throughout the right atrium. This ensures that both atria become depolarized to contract simultaneously.

- The **internodal pathway** extends from the SA node to the AV node. The AV node is the only point of electrical contact between the atria and ventricles; in other words, because the atria and ventricles are structurally connected by electrically nonconductive fibrous tissue, the only way an action potential in the atria can spread to the ventricles is by passing through the AV node. The internodal conduction pathway directs the spread of an action potential originating at the SA node to the AV node to ensure sequential contraction of the ventricles following atrial contraction.

CONDUCTION BETWEEN THE ATRIA AND THE VENTRICLES

The action potential is conducted relatively slowly through the AV node. This slowness is advantageous because it allows time for complete ventricular filling. The impulse is delayed about 100 msec (the AV nodal delay), which enables the atria to become completely depolarized and to contract, emptying their contents into the ventricles, before ventricular depolarization and contraction occur.

VENTRICULAR EXCITATION

After the AV nodal delay, the impulse travels rapidly down the septum via the right and left branches of the bundle of His and throughout the ventricular myocardium via the Purkinje fibers. The network of fibers in this ventricular conduction system is specialized for rapid propagation of action potentials. Its presence hastens and coordinates the spread of ventricular excitation to ensure that the ventricles contract as a unit.

The action potential of cardiac contractile cells

The action potential in cardiac contractile cells, although initiated by the nodal pacemaker cells, varies considerably in ionic mechanisms and shape from the SA node potential (compare Figures 9-6 and 9-10). Unlike autorhythmic cells, the membrane of contractile cells remains essentially at rest at about -90 mV until excited by electrical activity propagated from the pacemaker. Once the membrane of a ventricular myocardial contractile cell is excited, the membrane potential rapidly reverses to a positive value of + 30 m V as a result of activation of voltage-gated Na^+ channels and Na^+ subsequently rapidly entering the cell, as it does in other excitable cells undergoing an action potential. Unique to the cardiac contractile cells, however, the membrane potential is maintained close to this peak positive level for several hundred milliseconds, producing a plateau phase of the action potential. In contrast, the short action potential of

neurons and skeletal muscle cells lasts 1 to 2 msec. Whereas the rising phase of the action potential is brought about by activation of comparatively "fast" Na^+ channels, this plateau is maintained primarily by activation of relatively "slow" voltage-gated Ca^{2+} channels in the cardiac contractile cell membrane. These channels open in response to the sudden change in voltage during the rising phase of the action potential. Opening of these Ca^{2+} channels results in a slow, inward diffusion of Ca^{2+},because Ca^{2+} is in greater concentration in the ECF This continued influx of positively charged Ca^{2+} prolongs the positivity inside the cell and is primarily responsible for the plateau part of the action potential. The rapid falling phase of the action potential results from inactivation of the Ca^{2+} channels and delayed activation of voltage-gated K^+ channels. As in other excitable cells, the cell returns to resting potential as K^+ rapidly leaves the cell.

Ca^{2+} entry from the ECF

In cardiac contractile cells, the slow Ca^{2+} channels lie primarily in the T tubules. As you just learned, these voltage-gated channels open during a local action potential. Thus, unlike in skeletal muscle, Ca^{2+} diffuses into the cytosol from the ECF across the T tubule membrane during a cardiac action potential. This entering Ca^{2+} triggers the opening of nearby Ca^{2+} -release channels in the adjacent lateral sacs of the sarcoplasmic reticulum. In this way, a small amount Ca^{2+} entering the cytosol from the ECF induces a much larger release of Ca^{2+} into the cytosol from the intracellular stores (Figure 9-11). The resultant increase in cytosolic Ca^{2+} turns on the contractile machinery. The extra supply of Ca^{2+} from the sarcoplasmic reticulum is responsible for the long period of cardiac contraction, which lasts about three times longer than a single contraction of a skeletal muscle fiber (300 msec compared to 100 msec). This increased contractile time ensures adequate time to eject the blood.

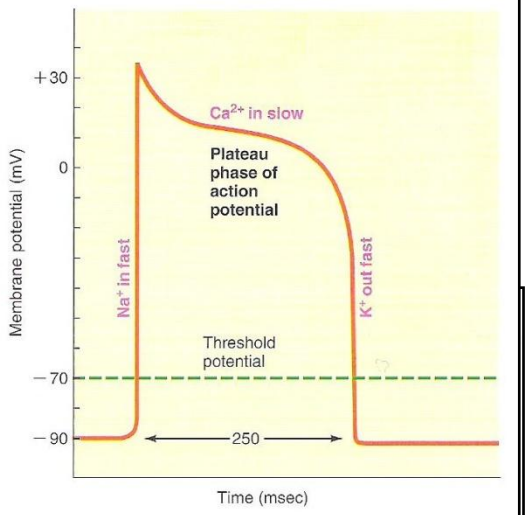


FIGURE 9-10

Action potential in contractile cardiac muscle cells. The action potential in cardiac contractile cells differs considerably from the action potential in cardiac autorhythmic cells (compare with Figure 9-6).

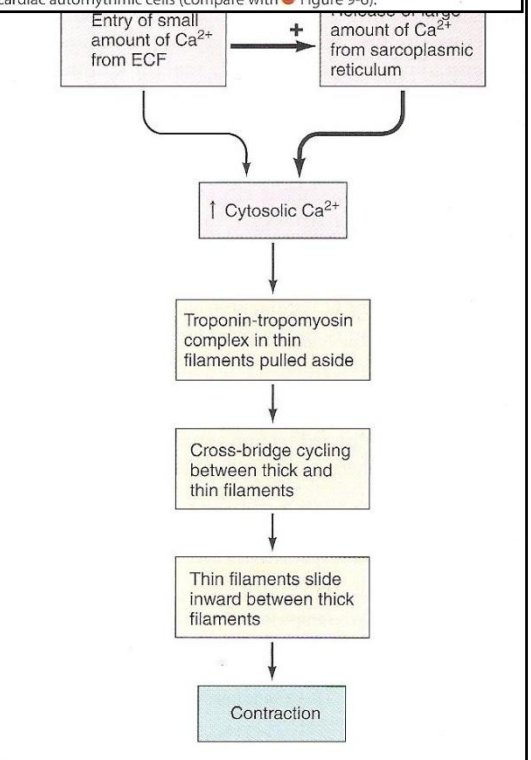


FIGURE 9-11

Excitation–contraction coupling in cardiac contractile cells

As in skeletal muscle, the role of Ca^{2+} within the cytosol is to bind with the troponin-tropomyosin complex and physically pull it aside to allow cross-bridge cycling and contraction (Figure 9-11). However, unlike skeletal muscle, in which sufficient Ca^{2+} is always released to turn on all the cross bridges, in cardiac muscle the extent of cross-bridge activity varies with the amount of cytosolic Ca^{2+} .Various regulatory factors can alter the amount of cytosolic Ca^{2+}.

Removal of Ca^{2+} from the cytosol by energy-

dependent mechanisms in both the plasma membrane and sarcoplasmic reticulum restores the blocking action of troponin and tropomyosin, so contraction ceases and the heart muscle relaxes.

Some drugs alter cardiac function by influencing Ca^{2+} movement across the myocardial cell membranes. For example, Ca^{2+}- channel blocking agents, such as *verapamil*, block Ca^{2+} influx during an action potential, reducing the force of cardiac contraction. Other drugs, such as digitalis, increase cardiac contractility by inducing an accumulation of cytosolic Ca^{2+}.

A long refractory period prevents tetanus of cardiac muscle:

Like other excitable tissues, cardiac muscle has a refractory period. During the refractory period, a second action potential cannot be triggered until an excitable membrane has recovered from the preceding action potential. In skeletal muscle, the refractory period is very short compared with the duration of the resulting contraction, so the fiber can be restimulated again before the first contraction is complete to produce summation of contractions. Rapidly repetitive stimulation that does not let the muscle fiber relax between stimulations results in a sustained, maximal contraction known as tetanus (Figure 8-14).

In contrast, cardiac muscle has a long refractory period that lasts about 250 msec because of the prolonged plateau phase of the action potential. This is almost as long as the period of contraction initiated by the action potential; a cardiac muscle fiber contraction averages about 300 msec (Figure 9-12). Consequently, cardiac muscle cannot be restimulated until contraction is almost over, precluding summation of contractions and tetanus of cardiac muscle. This is a valuable protective mechanism, because the pumping of blood requires alternate periods of contraction (emptying) and relaxation (filling). A prolonged tetanic contraction would prove fatal. The heart chambers could not be filled and emptied again.

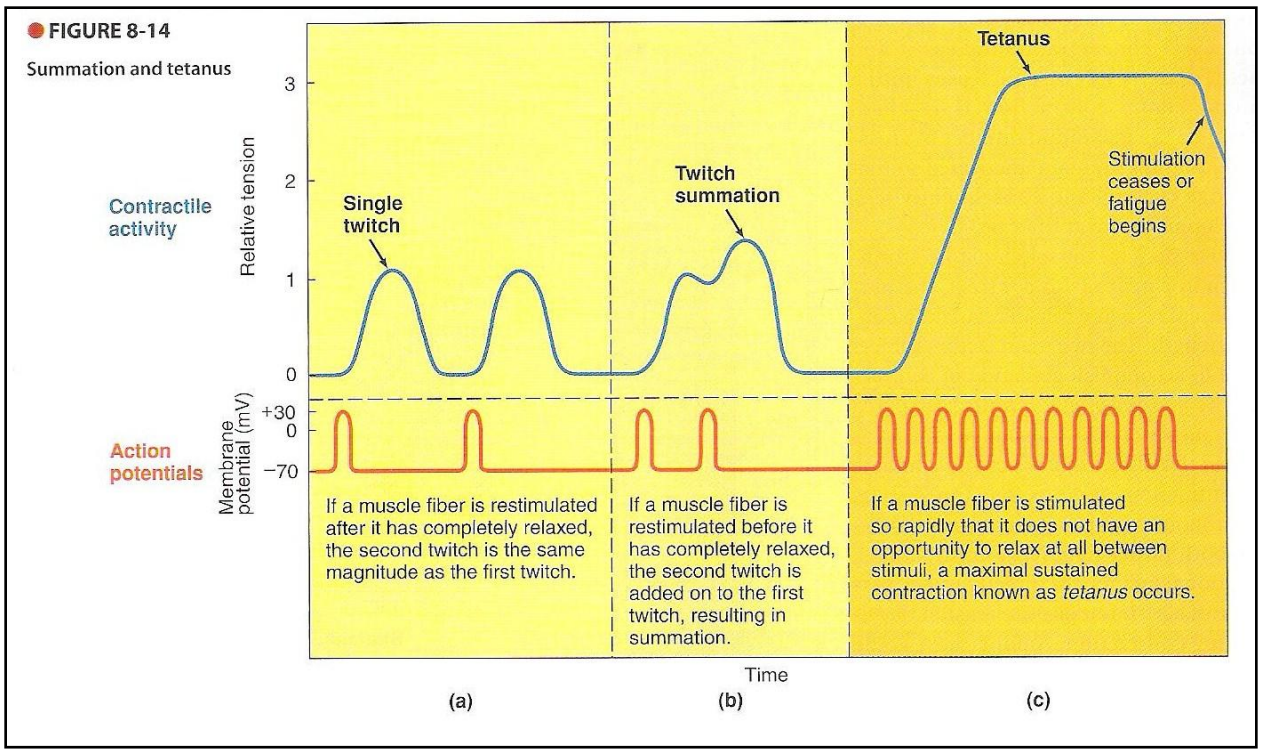


FIGURE 8-14
Summation and tetanus
Contractile activity
Relative tension
3
2
1
0
Single twitch
Twitch summation
Tetanus
Stimulation ceases or fatigue begins
Action potentials
Membrane potential (mV)
+30
0
−70
If a muscle fiber is restimulated after it has completely relaxed, the second twitch is the same magnitude as the first twitch.
If a muscle fiber is restimulated before it has completely relaxed, the second twitch is added on to the first twitch, resulting in summation.
If a muscle fiber is stimulated so rapidly that it does not have an opportunity to relax at all between stimuli, a maximal sustained contraction known as tetanus occurs.
Time
(a)
(b)
(c)

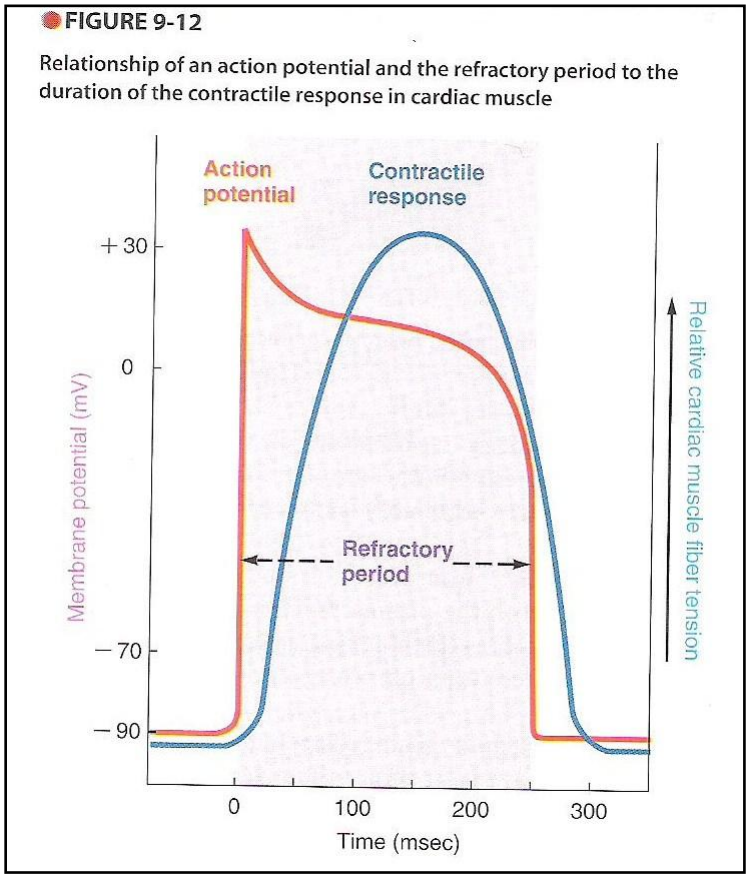


FIGURE 9-12
Relationship of an action potential and the refractory period to the duration of the contractile response in cardiac muscle
Action potential
Contractile response
+30
0
−70
−90
Membrane potential (mV)
Refractory period
Relative cardiac muscle fiber tension
0
100
200
300
Time (msec)

Electrocardiogram (ECG)

The electrical currents generated by cardiac muscle during depolarization and repolarization spread into the tissues around the heart and are conducted through the body fluids. A small part of this electrical activity reaches the body surface, where it can be detected using recording electrodes. The record produced is an electrocardiogram, or ECG.

Remember three important points when considering what an ECG represents:

1. An ECG is a recording of that part of the electrical activity induced in body fluids by the cardiac impulse that reaches the body surface, not a direct recording of the actual electrical activity of the heart.
2. The ECG is a complex recording representing the overall spread of activity throughout the heart during depolarization and repolarization. It is not a recording of a single action potential in a single cell at a single point in time. The record at any given time represents the sum of electrical activity in all the cardiac muscle cells, some of which may be undergoing action potentials while others may not yet be activated.
3. The recording represents comparisons in voltage detected by electrodes at two different points on the body surface, not the actual potential.

ECG record

A normal ECG has three distinct waveforms: the P wave, the QRS complex, and the T wave (Figure 9-14).

- The P wave represents atrial depolarization.
- The QRS complex represents ventricular depolarization.
- The T wave represents ventricular repolarization.

Because these shifting waves of depolarization and repolarization bring about the alternating contraction and relaxation of the heart respectively, the cyclic mechanical events of the heart lag slightly behind the rhythmic changes in electrical activity. The following points about the ECG record should also be noted:

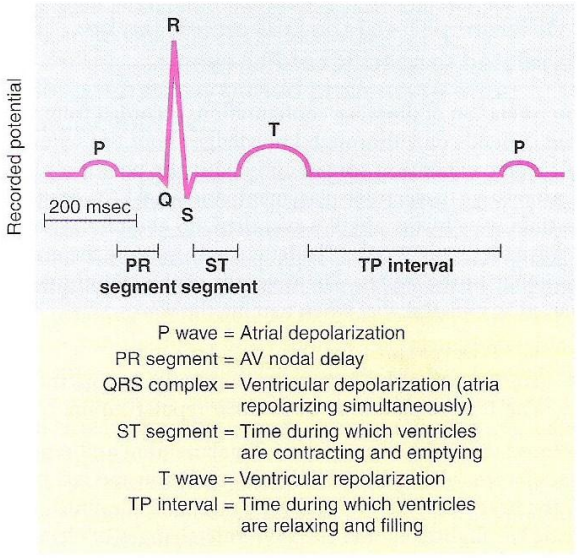


FIGURE 9-14
Electrocardiogram waveforms in lead II

1. Firing of the SA node does not generate enough electrical activity to reach the body surface, so no wave is recorded for SA nodal depolarization. Therefore, the first recorded wave, the P wave, occurs when the impulse or wave of depolarization spreads across the atria.

2. In a normal ECG, no separate wave for atrial repolarization is visible. The electrical activity associated with atrial repolarization normally occurs simultaneously with ventricular depolarization and is masked by the QRS complex.

3. The P wave is much smaller than the QRS complex, because the atria have a much smaller muscle mass than the ventricles and consequently generate less electrical activity.

4. At the following three points in time no net current flow is taking place in the heart musculature, so the ECG remains at baseline:

   a. During the AV nodal delay. This delay is represented by the interval of time between the end of P and the onset QRS; this segment of the ECG is known as the PR segment.

   b. When the ventricles are completely depolarized and the cardiac contractile cells are undergoing the plateau phase of their action potential before they repolarize, represented by the ST segment.

   c. When the heart muscle is completely repolarized and at rest and ventricular filling is taking place, after the T wave and before the next P wave; this period is called the TP interval.

ECG: diagnoses of abnormal heart rates, arrhythmias, and damage of heart muscle

Because electrical activity triggers mechanical activity, abnormal electrical patterns are usually accompanied by abnormal contractile activity of the heart. Thus evaluation of ECG patterns can provide useful information about the status of the heart. The main deviations from normal that can be found through electrocardiography are (1) abnormalities in rate, (2) abnormalities in rhythm, and (3) cardiac myopathies (Figure 9-15).

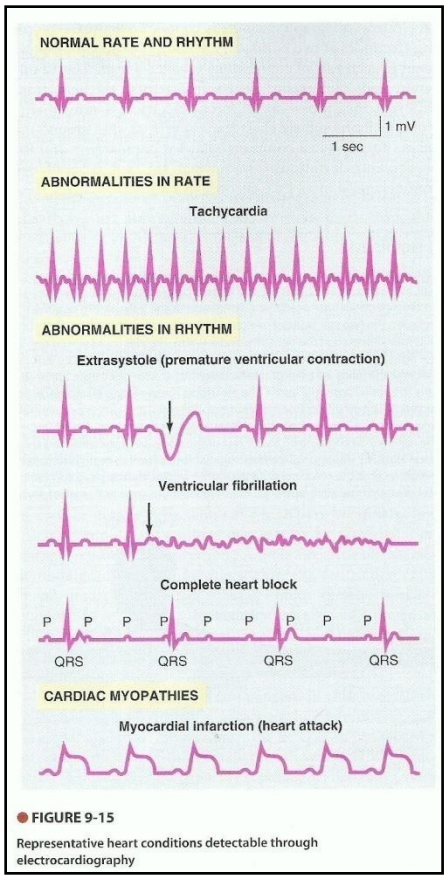


FIGURE 9-15
Representative heart conditions detectable through electrocardiography

ABNORMALITIES IN RATE

The distance between two consecutive QRS complexes on an ECG record is calibrated to the beat-to-beat heart rate. A rapid heart rate of more than 100 beats per minute is called tachycardia (tachy means "fast"), whereas a slow heart rate of fewer than 60 beats per minutes is called **bradycardia** (brady means "slow").

ABNORMALITIES IN RHYTHM

The term rhythm refers to the regularity or spacing of the ECG waves. Any variation from the normal rhythm and sequence of excitation of the heart is termed an **arrhythmia**. It

may result from ectopic foci, alterations in SA node pacemaker activity, or interference with conduction. For example, with complete heart block the SA node continues to govern atrial depolarization, but the ventricles generate their own impulses at a rate much slower than the atria. On the ECG, the P waves exhibit a normal rhythm. The QRS and T waves also occur regularly but much more slowly than the P waves and are completely independent of P wave rhythm. Because atrial and ventricular activity are not synchronized, waves for atrial repolarization may appear, no longer masked by the QRS complex.

CARDIAC MYOPATHIES

Abnormal ECG waves are also important in recognizing and assessing **cardiac myopathies** (damage of the heart muscle). **Myocardial ischemia** is inadequate delivery of oxygenated blood to the heart tissue. Actual death, or necrosis, of heart muscle cells occurs when a blood vessel supplying that area of the heart becomes blocked or ruptured. This condition is **acute myocardial infarction,** commonly called a **heart attack**. Abnormal QRS waveforms appear when part of the heart muscle becomes necrotic.

MECHANICAL EVENTS Of THE CARDIAC CYCLE

The mechanical events of the cardiac cycle-contraction, relaxation, and the resultant changes in blood flow through the heart-are brought about by the rhythmic changes in cardiac electrical activity.

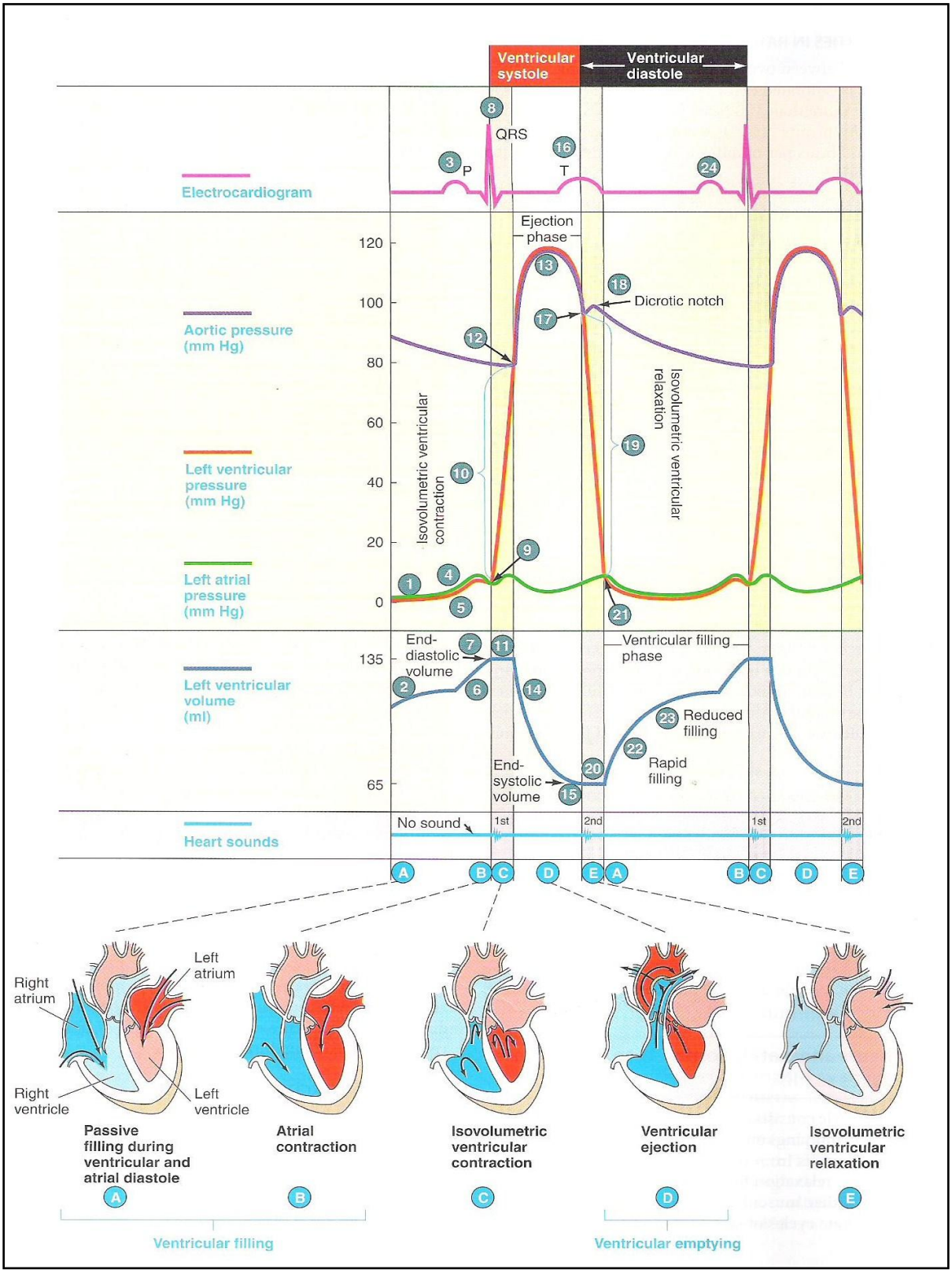
The heart alternately contracts to empty and relaxes to fill

The cardiac cycle consists of alternate periods of systole (contraction and emptying) and diastole (relaxation and filling). Contraction results from the spread of excitation across the heart, whereas relaxation follows the subsequent repolarization of the cardiac musculature. The atria and ventricles go through separate cycles of systole and diastole. Figure 9-16 correlate various events that occur concurrent during the cardiac cycle, including ECG features, pressure changes, volume changes, valve activity, and heart sounds. Only the events on the left side of the heart are described.

EARLY VENTRICULAR DIASTOLE

During early ventricular diastole, the atrium is still also in diastole. This stage corresponds to the TP interval on the ECG the interval after ventricular repolarization and before another atrial depolarization. Because of the continuous inflow of blood from the venous system into the atrium, atrial pressure slightly exceeds ventricular pressure even though both chambers are relaxed (point 1 in Figure 9-16). Because of this pressure differential, the AV valve is open, and blood flows directly from the atrium into the ventricle throughout ventricular diastole (heart A in Figure 9-I6). As a result of this passive filling, the ventricular volume slowly continues to rise even before atrial contraction takes place (point 2).

FIGURE 9-16. Cardiac cycle



LATE VENTRICULAR DIASTOLE

Late in ventricular diastole, the SA node reaches threshold and fires. The impulse spreads throughout the atria, which appears on the ECG as the P wave (point 3). Atrial depolarization brings about atrial contraction, raising the atrial pressure curve (point 4) and squeezing more blood into the ventricle. The corresponding rise in ventricular pressure (point 5) that occurs simultaneous to the rise in atrial pressure is due to the additional volume of blood added to the ventricle by atrial contraction (point 6 and heart B). Throughout atrial contraction, atrial pressure still slightly exceeds ventricular pressure, so the AV valve remains open.

END OF VENTRICULAR DIASTOLE

Ventricular diastole ends at the onset of ventricular contraction. By this time, atrial contraction and ventricular filling are completed. The volume of blood in the ventricle at the end of diastole (point 7) is known as the **end-diastolic volume (EDV),** which averages about 135 ml. No more blood will be added to the ventricle during this cycle. Therefore, the end diastolic volume is the maximum amount of blood that the ventricle will contain during this cycle.

VENTRICULAR EXCITATION AND ONSET OF VENTRICULAR SYSTOLE

After atrial excitation, the impulse travels through the AV node and specialized conduction system to excite the ventricle. Simultaneously, the atria are contracting. By the time ventricular activation is complete, atrial contraction is already over. The QRS complex represents this ventricular excitation (point 8), which induces ventricular contraction. The ventricular pressure curve sharply increases shortly after the QRS complex, signaling the onset of ventricular systole (point 9). As ventricular contraction begins, ventricular pressure immediately exceeds atrial pressure. This backward pressure differential forces the AV valve closed (point 9).

ISOVOLUMETRIC VENTRICULAR CONTRACTION

After ventricular pressure exceeds atrial pressure and the AV valve has closed, to open the aortic valve the ventricular pressure must continue to increase until it exceeds aortic pressure. Therefore, after closing of the AV valve and before opening of the aortic valve is a brief period of time when the ventricle remains a closed chamber (point 10). Because all valves are closed, no blood can enter or leave the ventricle during this time. This interval is termed the period of **isovolumetric ventricular contraction** (isovolumetric means "constant volume and length") (heart C). Because no blood enters or leaves the ventricle, the ventricular chamber stays at constant volume, and the muscle fibers stay at constant length. This isovolumetric condition is similar to an isometric contraction in skeletal muscle. During isovolumetric ventricular contraction, ventricular pressure continues to increase as the volume remains constant (point 11).

VENTRICULAR EJECTION

When ventricular pressure exceeds aortic pressure (point 12), the aortic valve is forced open and ejection of blood begins (heart D). The amount of blood pumped out of each ventricle with each contraction is called the **stroke volume** (SV). The aortic pressure curve rises as blood is forced into the aorta from the ventricle faster than blood is draining off into the smaller vessels at the other end (point 13). The ventricular volume decreases substantially as blood is rapidly pumped

out (point 14). Ventricular systole includes both the period of isovolumetric contraction and the ventricular ejection phase.

END OF VENTRICULAR SYSTOLE

The ventricle does not empty completely during ejection. Normally, only about half the blood within the ventricle at the end of diastole is pumped out during the subsequent systole. The amount of blood left in the ventricle at the end of systole when ejection is complete is the end-systolic volume (ESV), which averages about 65 ml (point 15). This is the least amount of blood that the ventricle will contain during this cycle.

The difference between the volume of blood in the ventricle before contraction and the volume after contraction is the amount of blood ejected during the contraction; that is. EDV - ESV = SV In our example, the end-diastolic volume is 135 ml, the end-systolic volume is 65 ml, and the stroke volume is 70 ml.

VENTRICULAR REPOLARIZATION AND ONSET OF VENTRICULAR DIASTOLE

The T wave signifies ventricular repolarization at the end of ventricular systole (point 16). As the ventricle starts to relax on repolarization, ventricular pressure falls below aortic pressure and the aortic valve closes (point 17). Closure of the aortic valve produces a disturbance or notch on the aortic pressure curve, the **dicrotic notch** (point 18). No more blood leaves the ventricle during this cycle, because the aortic valve has closed.

ISOVOLUMETRIC VENTRICULAR RELAXATION

When the aortic valve closes, the AV valve is not yet open, because ventricular pressure still exceeds atrial pressure, so no blood can enter the ventricle from the atrium. Therefore, all valves are once again closed for a brief period of time known as isovolumetric ventricular relaxation (point 19 and heart E). The muscle fiber length and chamber volume (point 20) remain constant. No blood leaves or enters as the ventricle continues to relax and the pressure steadily falls.

VENTRICULAR FILLING

When ventricular pressure falls below atrial pressure, the AV valve opens (point 21) and ventricular filling occurs again (point 22). Ventricular diastole includes both the period of isovolumetric ventricular relaxation and the ventricular filling phase. Atrial repolarization and ventricular depolarization occur simultaneously, so the atria are in diastole throughout ventricular systole. Blood continues to flow from the pulmonary veins into the left atrium. When the AV valve opens at the end of ventricular systole, blood that accumulated in the atrium during ventricular systole pours rapidly into the ventricle (heart A again). Ventricular filling thus occurs rapidly at first (point 22). Then ventricular filling slows down (point 23) as the accumulated blood has already been delivered to the ventricle. During this period of reduced filling, blood continues to flow from the pulmonary veins into the left atrium and through the open AV valve into the left ventricle. During late ventricular diastole, when the ventricle is filling slowly, the SA node fires again (point 24) , and the cardiac cycle starts over. Significantly, much of ventricular filling occurs early in diastole during the rapid filling phase. During times of rapid heart rate, diastole length is shortened much more than systole length is. For example, if the

heart rate increases from 75 to 180 beats per minute, the duration of diastole decreases about 75%, from 500 msec to 125 msec. This greatly reduces the time available for ventricular relaxation and filling. Importantly, because much ventricular filling is done during early diastole, filling is not seriously impaired during periods of increased heart rate, such as during tachycardia.

The two heart sounds are associated with valve closures

Two major heart sounds normally can be heard with a stethoscope during the cardiac cycle. The **first heart sound** is low pitched, soft, and relatively long-often said to sound like "lub." The **second heart sound** has a higher pitch and is shorter and sharper-often said to sound like "dup." Thus, one normally hears "lub-dup-Iub-dup-Iub-dup .... " The first heart sound is associated with closure of the AV valves, whereas the second sound is associated with closure of the semilunar valves (Figure 9-16). Opening of valves does not produce any sound.

Because the AV valves close at the onset of ventricular contraction, when ventricular pressure first exceeds atrial pressure, the first heart sound signals the onset of ventricular systole. The semilunar valves close at the onset of ventricular relaxation, as the left and right ventricular pressures fall below the aortic and pulmonary artery pressures, respectively. The second heart sound, therefore, signals the onset of ventricular diastole.

Turbulent blood flow produces heart murmurs

Abnormal heart sounds, or murmurs, are usually (but not always) associated with cardiac disease.

STENOTIC AND INSUFFICIENT VALVES

The most common cause of turbulence is valve malfunction, either a stenotic or an insufficient valve. A **stenotic valve** is a stiff, narrowed valve that does not open completely. Blood must be forced through the constricted opening at tremendous velocity, resulting in turbulence that produces an abnormal whistling sound

An **insufficient or incompetent valve** is one that cannot close completely, usually because the valve edges are scarred and do not fit together properly. Turbulence is produced when blood flows backward through the insufficient valve and collides with blood moving in the opposite direction, creating a swishing or gurgling murmur. Such backflow of blood is known as **regurgitation**. An insufficient heart valve is often called a **leaky valve**, because it lets blood leak back through at a time when the valve should be closed.

CARDIAC OUTPUT AND ITS CONTROL

Cardiac output (CO) is the volume of blood pumped by each ventricle per minute.

Cardiac output depends on the heart rate and stroke volume

The two determinants of cardiac output are heart rate (beats per minute) and stroke volume

(volume of blood pumped per beat or stroke). The average resting heart rate is 70 beats per minute, established by SA node rhythmicity, and the average resting stroke volume is 70 ml per beat, producing an average cardiac output of 4900 ml/min, or close to 5 liters/min:

Cardiac output (CO) = heart rate X stroke volume
= 70 beats/min X 70 ml/beat
= 4900 ml/min ≈ 5 liters/min

Because the body's total blood volume averages 5 to 5.5 liters, each half of the heart pumps the equivalent of the entire blood volume each minute. In other words, each minute the right ventricle normally pumps 5 liters of blood through the lungs, and the left ventricle pumps 5 liters through the systemic circulation. At this rate, each half of the heart would pump about 2.5 million liters of blood in just one year. Yet this is only the resting cardiac output! During exercise cardiac output can increase to 20 to 25 liters per minute, and outputs as high as 40 liters per minute have been recorded in trained athletes during heavy endurance-type exercise. The difference between the cardiac output at rest and the maximum volume of blood the heart can pump per minute is called the cardiac reserve.

Autonomic influences on the SA node

The SA node is normally the pacemaker of the heart, because it has the fastest spontaneous rate of depolarization to threshold. When the SA node reaches threshold, an action potential is initiated that spreads throughout the heart, inducing the heart to contract or have a "heartbeat." This happens about 70 times per minute, setting the average heart rate at 70 beats per minute. The heart is innervated by both divisions of the autonomic nervous system, which can modify the rate (as well as the strength) of contraction, even though nervous stimulation is not required to initiate contraction. The parasympathetic nerve to the heart, the **vagus nerve**, primarily supplies the atrium, especially the SA and AV nodes. Parasympathetic innervation of the ventricles is sparse. The cardiac sympathetic nerves also supply the atria, including the SA and AV nodes, and richly innervate the ventricles as well. Parasympathetic and sympathetic stimulation have the following specific effects on the heart (Table 9-3).

EFFECT OF PARASYMPATHETIC STIMULATION ON THE HEART

- Parasympathetic stimulation decreases the SA node's rate of spontaneous depolarization, prolonging the time required to drift to threshold. Therefore, the SA node reaches threshold and fires less frequently, decreasing the heart rate (Figure 9-18).
- Parasympathetic influence on the AV node decreases the node's excitability, prolonging transmission of impulses to the ventricles even longer than the usual AV nodal delay.
- Parasympathetic stimulation of the atrial contractile cells shortens the action potential, reducing the slow inward current carried by Ca^{2+}; that is, the plateau phase is shortened. As a result, atrial contraction is weakened.
- The parasympathetic system has little effect on ventricular contraction, because of the sparseness of parasympathetic innervation to the ventricles.

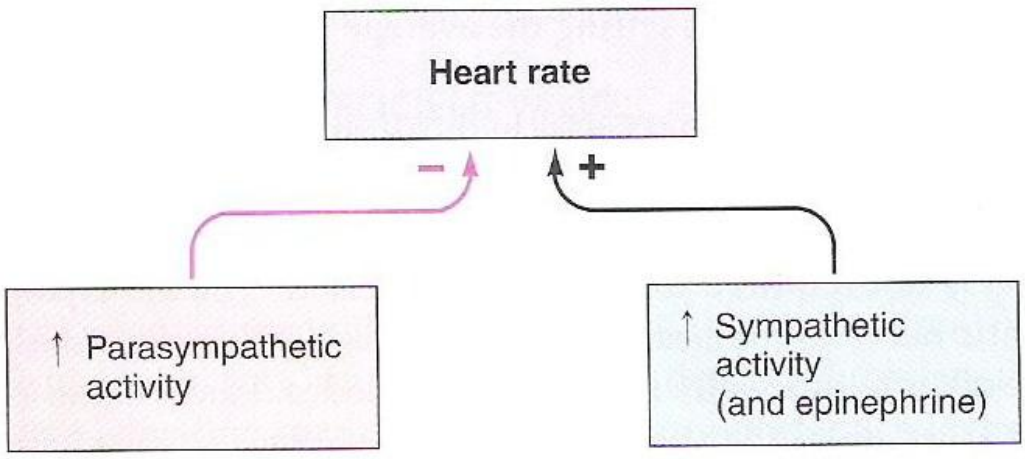
TABLE 9-3

Effects of the Autonomic Nervous System on the Heart and Structures That Influence the Heart

AREA AFFECTED	EFFECT OF PARASYMPATHETIC STIMULATION	EFFECT OF SYMPATHETIC STIMULATION
SA Node	Decreases rate of depolarization to threshold; decreases heart rate	Increases rate of depolarization to threshold; increases heart rate
AV Node	Decreases excitability; increases AV nodal delay	Increases excitability; decreases AV nodal delay
Ventricular Conduction Pathway	No effect	Increases excitability; hastens conduction through bundle of His and Purkinje cells
Atrial Muscle	Decreases contractility; weakens contraction	Increases contractility; strengthens contraction
Ventricular Muscle	No effect	Increases contractility; strengthens contraction
Adrenal Medulla (an endocrine gland)	No effect	Promotes adrenomedullary secretion of epinephrine, a hormone that augments the sympathetic nervous system's actions on the heart
Veins	No effect	Increases venous return, which increases strength of cardiac contraction through Frank-Starling mechanism

FIGURE 9-18

Autonomic control of heart rate. Increased parasympathetic activity decreases the heart rate, whereas increased sympathetic activity increases the heart rate.



EFFECT OF SYMPATHETIC STIMULATION ON THE HEART

- In contrast, the sympathetic nervous system, which controls heart action in emergency or exercise situations, when there is a need for greater blood flow, speeds up the heart rate through its effect on the pacemaker tissue. The main effect of sympathetic stimulation on the SA node is to speed up depolarization so that threshold is reached more rapidly. This swifter drift to threshold under sympathetic influence permits more frequent action potentials and a correspondingly faster heart rate (Figure 9-18 and Table 9-3).

- Sympathetic stimulation of the AV node reduces the AV nodal delay by increasing conduction velocity.

- Similarly, sympathetic stimulation speeds up spread of the action potential throughout the specialized conduction pathway.

- In the atrial and ventricular contractile cells, both of which have lots of sympathetic nerve endings, sympathetic stimulation increases contractile strength so the heart beats more forcefully and squeezes out more blood. This effect is produced by increasing Ca^{2+} permeability, which enhances the slow Ca^{2+} influx and intensifies Ca^{2+} participation in excitation-contraction coupling.

The overall effect of sympathetic stimulation on the heart, therefore, is to improve its effectiveness as a pump by increasing heart rate, decreasing the delay between atrial and ventricular contraction, decreasing conduction time throughout the heart, and increasing the force of contraction.

CONTROL OF HEART RATE

Thus, as is typical of the autonomic nervous system, parasympathetic and sympathetic effects on heart rate are antagonistic (oppose each other). At any given moment, heart rate is determined largely by the balance between inhibition of the SA node by the vagus nerve and stimulation by the cardiac sympathetic nerves. Under resting conditions, parasympathetic discharge dominates. The relative level of activity in these two autonomic branches to the heart in turn is primarily coordinated by the cardiovascular control center in the brain stem.

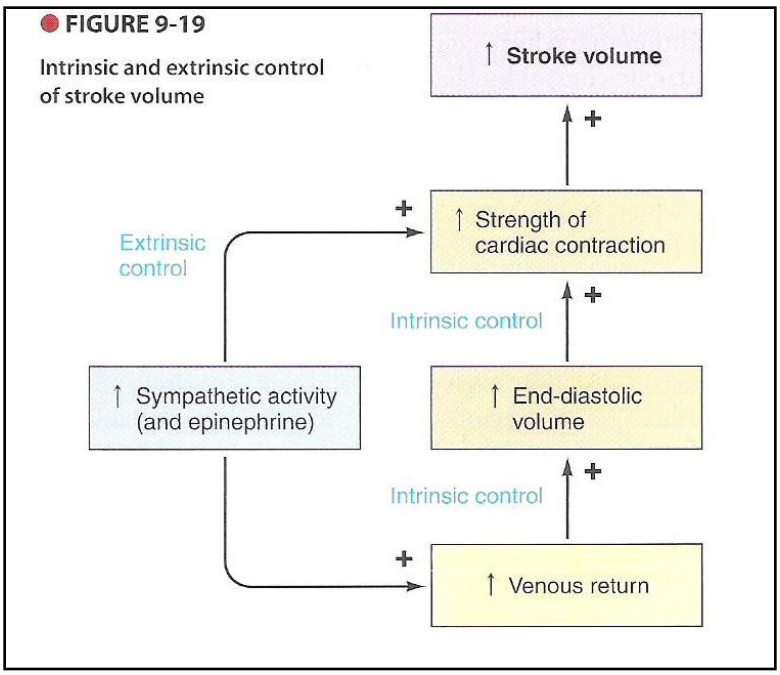
Although autonomic innervation is the primary means by which heart rate is regulated, other factors affect it as well. The most important is epinephrine, a hormone that on sympathetic stimulation is secreted into the blood from the adrenal medulla and that acts on the heart in a manner similar to norepinephrine (the sympathetic neurotransmitter) to increase the heart rate. Epinephrine reinforces the direct effect that the sympathetic nervous system has on the heart.

Stroke volume

The other component besides heart rate that determines cardiac output is stroke volume, the amount of blood pumped out by each ventricle during each beat. Two types of controls influence stroke volume: (1) intrinsic control related to the extent of venous return and (2) extrinsic control related to the extent of sympathetic stimulation of the heart. Both factors increase stroke volume by increasing the strength of heart contraction (Figure 9-19).

Increased end-diastolic volume results in increased stroke volume

Intrinsic control of stroke volume, which refers to the heart's inherent ability to vary stroke volume, depends on the direct correlation between end-diastolic volume and stroke volume. As more blood returns to the heart, the heart pumps out more blood, but the relationship is not quite as simple as might seem, because the heart does not eject all the blood it contains.



Sympathetic stimulation increases the contractility of the heart.

In addition to intrinsic control, stroke volume is also subject to **extrinsic control** by factors originating outside the heart, the most important of which are actions of the cardiac sympathetic nerves and epinephrine (Table 9-3). Sympathetic stimulation increases stroke volume not only by strengthening cardiac contractility but also by enhancing venous return (Figure 9-21c). Sympathetic stimulation constricts the veins, which squeezes more blood forward from the veins to the heart, increasing the end-diastolic volume and subsequently increasing the stroke volume even further.

SUMMARY OF FACTORS AFFECTING STROKE VOLUME AND CARDIAC OUTPUT

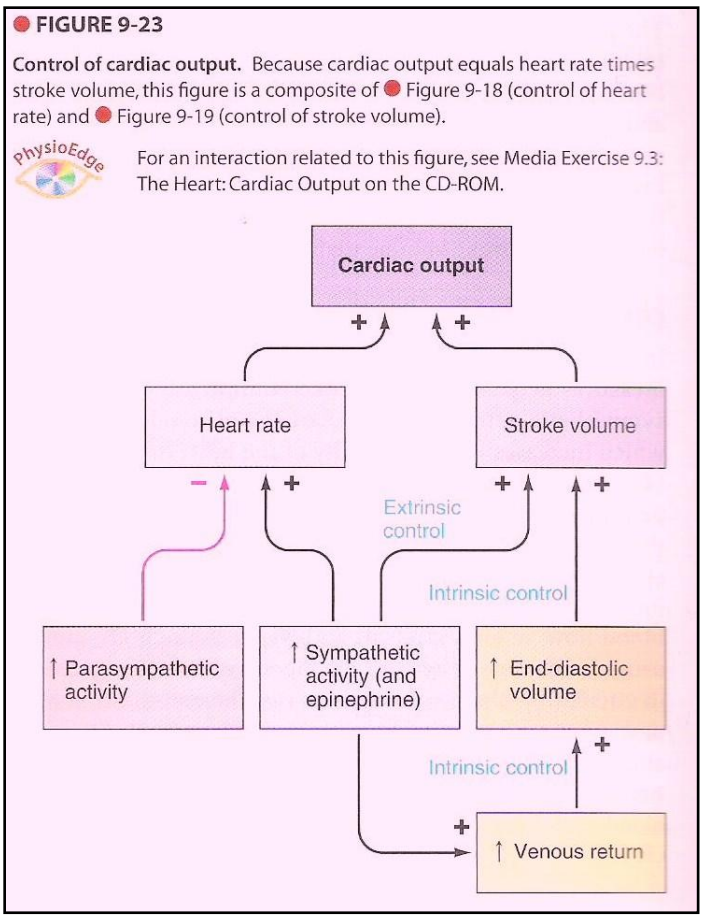
All the factors that determine cardiac output by influencing heart rate or stroke volume are summarized in Figure 9-23. Note that sympathetic stimulation increases cardiac output by increasing both heart rate and stroke volume. Sympathetic activity to the heart increases, for example, during exercise when the working skeletal muscles need increased delivery of O_2-laden blood to support their high rate of ATP consumption.

Heart failure

Heart failure may occur for a variety of reasons, but the two most common are (1) damage to the heart muscle as a result of a heart attack or impaired circulation to the cardiac muscle and (2) prolonged pumping against a chronically elevated blood pressure.

COMPENSATORY MEASURES FOR HEART FAILURE

In the early stages of heart failure, two major compensatory measures help restore the stroke volume to normal. First, sympathetic activity to the heart is reflexively increased, which increases the contractility of the heart toward normal. Second, when cardiac output is reduced, the kidneys, in a compensatory attempt to improve their reduced blood flow, retain extra salt and water in the body during urine formation, to expand the blood volume.



DECOMPENSATED HEART FAILURE

As the disease progresses and heart contractility deteriorates further, the heart reaches a point at which it can no longer pump out a normal stroke volume despite compensatory measures. At this point, the heart slips from compensated heart failure into a state of decompensated heart failure. Backward failure occurs as blood that cannot enter and be pumped out by the heart continues to dam up in the venous system. Forward failure occurs simultaneously as the heart fails to pump an adequate amount of blood forward to the tissues because the stroke volume becomes progressively smaller. The congestion in the venous system is why this condition is sometimes termed congestive heart failure.

Left-sided failure has more serious consequences than right-sided failure. Backward failure of the left side leads to pulmonary edema (excess tissue fluid in the lungs) because blood dams up in the lungs. This fluid accumulation in the lungs reduces exchange of O_2 and CO_2 between the air and blood in the lungs, reducing arterial oxygenation and elevating levels of acid-forming CO_2 in the blood. In addition, one of the more serious consequences of left-sided forward failure is an inadequate blood flow to the kidneys, which causes a twofold problem. First, vital kidney function is depressed; and second, the kidneys retain even more salt and water in the body during urine formation as they try to expand the plasma volume even further to improve their reduced blood flow. Excessive fluid retention further exacerbates the already existing problems of venous congestion.

Treatment of congestive heart failure therefore includes measures that reduce salt and water retention and increase urinary output as well as drugs that enhance the contractile ability of the weakened heart-digitalis, for example.

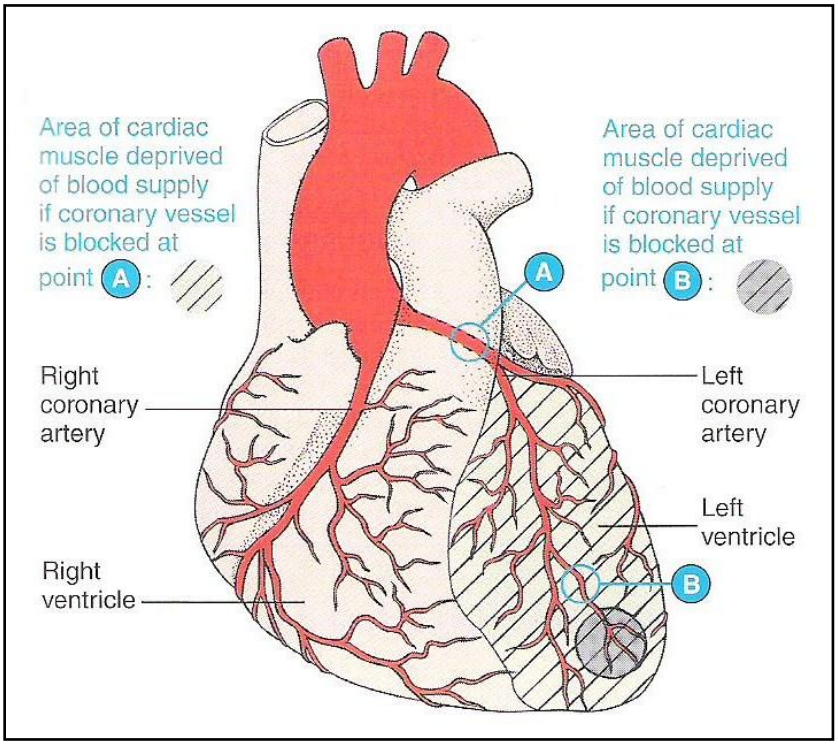
NOURISHING THE HEART MUSCLE

The heart depends on O_2 delivery and aerobic metabolism to generate the energy necessary for contraction.

The heart receives most of its own blood supply through the coronary circulation during diastole

Although all the blood passes through the heart, the heart muscle cannot extract O_2 or nutrients from the blood within its chambers for two reasons. First, the watertight endocardial lining does not permit blood to pass from the chamber into the myocardium. Second, the heart walls are too thick to permit diffusion of O_2 and other supplies from the blood in the chamber to the individual cardiac cells. Therefore, like other tissues of the body, heart muscle must receive blood through blood vessels, specifically via the coronary circulation. The coronary arteries branch from the aorta just beyond the aortic valve (Figure 9-27), and the coronary veins empty into the right atrium.

FIGURE 9-27. Extent of myocardial damage as a function of the size of the occluded vessesl



The heart muscle receives most of its blood supply during diastole. Blood flow to the heart muscle cells is substantially reduced during systole for two reasons. First, the contracting myocardium compresses the major branches of the coronary arteries, and, second, the open aortic valve partially blocks the entrance to the coronary vessels. Thus most coronary arterial flow (about 70%) occurs during diastole, driven by the aortic blood pressure, with flow declining as aortic pressure drops. Just when increased demands are placed on the heart to pump more rapidly, it has less time to provide O_2 and nourishment to its own musculature to accomplish the increased workload.

Nevertheless, under normal circumstances the heart muscle does receive adequate blood flow to support its activities, even during exercise, when the rate of coronary blood flow increases up to five times its resting rate. Extra blood is delivered to the cardiac cells primarily by vasodilation, or enlargement, of the coronary vessels, which lets more blood flow through them, especially during diastole. Coronary blood flow is adjusted primarily in response to changes in the heart's

O_2 requirements. When cardiac activity increases and the heart thus needs more O_2 local chemical changes induce dilation of the coronary blood vessels, allowing more O_2-rich blood to flow to the more active cardiac cells to meet their increased O_2 demand. This matching of O_2 delivery with O_2 needs is crucial, because the heart muscle depends on oxidative processes to generate energy. The heart cannot get enough ATP through anaerobic metabolism.

Atherosclerotic coronary artery disease can deprive the heart of essential oxygen

Adequacy of coronary blood flow is relative to the heart's O_2 demands at any given moment. With coronary artery disease, coronary blood flow may not be able to keep pace with rising O_2 needs. The term coronary artery disease (CAD) refers to pathologic changes, within the coronary artery walls, that diminish blood flow through these vessels. A given rate of coronary blood flow may be adequate at rest but insufficient in physical exertion or other stressful situations. Complications of CAD, including heart attacks

CAD can cause myocardial ischemia and possibly lead to acute myocardial infarction by three mechanisms: (1) profound vascular spasm of the coronary arteries, (2) formation of atherosclerotic plaques, and (3) thromboembolism.

VASCULAR SPASM

Vascular spasm is an abnormal spastic constriction that transiently narrows the coronary vessels. Vascular spasms are associated with the early stages of CAD and are most often triggered by exposure to cold, physical exertion, or anxiety. The condition is reversible and usually does not last long enough to damage the cardiac muscle.

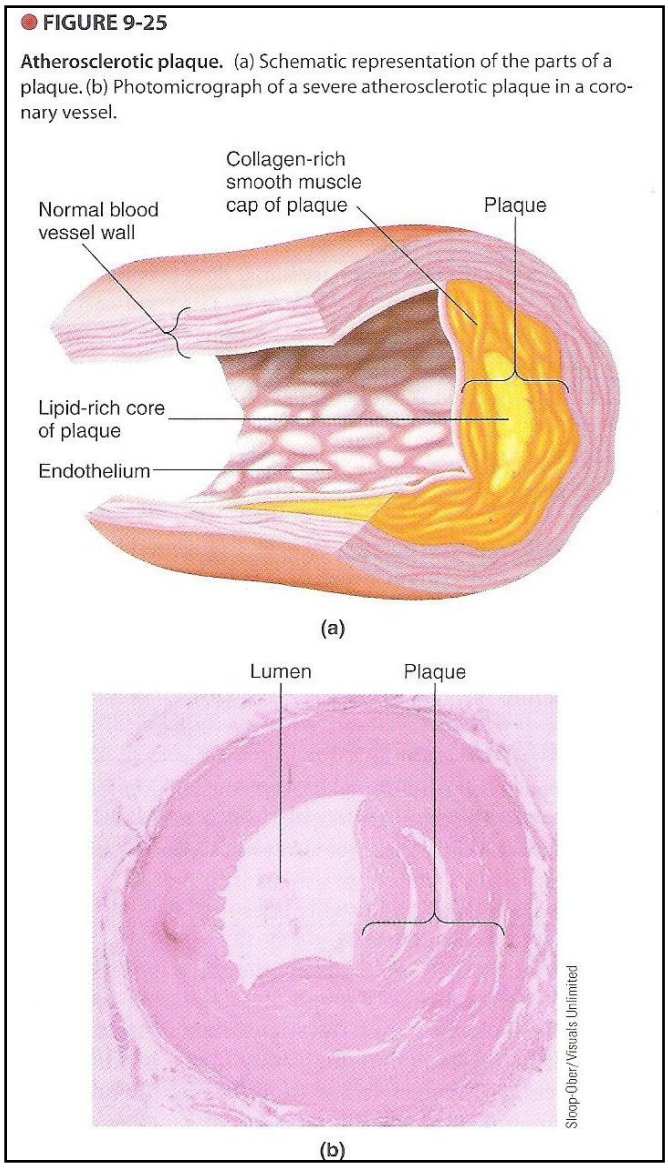
When too little O_2 is available in the coronary vessels, the endothelium (blood vessel lining) releases platelet-activating factor (PAF). PAF, which exerts a variety of actions, was named for its first discovered effect, activating platelets. Among its other effects, PAF, once released from the endothelium, diffuses to the underlying vascular smooth muscle and causes it to contract, bringing about vascular spasm.

DEVELOPMENT OF ATHEROSCLEROSIS

Atherosclerosis is a progressive, degenerative arterial disease that leads to occlusion (gradual blockage) of affected vessels, reducing blood flow through them. Atherosclerosis is characterized by plaques forming beneath the vessel lining within arterial walls. An **atherosclerotic plaque** consists of a lipid-rich core covered by an abnormal overgrowth of smooth muscle cells, topped off by a collagen-rich connective tissue cap. As plaque forms, it bulges into the vessel lumen (Figure 9-25).

Although not all the contributing factors have been identified, in recent years investigators have sorted out the following complex sequence of events in the gradual development of atherosclerosis:

1. Atherosclerosis is believed to start with injury to the blood vessel wall, which triggers an inflammatory response that sets the stage for plaque buildup. Normally inflammation is a protective response that fights infection and promotes repair of damaged tissue. However, when the cause of the injury persists within the vessel wall, the sustained, low grade inflammatory response over a course of decades can insidiously lead to arterial plaque formation and heart disease. Plaque formation likely has many causes. Suspected artery abusing agents that may set off the vascular inflammatory response included oxidized cholesterol, free radicals, high blood pressure, homocysteine, chemicals released from fat cells, or even bacteria and viruses that damage blood vessel walls. The most common triggering agent appears to be oxidized cholesterol.



2. Typically, the initial stage of atherosclerosis is characterized by the accumulation beneath the endothelium of excessive amounts of low-density lipoprotein (LDL), the so-called "bad" cholesterol, in combination with a protein carrier. As LDL accumulates within the vessel wall, this cholesterol product becomes oxidized, primarily by oxidative wastes produced by the blood vessel cells. These wastes are free radicals, very unstable electron-deficient particles that are highly reactive. Antioxidant vitamins that prevent LDL oxidation, such as vitamin E, vitamin C, and beta-carotene, have been shown to slow plaque deposition.
3. In response to the presence of oxidized LDL and/or other irritants, the endothelial cells produce chemicals that attract monocytes, a type of white blood cell, to the site. These immune cells trigger a local inflammatory response.
4. Once they leave the blood and enter the vessel wall, monocytes settle down permanently, enlarge, and become large phagocytic cells called macrophages. Macrophages voraciously phagocytize the oxidized LDL until these cells become so packed with fatty droplets that

they appear foamy under a microscope. Now called foam cells, these greatly engorged macro phages accumulate beneath the vessel lining and form a visible fatty streak, the earliest form of an atherosclerotic plaque.

5. Thus the earliest stage of plaque formation is characterized by the accumulation beneath the endothelium of a cholesterol-rich deposit. The disease progresses as smooth muscle cells within the blood vessel wall migrate from the muscular layer of the blood vessel to a position on top of the lipid accumulation, just beneath the endothelium. This migration is triggered by chemicals released at the inflammatory site. At their new location, the smooth muscle cells continue to divide and enlarge, producing atheromas, which are benign (noncancerous) tumors of smooth muscle cells within the blood vessel walls. Together the lipid-rich core and overlying smooth muscle form a maturing plaque.
6. As it continues to develop, the plaque progressively bulges into the lumen of the vessel. The protruding plaque narrows the opening through which blood can flow.
7. Further contributing to vessel narrowing, oxidized LDL inhibits release of nitric oxide from the endothelial cells. Nitric oxide is a local chemical messenger that relaxes the underlying layer of normal smooth-muscle cells within the vessel wall. Relaxation of these smooth muscle cells dilates the vessel. Because of reduced nitric oxide release, vessels damaged by developing plaques cannot dilate as readily as normal.
8. A thickening plaque also interferes with nutrient exchange for cells located within the involved arterial wall, leading to degeneration of the wall in the vicinity of the plaque. The damaged area is invaded by fibroblasts (scar-forming cells), which form a connective tissue cap over the plaque. (The term sclerosis means excessive growth of fibrous connective tissue, hence the term atherosclerosis for this condition characterized by atheromas and sclerosis, along with abnormal lipid accumulation.)
9. In the later stages of the disease, Ca^{2+} often precipitates in the plaque. A vessel so afflicted becomes hard and cannot distend easily

THROMBOEMBOLISM AND OTHER COMPLICATIONS OF ATHEROSCLEROSIS

Atherosclerosis attacks arteries throughout the body; but the most serious consequences involve damage to the vessels of the brain and heart. In the brain, atherosclerosis is the prime cause of strokes, whereas in the heart it brings about myocardial ischemia and its complications. The following are potential complications of coronary atherosclerosis:

- *Angina pectoris*. Gradual enlargement of protruding plaque continues to narrow the vessel lumen and progressively diminishes coronary blood flow, triggering increasingly frequent bouts of transient myocardial ischemia as the ability to match blood flow with cardiac O_2 needs becomes more limited. Although the heart cannot normally be "felt," pain is associated with myocardial ischemia. Such cardiac pain, known as angina pectoris ("pain of the chest"), can be felt beneath the sternum and is often referred to (appears to come from) the left shoulder and down the left arm. The symptoms of angina pectoris recur whenever cardiac O_2 demands become too great in relation to the coronary blood flow-for example, during exertion or emotional stress. The ischemia associated with the characteristically brief angina attacks is usually temporary and reversible and can be relieved by rest, taking vasodilator drugs such as nitroglycerin, or both. Nitroglycerin brings about coronary vasodilation by being metabolically converted to nitric oxide, which in turn relaxes the vascular smooth muscle.

- *Thromboembolism*. The enlarging atherosclerotic plaque can break through the weakened endothelial lining that covers it, exposing blood to the underlying collagen in the collagen-rich connective tissue cap of the plaque. Foam cells release chemicals that can weaken the fibrous cap of a plaque by breaking down the connective tissue fibers. Plaques with thick fibrous caps are considered stable, because they are not likely to rupture. However, plaques with thinner fibrous caps are unstable, because they are likely to rupture and trigger clot formation.

  Blood platelets (formed elements of the blood involved in plugging vessel defects and in clot formation) normally do not adhere to smooth, healthy vessel linings. However, when platelets contact collagen at the site of vessel damage, they stick to the site and help promote the formation of a blood clot. Furthermore, foam cells produce a potent clot promoter. Such an abnormal clot attached to a vessel wall is called a thrombus. The thrombus may enlarge gradually until it completely blocks the vessel at that site, or the continued flow of blood past the thrombus may break it loose. As it heads downstream, such a freely floating clot, or embolus, may completely plug a smaller vessel (Figure 9-26). Thus, through thromboembolism atherosclerosis can result in a gradual or sudden occlusion of a coronary vessel (or any other vessel).

- *Heart attack*. When a coronary vessel is completely plugged, the cardiac tissue served by the vessel soon dies from O_2 deprivation, and a heart attack occurs, unless the area can be supplied with blood from nearby vessels.

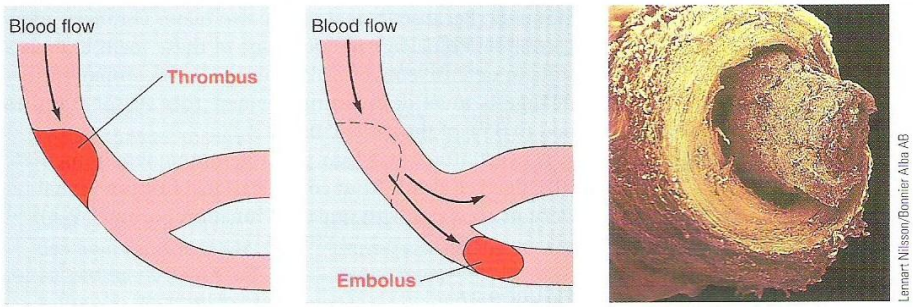


FIGURE 9-26

Results of thromboembolism. (a) A thrombus may enlarge gradually until it completely occludes the vessel at that site. (b) A thrombus may break loose from its attachment, forming an embolus that may completely block a smaller vessel downstream. (c) Scanning electron micrograph of a vessel completely occluded by a thromboembolic lesion.

Sometimes a deprived area is lucky enough to receive blood from more than one pathway **Collateral circulation** exists when small terminal branches from adjacent blood vessels nourish the same area. These accessory vessels cannot develop suddenly after an abrupt blockage but may be lifesaving if already developed. Such alternate vascular pathways often develop over a period of time when an atherosclerotic constriction progresses slowly, or they may be induced by sustained demands on the heart through regular aerobic exercise.

In the absence of collateral circulation, the extent of the damaged area during a heart attack depends on the size of the blocked vessel. The larger the vessel occluded, the greater the area deprived of blood supply. As Figure 9-27 illustrates, a blockage at point A in the coronary

circulation would cause more extensive damage than would a blockage at point B. Because there are only two major coronary arteries, complete blockage of either one of these main branches results in extensive myocardial damage. Left coronary-artery blockage is most devastating because this vessel supplies blood to 85% of the cardiac tissue.

A heart attack has four possible outcomes: immediate death, delayed death from complications, full functional recovery, or recovery with impaired function (Table 9-4).

TABLE 9-4

Possible Outcomes of Acute Myocardial Infarction (Heart Attack)

IMMEDIATE DEATH	DELAYED DEATH FROM COMPLICATIONS	FULL FUNCTIONAL RECOVERY	RECOVERY WITH IMPAIRED FUNCTION
Acute cardiac failure because heart is too weak to pump effectively to support body tissues Fatal ventricular fibrillation from damage to specialized conducting tissue or from O_2 deprivation	Fatal rupture of dead, degenerating area of heart wall Slowly progressing congestive heart failure because weakened heart cannot pump out all the blood returned to it	Replacement of damaged area with a strong scar, accompanied by enlargement of remaining normal contractile tissue to compensate for lost cardiac musculature	Persistence of permanent functional defects, such as bradycardia or conduction blocks, caused by destruction of irreplaceable autorhythmic or conductive tissues