Lectures in Cardiovascular Physiology

By Patrick Eggena, M.D.

Novateur Medmedia LLC.
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Dedication

This book is dedicated to Bonnie

and to our children, Kendra and Brandon,

and our grandchildren, Basia, Anika, and August.
Preface

This is a thirteen hour lecture series in Cardiovascular Physiology given by the author to First Year Medical Students. Each of these lectures has been captured on video and is followed with relevant reading material from the author’s ebook, “Medical Physiology of the Heart-Lung-Kidney”.

Many of the basic physiological concepts discussed in these lectures are applied to clinical situations, for example, the lectures on interpreting ECGs and listening to heart murmurs, so that these programs should be helpful not only in Physiology Courses but also in Pathophysiology Courses for Medical, Osteopathic, Podiatric or Nurse Practitioner students.
About the Author

The author was born in London, grew up on the Isle of Man and in Germany where he attended the Gymnasium Laurentianum in Warendorf, Westfalia.

He emigrated to America at the age of 18, was drafted into the Army, and sent overseas where he served as a Medic. Upon returning to the US he attended Kenyon College and Medical School at the University of Cincinnati. After serving as a house officer at the Cincinnati General Hospital he started a career in Medical Research, first as an NIH post-doctoral fellow at the Brookhaven National Laboratories and the University of Copenhagen, and then as an Established Investigator of the American Heart Association at the Mount Sinai School of Medicine. There he chaired the Physiology Course for many years, taught all aspects of Physiology, and participated in the Art and Science of Medicine courses for First and Second Year Medical Students.

Students at The Mount Sinai Medical School awarded him The Excellence in Teaching Award on twelve occasions. Besides teaching and basic research concerning the cellular mechanism of action of vasopressin, the author has served as an Emergency Physician for the 16-hour night shift at a Veterans Administration Hospital once a week for many years before retiring last year.
In this one hour video-lecture Dr. Eggena gives an overview of the cardiovascular system and considers cardiac action potentials.
Basic Structure and Function of the Heart
1. The Chambers of the Heart

The heart is made of four chambers, two atria and two ventricles (Fig.4-2). Venous blood from the peripheral organs and tissues enters the right atrium through the superior and inferior vena cava and then flows through the tricuspid valve into the right ventricle; from there it is pumped through the pulmonic valve into the pulmonary artery and distributed to the capillary beds of the right and left lungs. Here oxygen is added and carbon dioxide removed, that is, venous blood is arterialized. Arterialized blood collects in pulmonary veins, flows into the left atrium, then enters the left ventricle through the mitral valve and is ejected through the aortic valve to be distributed to the organs and tissues of the body.

The left ventricle is a powerful muscle shaped into a chamber that functions as a pump when it contracts. Because the left ventricle must generate great pressure to move blood to the head, arms, legs, and to all the visceral organs (i.e., the kidneys, gut, liver, pancreas, and spleen), the wall of the left ventricle bulges with muscle. The wall of the right ventricle is much thinner because much less pressure is needed to force blood through the vessels in the lungs. Compared to the ventricles, the walls of the atria are flabby because there
is normally little resistance as blood flows unimpeded across the tricuspid or mitral valves into the ventricles. Of course, the atrial walls do contain muscle that contracts to fill the ventricles with about one-third more blood than they would otherwise contain. But contraction of the atria is usually not essential, because when they fail to contract in a coordinated and effective way - as seen commonly in patients with atrial fibrillation - the heart still delivers sufficient blood to adequately perfuse the tissues, at least at rest. As we shall discuss shortly, the electrical potentials - which are generated by the heart and can be measured with electrodes at the surface of the body (i.e., by electrocardiogram) - are proportional to the amount of muscle in the walls of the various heart chambers, so that the electrical signals generated by the atria (the P waves) are weak compared to the signals coming from the ventricles (the QRS waves).

2. Innervation of the Heart

The heart is innervated by the autonomic nervous system. Activation of parasympathetic fibers in the vagi decreases contractility of atrial muscle. Impulses received from the right vagus slow impulse formation by the SA node; impulses received from the left vagus inhibit conduction of impulses through the AV node. Parasympathetic fibers have little, if any, effect on contractility of ventricular muscle. By contrast, sympathetic fibers (and circulating epinephrine) have important effects on increasing contractility of the ventricles and altering coronary blood flow. Sympathetic stimuli also increase the firing rate of SA nodal pacemaker cells and increase the velocity of impulse conduction through the AV node. These effects of sympathetic stimulation become apparent during exercise but at rest are overshadowed by the parasympathetic restraint imposed on the heart.
This is seen in patients with heart transplants where the denervated heart beats about 100 beats per minute - well above the usual resting heart rate of about 70 beats per minute. This indicates that under normal (resting) conditions the parasympathetic system tonically restrains the heart from beating faster.

3. The Specialized Conducting System of the Heart

A heart that is disconnected from its nerve input continues to beat in a regular rhythm, albeit somewhat faster than normal. This intrinsic rhythm of the heart is generated by pacemaker cells located in the sinoatrial (SA) node where the superior vena cava joins the right atrium (Fig.4-3). Impulses spread from here over the atria. Although the regular muscle fibers of the atrial wall can conduct impulses from one fiber to the next through gap junctions, there are three specialized pathways over which impulses travel more rapidly. These and other specialized pathways for conduction of impulses in the heart (including the Purkinje fibers in the ventricles) are not real nerves but rather modified muscle fibers adapted to the special needs of the heart (i.e., a relatively slow conduction and long refractory period).

Impulses spread over both the right and left atria to reach the atrio-ventricular (AV) node, which lies at the septum between the atria near the tricuspid valve. The fibrous tissue around the tricuspid and mitral valves that separates the atrial chambers from the ventricles forms an electrically tight seal, so that the only pathway over which impulses can reach the ventricles from the atria is via the AV node. Thus, the AV node serves as a gate that regulates the impulse traffic from atria to ventricles. Impulses are conducted slowly through the AV node, which gives the atria sufficient time to contract and to fill the ventricles with blood before they, in turn, contract. An impulse spreads from the SA node through the AV node in about 0.16 seconds.

On leaving the AV node, electrical impulses travel via the bundle of His, which then divides into a right and a left branch at the top of the interventricular septum. The left branch, in turn, subdivides into an anterior and a posterior division. Both branches terminate in a network of Purkinje fibers that spread over the inside surface (the endocardium) and serve to depolarize the right and left ventricles almost simultaneously. The time interval required for depolarization of the ventricles is less than
0.12 seconds. Although rapid conduction via the His-Purkinje system is important for optimal contraction of the ventricles, when one of the major branches of the conducting system is blocked by disease, the affected ventricle will still contract. The reason is that the muscle cells of both ventricles have gap junctions that carry electrical currents from one cell to the next, albeit much more slowly than would normally be accomplished by the specialized conduction system.
Cardiac Action Potential
The conduction of impulses and contraction of muscle fibers in the heart depends upon the ability of heart muscle cells to generate action potentials, which are transient changes in the electrical potential across their membranes. Cardiac action potentials have been recorded from individual cells impaled with delicate electrodes in animal experiments.

1. The Action Potential of Ventricular Muscle

We can distinguish five phases in the action potential of a typical ventricular (contractile) muscle cell. Each phase is associated with a characteristic set of membrane channels through which ions move down their electrochemical gradients into or out of the cell. As cations such as potassium diffuse out, they produce an outwardly directed current that tends to make the inside of the cell membrane more negative. When cations such as sodium or calcium diffuse in, they produce an inward current that tends to make the inside of the cell membrane more positive (Fig.4-4).

Fig. 4-4. The five phases of an action potential of a ventricular muscle cell. Phase 4: resting membrane potential is stable at -90 mV (close to the potassium equilibrium potential \(E_{K^+}\)), which is largely due to outward flux of potassium ions through leak channels. Phase 0: rapid depolarization of the membrane drives the potential to about +20 mV (just short of the sodium equilibrium potential \(E_{Na^+}\)), which is due to inward sodium flux through fast channels. (The h-gate of these channels is already open during phase 4, but the m-gate is opened during phase 0). Phase 1: transient repolarization of the membrane is due to closure of h-gates of fast sodium channels. Phase 2: inward calcium flux via slow channels is balanced by outward potassium flux, keeping the membrane potential at a plateau. Phase 3: repolarization of the membrane is accomplished by outward diffusion of potassium through voltage-gated channels (and closure of the f-gates of the slow channels). All these processes are caused by passive diffusion of ions. Active transport is required during phase 4 to re-establish the original concentration gradients through sodium/potassium exchange pumps, calcium pumps, and sodium/calcium antiporters.
A. The Resting Membrane Potential (Phase 4)

During diastole, when the ventricular muscle cell is at rest, the potential across its membrane is about -90 mV (inside negative). This is phase 4 of the action potential, the *resting membrane potential*. At this time the membrane is more permeable to potassium than it is to sodium or calcium ions, so that outward diffusion of potassium ions through potassium leak channels is primarily responsible for the resting membrane potential. The resting membrane potential is, therefore, close to the potassium equilibrium potential (E_{K+}) of -94 mV predicted by the Nernst equation for a cell with a potassium ion concentration of 140 mEq/L inside and 4 mEq/L outside. As discussed previously, the resting membrane potential is slightly different from E_{K+} because some sodium and calcium ions do diffuse into the cell during phase 4 (which makes the potential more positive), and, moreover, the sodium/potassium exchange pump is electrogenic (which makes the potential about 5% more negative than it would otherwise be).

B. The Spike of the Action Potential (Phase 0)

Voltage-gated sodium channels in the membrane are regulated by an m-gate on the outside and an h-gate on the inside of the channel (Fig.4-4). In the resting state, when the membrane potential is about -90 mV, the h-gate (or *inactivation gate*) on the inside of the cell membrane is open, but sodium ions still cannot diffuse into the cell because the m-gate (or *activation gate*) on the outside of the cell membrane is closed. However, when the cell is stimulated the m-gates open and sodium ions rush into the cell and make the inside of the cell more positive. This change in the membrane potential to a less negative value (or in the direction of zero mV) is called *depolarization*. Depolarization of the membrane, in turn, opens more m-gates and allows even more sodium ions to rush into the cell, which, in turn, further depolarizes the membrane and opens more m-gates, etc. This positive feedback system rapidly drives the membrane from its resting state of -90 mV in the direction of the Nernst equilibrium potential for sodium (E_{Na+}) of roughly +60 mV. However, the potential peaks at about +20 mV, before E_{Na+} is reached. The brief, but intense, period of depolarization from -90 to +20 mV is *phase 0* of the action potential. The
channels responsible for phase 0 are appropriately named fast sodium channels.

C. Transient Repolarization (Phase 1)

When the membrane potential peaks at about +20 mV during phase 0 of the action potential, a negative feedback system inactivates the inward sodium current by closing the h-gates of fast sodium channels. This decrease in the inward sodium current is primarily responsible for the partial repolarization (from +20 to about 0 mV) of the membrane, which is called phase 1 of the action potential (Fig. 4-4). The h-gates will remain closed until the membrane is almost completely repolarized (at the end of phase 3). As long as the h-gates remain closed, another action potential cannot be generated; sodium ions could not enter even if the cell were stimulated and the m-gates were opened. Impulses cannot be conducted along the His-Purkinje system nor can ventricular muscle cells be stimulated to contract. In other words, the cell is refractory as long as the h-gates of the fast sodium channels remain closed.

D. The Plateau of the Action Potential (Phase 2)

Phase 2 is the plateau of the cardiac action potential (Fig. 4-4). A slow influx of calcium ions (balanced by a slow outflux of potassium ions) is primarily responsible for this prolonged phase of depolarization. Calcium ions diffuse through voltage-gated channels that open and close more gradually than the fast sodium channels. Accordingly, these calcium channels are also called slow channels or long-lasting (L-type) channels.

These slow channels, like fast sodium channels, also have dual gates that open and close primarily in response to changes in transmembrane voltage. D-gates on the outside of the membrane start to open during phase 0 when the membrane is depolarized past -50 mV (f-gates on the inside of the membrane are already open). Thus, the slow channels also contribute to phase 0 of the action potential. The slow channels remain open for a relatively long period before they are inactivated by closing of the f-gates. The long plateau phase of the action potential (characteristic for cardiac muscle and not seen in either skeletal muscle or nerve cells) leaves time for calcium ions to diffuse into the cell where they play an important function in muscle contraction.
E. Repolarization (Phase 3)

Repolarization of the membrane represents phase 3 of the action potential. As slow calcium channels start to close near the end of phase 2, voltage-gated potassium channels open, facilitated by the increase in intracellular calcium. These calcium-sensitive potassium channels are activated more gradually than the fast sodium or the L-type calcium channels. The outward flux of potassium ions repolarizes the membrane, driving the membrane potential back down toward its resting state.

F. Back at the Resting State (Phase 4).

As the membrane returns to its resting state (i.e., to phase 4), the voltage-gated potassium channels close and the outward flow of potassium ions through leak channels is now sufficient to hold the membrane potential close to -90 mV until another action potential is initiated. During the latter part of phase 3, the inactivation gates (h and f) of the fast sodium and slow calcium channels, respectively, start to open, though their activation gates (m and d) remain closed until the membrane is once again depolarized during phase 0 of an action potential.

Until the f-gates reopen slow inward current cannot flow through the slow calcium channels even if the d-gates open when the cell is stimulated. The membrane potential at which the f-gates re-open in slow calcium channels is more positive than the potential at which the h-gates of the fast sodium channels re-open. This has important consequences for cells with more positive resting membrane potentials, such as ischemic cells, cells that have been deprived of adequate amounts of oxygen. Ischemic cells do not have functional fast channels, so that inward currents (during phase 0 of the action potential) must be carried by calcium and sodium ions via slow channels. This prolongs depolarization in phase 0 of the action potential and, as will be discussed shortly, slows the conduction of impulses through ischemic tissues.

Myocardial cells gradually accumulate sodium and calcium ions and lose potassium ions during action potentials. To restore the intracellular ionic composition to normal, sodium ions are actively transported out of the cell in exchange for potassium ions by sodium/potassium exchange pumps, and calcium ions are removed from the cell by primary active transport (with calcium activated ATPases) and by
2. Pacemakers of the Heart

Between contractions of the heart, individual ventricular muscle cells have a stable resting membrane potential. In other words, phase 4 of the action potential is flat (there is no diastolic depolarization). This is not true, however, for all myocardial cells. In cells of the SA and AV nodes and in the His-Purkinje system, the membrane potential during diastole slowly drifts toward zero (Fig.4-5). When enough sodium channels have opened to reach a critical threshold voltage, an action potential is generated that then travels down the conduction system, spreads over myocardial cells, and causes contraction, i.e., systole. Cells that reach threshold fastest (normally cells in the SA node) will set the pace for the heart because all the other potential pacemakers (such as AV nodal cells and His-Purkinje cells) will be depolarized before they can reach their threshold by the wave of depolarization spreading from above.

A. The Sino-atrial Node

The SA node consists of specialized muscle cells situated in the right atrium where the superior vena cava enters. Some cells
in the SA node depolarize regularly, and this rhythmic discharge spreads to other cells in the heart that, in turn, depolarize and cause the atria and ventricles to contract. The cells in the SA node are not unique in their ability to discharge rhythmically, as mentioned, but they have the fastest rhythm, and this allows them to function as the normal pacemaker of the heart.

The resting membrane potential (phase 4) of these pacemaker cells is less negative (their maximal diastolic depolarization is about -60 mV) than the potential of working heart muscle cells (i.e., about -90 mV). During diastole the membrane potential slowly drifts to a threshold potential of about -50 mV, at which point an action potential is generated (Fig. 4-6). The slow depolarization of the SA node during phase 4 is caused by a gradual decrease in the outward flux of potassium ions as well as a progressive increase in the inward flux of sodium ions (so-called funny current, If) and then of calcium ions.

Compared to the very steep phase 0 of the action potential in ventricular muscle or Purkinje cells, phase 0 in cells of the SA node is a more gradual slope (see Fig. 4-5). The reason is that there are no fast sodium channels in the SA node (or if they are present, their h-gates remain closed at the more positive membrane potentials), so that the inward current is carried primarily initially through slow T-type (transient)
calcium channels and then through L-type (long-lasting) calcium channels. Calcium ions enter cells by these channels, causing an action potential that has no spike (phase 1) and no plateau (phase 2) compared to a ventricular muscle cell.

The pacemaker cells of the SA node generate 60 to 100 action potentials each minute. The rate depends upon three factors: (1) the level of maximal diastolic depolarization, (2) the slope of phase 4 depolarization, and (3) the threshold potential (see Fig. 4-7).

(1) Acetylcholine or vagal stimulation (for example, by massaging the carotid sinus in a patient with PSVT) causes the resting membrane potential to become more negative by increasing membrane permeability to potassium ions (Fig. 4-7, A). This increases the time required for the resting membrane potential to reach threshold, so that heart rate decreases. (This action of acetylcholine is mediated by muscarinic receptors and can, therefore, be blocked by atropine. For this reason atropine is used to accelerate the heart beat in patients with slow heart beats where an abnormal increase in vagal tone is suspected as being the cause for the bradycardia.) Moreover, acetylcholine decreases the slope of phase 4 by decreasing the funny current (If) and the inward calcium current (I_Ca).

(2) In contrast, sympathetic stimulation (or norepinephrine or epinephrine) increases the slope of phase 4 depolarization by increasing the funny current (If) and the inward calcium current (I_Ca). This decreases the time required for the resting membrane
potential to reach threshold, so that heart rate increases (Fig.4-7,B). This so-called **chronotropic** action of the catecholamines is mediated by beta-1-adrenergic receptors. For this reason beta-1-receptor blockers are frequently used to prevent excessive sympathetic stimulation of the heart (from excitement, stress, or exercise) in patients recovering from a myocardial infarction.

**B. The Atrio-ventricular Node**

Pacemaker cells in the AV node fire rhythmically at rates between 40 to 60 times per minute. The action potential in these cells is similar to those in the SA node except that the maximal diastolic potential is lower (-70 mV versus -60 mV, see Fig.4-5). These AV cells are depolarized to threshold by an action potential transmitted from the SA node before phase 4 reaches threshold. Thus, the inherent rhythm of the AV node is normally not seen. Only when the SA node fails to discharge at a faster rate than the AV node (or when impulses from the SA to the AV node are blocked) do the AV nodal cells function as **back-up pacemakers** for the heart.

More important than phase 4 is phase 0 of the AV node action potential, because the slope of phase 0 determines the speed at which impulses are conducted from the atria to the ventricles. The slope of phase 0 (and, therefore, the speed of conduction) is decreased by parasympathetic stimulation and by agents that decrease calcium influx into AV nodal cells, such as adenosine, verapamil, beta-1-adrenergic blockers, or digoxin -- medicines frequently used to reduce fast heart beats. On the other hand, the slope of phase 0 (and the speed of conduction) is increased by sympathetic stimulation or beta-1-adrenergic agonists. This action of epinephrine on the heart is called the **dromotropic action**.

**C. Purkinje Fibers**

The Purkinje fibers are potential pacemakers for the heart when transmission of impulses through the AV node is blocked. Because Purkinje cells have an upward sloping phase 4 (see Fig.4-5), they will reach threshold and discharge periodically even if they are not depolarized from above. These pacemaker cells can maintain a regular, albeit very slow, rhythm of 20 to 40 beats per minute. This distinguishes Purkinje cells from ventricular muscle cells, in which phase 4 of the action potential is flat. Another important difference is that the plateau (phase 2) of the action poten-
tial is longer for Purkinje fibers than it is for working ventricular muscle cells. This arrangement limits the frequency that impulses can be conducted along Purkinje fibers and leaves sufficient time between contractions for working ventricular muscle cells to recover.

3. Refractoriness

An important difference between the contraction of skeletal and myocardial muscle is that skeletal muscle can be stimulated so rapidly that the muscle goes into spasm (or tetanus) and contracts without relaxing intermittently. This does not happen to cardiac muscle. If it did, the heart would not be able to pump blood and death would soon result.

Heart muscle is protected from rapid stimulation by a long refractory period. A ventricular muscle cell will not contract, (and a Purkinje cell will not conduct an impulse) when it is stimulated (no matter how intensely) during the absolute refractory period (Fig.4-8). The **absolute refractory period** corresponds to the interval when the h-gates of the fast sodium channels are closed (phases 1, 2, and the first part of 3), so that no matter how many m-gates are opened, sodium ions cannot rush into the cell and superimpose a second action potential on the first. When repolarization is about half complete during phase 3 of the action potential, some h-gates of fast sodium channels have opened and an unusually strong stimulus may now induce another action potential. This period of diminished sensitivity is called the **relative refractory period**. When the cell is com-
 completamente repolarized at the end of phase 3 and all h-gates have opened, the membrane regains its normal sensitivity. Thus, in effect, the membrane will not respond to a normal stimulus for the duration of its action potential. This interval is therefore called the effective refractory period.

Because Purkinje cells have longer lasting action potentials (due to a prolonged plateau phase) than ventricular myocardial cells; their effective refractory periods are also longer. This limits the frequency at which ventricular muscle cells can be stimulated by impulses traveling along Purkinje fibers and prevents heart muscle from cramping the way leg muscles sometimes do. The Purkinje fibers first depolarize myocardial cells on the endocardial (inside) surface of the ventricles. The wave of depolarization then spreads to myocardial cells at the epicardial (outside) surface. The epicardial cells have shorter action potentials than the endocardial cells (see Fig.4-9). Thus, although phase 0 of endocardial cells precedes phase 0 of epicardial cells, phase 3 of epicardial cells precedes phase 3 of endocardial cells. As a result, depolarization (related to phase 0) proceeds from endocardium to epicardium, but repolarization (related to phase 3) proceeds from epicardium to endocardium.

**Amiodarone** is an antiarrhythmic agent that prolongs the effective refractory period of myocardial cells by blocking potassium channels and is used in the treatment of cardiac arrhythmias.
4. Propagation of the Action Potential (Conduction)

When a patch of membrane is depolarized during the rapid influx of sodium ions during phase 0 of the action potential, the deficit of positive surface charges attracts sodium ions from neighboring areas and an electrical current starts to flow on both sides of the membrane (see Fig. 4-10). As the neighboring patch of membrane is, in turn, depolarized to its threshold, the m-gates of the fast sodium channels open and an action potential is generated. In this way an action potential is propagated from one end of a cell to the other and across gap junctions from one cell to the next.

The rate at which an impulse is conducted depends upon the thickness of the conducting fibers as well as on the steepness of phase 0 of the action potential. The thicker the fiber and the steeper phase 0, the faster is conduction. For this reason Purkinje fibers conduct impulses much faster than AV nodal fibers. In Purkinje fibers (and ventricular muscle cells), phase 0 depends upon rapid influx of sodium ions through fast sodium channels; whereas, in AV nodal cells phase 0 depends upon slow influx of calcium (and some sodium ions) through slow channels. These distinctions have important therapeutic implications, because you can selectively decrease phase 0 depolarization...
(and conduction) in the AV node or ventricular muscle with agents that selectively block either slow channels in the AV node or fast channels in the ventricles. Slow channels are selectively blocked by calcium channel blockers such as verapamil or adenosine (in PSVT). On the other hand fast sodium channels are selectively blocked by agents, such as lidocaine which is effective in terminating arrhythmias arising in the ventricles.

Lidocaine is also commonly employed as a local anesthetic for suturing wounds or when filling a tooth at the dentist. Here lidocaine prevents conduction of painful stimuli along nerves also by blocking fast sodium channels.

Another important point is that conduction of impulses through an ischemic portion of ventricular muscle is slower than normal. The resting membrane potential is less negative in ischemic tissue than it is in normal tissue, and, as a consequence, the inactivation gates of the fast sodium channels remain closed. Impulses must, therefore, be propagated by action potentials where depolarization (phase 0) is caused by a slow inward current generated by diffusion of calcium and sodium ions through slow channels. As the slope of phase 0 decreases, it takes longer to depolarize neighboring patches of membrane to threshold, so that the wave of depolarization spreads more slowly and conduction decreases.
Introduction to Electrocardiography

In this 46 minute video-lecture Dr. Eggena discusses depolarization and repolarization of the heart and considers cardiac vectors, waves and intervals.
Depolarization and Repolarization of Cardiac Muscle
As the ventricle depolarizes (and then contracts), positively charged sodium ions move from the surfaces to the interior of all the individual cells that make up the ventricle. When the ventricle then repolarizes (and relaxes), positively charged potassium ions move from the interior to the exterior surface of cell membranes. Depolarization does not occur at precisely the same instant in all cells, so that cells near the endocardial surface of the ventricles are depolarized before those at the epicardial surfaces. Similarly, repolarization does not occur simultaneously in all cells, so that cells toward the epicardial surface of the ventricles are repolarized before others at the endocardial side. As a consequence, dipoles (regions with opposite electric charges, like the positive and negative poles of a battery) are generated across the ventricular wall during depolarization and repolarization. These dipoles can be measured with a sensitive voltmeter connected to electrodes placed around the heart at the surface of the chest. A recording of the changes in dipoles across the atrial and ventricular walls during the cardiac cycle is called the electrocardiogram (ECG or EKG). The ECG apparatus contains a voltmeter, a series of electrodes (its leads), and a recording device (a strip chart recorder). As we shall see shortly, the ECG
machine has 12 leads with which the voltage across the heart is measured from 12 different angles. However, let us start our discussion with only one pair of electrodes and let’s consider a hypothetical experiment in which we follow the voltage changes across a section of left ventricular wall as it first depolarizes and then repolarizes.

In the experiment shown in Figure 4-11, one electrode has been placed on the endocardial side of a strip of ventricular muscle and the other electrode on the epicardial side, with a sensitive voltmeter (ECG machine) connecting the two electrodes. Let us make the electrode on the epicardial side positive relative to the other, and let us set the polarity on the ECG machine so that it records a positive voltage (and inscribes an upward deflection on the recording paper) when the epicardial surface is positive relative to the endocardial surface. Before starting with the experiment, let us calibrate the ECG machine so that a 1 mV pulse gives an upward deflection equal to 1 cm (or 10 mm), and let us set the speed at which the paper moves past the recording pen at 25 mm/second. In this way we will obtain a precise record of the magnitude of the voltage generated by the muscle strip and the time it takes. To facilitate precise timing we will use special ECG chart paper on which distances are marked by thin lines that are 1 mm apart and by thicker lines that are 5 mm apart. Thus, the distance between two thin lines (or within one small box) equals 0.04 seconds (1 mm/25 mm/second), and the distance between two thick lines (or within one large box) equals 0.2 seconds (5 mm/25 mm/second).

Let us start the experiment by observing the muscle strip at rest (Fig.4-11,A). When all the individual muscle cells in the strip of muscle are at rest (in phase 4 of their individual action potentials), sodium ions will be evenly distributed over the surface of the muscle strip and the voltmeter will record zero mV (the needle of the recorder will draw a flat line on graph paper). As muscle cells at the endocardial surface of the strip are stimulated (phase 0 of their action potentials), sodium ions rush into the cells, causing a (relative) deficit in positive surface charges at the endocardial side. The resulting voltage change across the muscle strip is recorded as an upward (or positive) deflection on the graph paper. This positive deflection reaches a maximum when the endocardial half of all the cells in the muscle strip has been depolarized (Fig.4-11,B). As the other (epicardial) half of the cells becomes depolarized, the voltage across the strip returns to zero.
These voltage changes, recorded as a function of time as ventricular muscle cells are progressively depolarized, are called the **R wave**. Just after the R wave, all cells in the muscle strip remain depolarized (these cells are in phase 2 of their action potentials), so that the voltmeter again records zero mV (a flat line on the graph paper), (Fig.4-11,C).

After muscle cells have been depolarized for a while (leaving time for the cells to contract), they start to repolarize (so they can relax). Repolarization of the muscle strip is initiated by cells at the epicardial side. Potassium ions move out onto the surface of these cells during phase 3 of their action potentials, which results in a relative excess in surface charges at the epicardial side and causes a voltage change that is recorded as an upward deflection. Again, voltage is maximal when one-half the cells has repolarized (Fig.4-11,D). The voltage then returns to zero mV as the other (endocardial) half of cells is repolarized (Fig.4-11,E). These voltage changes during repolarization of ventricular muscle are called the **T wave**. The T wave is wider than the R wave, because repolarization takes longer than depolarization. The polarity of the T and R waves is normally the same, i.e., they are both upright, because depolarization of the muscle strip occurs from endocardium to epicardium; whereas, repolarization occurs from epicardium to endocardium.

Why does repolarization occur in a direction opposite to depolarization? The reason is that the action potentials in epicardial cells are shorter than they are in endocardial cells (Fig.4-11,F). Because epicardial cells have a shorter plateau phase (phase 2), repolarization (phase 3) occurs in epicardial cells before it does in endocardial cells.

When ventricular muscle becomes **ischemic** (lacks adequate oxygen), repolarization occurs in a direction opposite from normal, i.e., from endocardium to epicardium, which results in inversion of the T wave (Fig.4-12,A).

The reasons for this are complex. First, when the coronary blood supply to ventricular muscle is diminished, endocardial cells become ischemic before epicardial cells because blood vessels in the **subendocardium** (area toward the inside of the ventricular wall) are more compressed during systole than are vessels on the outside of the heart. Second, when endocardial cells become ischemic, rapid depolarization (phase 0) occurs more slowly than in normal cells (compare the ischemic endo-
cardiac cell with normal epicardial cell in Figure 4-12,B). Because the speed at which impulses are conducted decreases as the slope of phase 0 depolarization diminishes, the wave of depolarization from endocardium to epicardium is slowed. In part, because of this delay in epicardial cell depolarization, the ischemic endocardial cell starts to repolarize (phase 3) before the epicardial cell. Another reason for early repolarization of the ischemic endocardial cell, is that the plateau (phase 2) is shortened so that repolarization (phase 3) starts earlier than usual. Because ischemic endocardial cells repolarize before normal epicardial cells do, the direction of repolarization is reversed, and the T wave on the ECG becomes inverted. For these reasons, sudden inversion of T waves in a subject who has been asked to exercise in the cardiac function laboratory during a stress test is a sign of coronary artery insufficiency.
Cardiac Vectors, Waves and Intervals
A. Vectors

Let us now apply the lesson learned from the isolated muscle strip to interpreting the waves seen on an ECG, recorded with two electrodes on the chest wall across the heart (Fig. 4-13,A). Let us make the electrode on the left chest, overlying the left ventricle, positive with respect to the electrode on the right chest. As the left ventricle depolarizes from endocardium to epicardium, the wave of depolarization moves toward the positive electrode (or lead) on the chest and, accordingly, inscribes an upright (or positive) deflection on the ECG paper. Let us pretend that we could depolarize the right ventricle independent of the left. Now the wave of depolarization moves away from the positive electrode, and a downward (or negative) deflection is made on the ECG tracing.

The upward deflection by left ventricular depolarization would be greater than the downward deflection by right ventricular depolarization, because the ventricular muscle mass is considerably greater on the left than it is on the right. The peak voltages of these upward or downward deflections could be measured (in mV or mm) and expressed as vectors (arrows with lengths proportional to their magnitudes) directed toward or away from the position.

Fig. 4-13. Cardiac vectors during right and left ventricular depolarization. Voltages are measured across the heart with a negative electrode on the right side of the chest and a positive electrode on the left side of the chest. Depolarization of ventricular muscle toward the positive electrode (or lead) produces a positive vector and results in a positive (or upward) deflection (or wave) on the ECG tracing. In (A) simultaneous depolarization of right and left ventricles, a negative vector from right ventricular depolarization is generated simultaneously with a positive vector from left ventricular depolarization. Because the left ventricular muscle mass is considerably greater than the right ventricular muscle mass, the positive vector is greater than the negative vector so that the resultant vector is positive. Thus an R wave appears in the ECG tracing for this lead. In (B) sequential depolarization of right and left ventricles is illustrated for a premature ventricular contraction (PVC). The irritable focus in the left ventricle first depolarizes the left ventricle, resulting in an upright deflection (R wave) in this lead, and subsequently depolarizes the right ventricle, resulting in a downward deflection (an S wave) in this lead. This accounts for the characteristically large and wide QRS complexes seen with PVCs.
where the lead was placed on the left chest wall. Now, if the right and left ventricles depolarize simultaneously (as they normally do), the opposing vectors would tend to cancel one another. Accordingly, the upright deflection in a lead overlying the left ventricle is normally less than it would be if the right ventricle were not depolarizing at the same time as the left (Fig. 4-13, A).

Now let us assume that the two ventricles do not depolarize simultaneously, but sequentially, first the left ventricle and then the right. One sees this with premature ventricular contractions (PVCs), (Fig. 4-13, B). If an irritable focus discharges in the left ventricle, the left ventricle will depolarize before the right, because the impulse is now conducted much more slowly than usual to the right ventricle (conduction occurs via gap junctions of muscle cells rather than along the specialized Purkinje system). Now the upward deflection caused by the wave of depolarization across the left ventricular wall will be unopposed, giving rise to a much larger positive deflection, and the wave of depolarization in the opposite direction across the right ventricular wall will no longer be hidden and will show itself as a large negative deflection. For this reason, PVCs show much taller upright waves (R waves) and much deeper inverted waves (S waves) than normal, and, because depolarization of the two ventricles in sequence takes longer than usual, PVCs characteristically have much wider R and S waves than normal.

B. Waves

During the cardiac cycle different parts of the heart depolarize and repolarize - some parts simultaneously, others not. As a consequence some vectors are hidden (e.g., the right ventricle) and others are blunted (e.g. the left ventricle). Vectors that occur sequentially can be identified as upward or downward deflections on the ECG tracing; these deflections are called waves and are identified by letter names (Fig. 4-14). Whenever the net (or averaged) vector is directed toward an ECG lead (always the positive pole of an electrode), an upward or positive wave will appear on the ECG record. Whenever the net vector is directed away from an ECG lead, a downward or negative wave will be seen.

The cardiac cycle starts with depolarization of the SA node. As the impulse spreads from the SA node over specialized conductive pathways to the right and left atria, the muscle depolarizes toward the lead, which causes an upright deflection to be inscribed on the ECG tracing, called
the **P wave** (Fig. 4-14). The P wave is followed by a short delay (a flat line at zero mV) as the impulse is slowly conducted through the AV node (the mass of these conducting fibers is too small to register a depolarization on the surface ECG). The delay at the AV node allows the atria to contract and to pump blood into the ventricles. (Keep in mind that the P wave represents the electrical activity of atrial muscle and not the mechanical event, i.e., contraction).

The impulse emerges from the AV node and enters the ventricular septum via the right and left bundle branches. The ventricular septum is the first part of the ventricles to be depolarized. Because the left ventricle contributes more muscle to the septum than does the right ventricle, the net vector during depolarization (from endocardium to epicardium) is from left to right, i.e., it is directed away from the left chest lead. Therefore, this vector is recorded as a downward deflection, called a **Q wave**. Small Q waves are normal; large ones are not. (They indicate myocardial infarction.) Small, normal Q waves are sometimes referred to as **septal Q waves**.

The impulse spreads rapidly and almost simultaneously from the interventricular septum via the Purkinje network to the right

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**Fig. 4-14.** The waves and intervals of the ECG. In (A) a lead on the chest over the left heart explores vectors coming toward or moving away from it. Positive vectors (moving toward the lead) result from atrial depolarization (P), left ventricular depolarization (R), and left ventricular repolarization (T). Negative vectors (moving away from the lead) result from depolarization of the interventricular septum (Q), and depolarization of the most lateral/superior part of the left ventricle (S). All of these vectors occur sequentially and, therefore, produce characteristic waves, as is shown in the ECG tracing in (B). In (C), the various intervals and segments of the normal ECG along with the J-point are illustrated for a heart rate of 60 beats/min.
and left ventricles where the net vector for depolarization is toward the left (because the muscle mass is considerably greater on the left than the right), causing an upward deflection, the **R wave**. As the wave of depolarization reaches the furthest and most lateral parts of the thick left ventricle, the vector is once again directed away from the lead, causing a downward deflection, called an **S wave**. (Unlike a Q wave, an S wave must always follow an R wave. If there is no R wave, i.e. no upward deflection, the downward deflection is not called an S wave, but rather a **QS complex**. A QS complex is abnormal and signifies myocardial infarction. Following the QRS complex is a delay (a flat line at zero mV), as the ventricles contract and blood is pumped to the lungs and the peripheral organs. (Keep in mind that the QRS complex represents the electrical activity of the ventricles just before the As the ventricles repolarize from epicardium to endocardium and relax, the vector of ventricular repolarization is directed toward the lead on the left chest wall, which causes an upright deflection, the **T wave**. (One might expect a similar, albeit smaller, wave for atrial repolarization. However, atrial repolarization occurs during ventricular depolarization and is, presumably, obscured by the much larger QRS complex.) Immediately follow-

![Table 4-1]

**Table 4-1 Normal Values for ECG Waves and Intervals**

<table>
<thead>
<tr>
<th>Wave</th>
<th>Duration (seconds)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>0.12 - 0.20</td>
<td>&lt;1 large box</td>
</tr>
<tr>
<td>Q</td>
<td>&lt; 0.04</td>
<td>&lt;1 small box, &lt;2.5 small boxes</td>
</tr>
<tr>
<td>QRS</td>
<td>0.05 - 0.10</td>
<td>&lt;2 large boxes (if heart rate = 60 /minute)</td>
</tr>
<tr>
<td>QT</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

ing the T wave a small upright deflection is sometimes seen (e.g., with hypokalemia. This is a **U wave**. Its origin is uncertain. It may represent delayed after depolarization of ventricular muscle or delayed repolarization of Purkinje fibers with electrolyte imbalance.

**C. Intervals**

Table 4-1 gives normal values for the duration of ECG waves and intervals expressed both in seconds and in number of boxes on the ECG graph paper.

The **PR interval** is the time interval from the beginning of the P wave to the beginning of the R wave. It represents the time required for the atria to depolarize and for the impulse to be conducted through the AV node and along the His-Purkinje network. The PR interval is primarily affected
by changes in conduction at the AV node. When conduction is abnormally slowed (i.e., in first degree AV block), the PR interval is prolonged to more than 0.20 seconds (more than 1 large box). When conduction is abnormally fast (e.g., in Wolff-Parkinson-White and Lown-Ganong-Levine syndromes), the PR interval is shortened to less than 0.12 seconds.

The **QRS interval** is the time interval from beginning of the Q wave (or more often the R wave) to the end of the S wave. It represents the time required for the ventricles to depolarize. This interval is normally less than 0.10 seconds, so the QRS complex fits into 2.5 small boxes. This interval is prolonged to more than 0.12 seconds in bundle branch blocks. Wide QRS complexes are also seen in the Wolff-Parkinson-White syndrome.

The **QT interval** is the time interval from the beginning of the Q wave (or R wave) to the end of the T wave. It reflects the duration of cardiac systole and varies with age and heart rate. At a heart rate of 60 beats per minute, the QT interval is 0.40 seconds or the width of 2 large boxes. The QT interval is usually less than one-half of the RR **interval** at normal heart rates, reflecting the fact that systole is normally shorter than diastole. At a heart rate of 60 beats/minute, for instance, the RR interval equals one second (i.e., 5 large boxes between R waves), and the heart spends 40% of the time in systole and 60% in diastole. As heart rate increases, the RR interval (and the cardiac cycle) is shortened, but diastole is shortened more than is systole. The following equation corrects the observed QT interval for heart rate:

$$\text{QTc} = \frac{\text{QT}}{\sqrt{\text{RR}}}$$

where QTc is the observed QT interval corrected for heart rate. At a heart rate of 60 beats/min, for example, the QTc interval equals the QT interval (0.40 seconds divided by the square root of 1 equals 0.40 seconds). The QT interval defines the duration of systole and, as such, reflects the velocity of ventricular contraction and relaxation. In patients with hypercalcemia, for instance, the QT interval is shortened, while it is longer than normal with hypocalcemia. The QT interval is also longer than normal in patients with congestive heart failure; following treatment with digoxin the QT interval shortens again. It is interesting to note that digoxin increases myocardial contractility by raising the level of intracellular calcium (see Fig. 2-24).

The **ST segment** extends from the end of the S wave (the J-point) to the beginning
of the T wave. This segment is normally flat and has the same voltage as the baseline just before the QRS complex (i.e., this segment is isoelectric). Depression or elevation of this segment is often associated with myocardial ischemia, but non-specific changes are also seen quite commonly. ST segments are raised in pericarditis, for instance, and depressed in patients on digoxin.
In this 52 minute video-lecture Dr. Eggena discusses the leads of the ECG, myocardial hypertrophy, and the mean electrical axis of the heart.
EKG Leads
A. The Limb Leads

Einthoven used three sets of electrodes (or leads) to record voltage changes across the heart during the cardiac cycle (Fig. 4-15).

With lead I he compared the voltage between the right arm (negative pole) and the left arm (positive pole), with lead II the voltage between the right arm (negative pole) and left leg (positive pole), and with lead III the voltage between the left arm (negative pole) and left leg (positive pole). The dipoles measured by these three sets of leads are approximately 60 degrees apart in the frontal plane, forming a triangle around the heart (Einthoven’s triangle). Thus, the dipole (or vector) measured in lead II is 60° removed from the dipole in lead I (which is directed toward 0°); whereas, the dipole in lead III is 120° removed from the dipole in lead I. These three leads are referred to as the standard limb leads. Although the electrodes used to be strapped to limbs (close to the wrists and ankles), identical records are now-a-days obtained with electrodes glued to skin on the upper chest near the shoulders and on the lower abdomen.

The three standard leads probe cardiac vectors only at 60° intervals. Wilson developed three additional leads, the augmented limb leads, to sample cardiac vectors at 30° intervals. They were called augmented leads, because he had to augment their voltages to equal those of the standard limb leads. The augmented leads did not require placement of additional electrodes but simply involved electrical manipulations of the three standard leads.
already present on arms and leg. In **aVR** (augmented voltage right arm) the right arm (now positive) was compared to both other limb leads, in **aVL** (augmented voltage left arm) the left arm (positive) was compared with the other limb leads, and in **aVF** (augmented voltage left foot) the left foot (positive) was compared with both other leads. Lead aVR views cardiac vectors from the perspective of the right shoulder (-150°), aVL from the left shoulder (-30°) and aVF from the feet (+90°) (see Fig. 4-16 for a summary of all the limb leads).

The average, normal heart is situated in the chest in such a way that the average vector during ventricular depolarization (the **mean QRS axis** in the frontal plane) is toward +60°. In such a heart the major vector during ventricular depolarization will be toward lead II. Accordingly, one would expect to see the tallest R wave in lead II (recall that depolarization of the ventricle toward a lead gives an upward deflection on the ECG tracing). This is illustrated in Figure 4-16.

Each of the other leads views the very same QRS vector, but simply from a different angle or from a different point of view. For instance, let us pretend to be viewing this mean QRS vector that is directed at +60° from the point of view of aVL (-30°) which is at the left shoulder. The mean QRS vector would be neither coming toward us nor would it be moving away. In other words, the vector would be exactly 90° removed from our point of view, so that the average vector would equal zero. A mean QRS vector of zero implies that the R wave is equal in magnitude (i.e., in mV or mm) to the S wave in aVL (the sep-
tal Q wave is too small to matter) as is illustrated in Figure 4-16.

Leads I and aVL view the electrical activity of the heart (in the frontal plane) from its lateral aspect. They are the lateral limb leads. Leads II, III, and aVF examine the electrical activity of the heart (in the frontal plane) from its inferior aspect. They are the inferior limb leads. Lead aVR does not fit either of these classifications. Situated at the right shoulder, this lead sees similar information to lead II, except it is all in reverse. (Thus, the apparent Q wave in aVR is really an inverted R wave and does not signify infarction as large Q waves do in other leads.)

**B. The Precordial Leads**

It would seem that the six limb leads should suffice to detect any abnormalities since they all show the same electrical events merely from different angles. Indeed, a single lead - as is used on cardiac monitors - is adequate for diagnosing abnormalities in cardiac rhythm. However, if one wants to localize a given abnormality, such as a myocardial infarct or hypertrophy of a heart chamber, six precordial leads are needed to view cardiac vectors from a horizontal plane in addition to the six limb leads that view cardiac vectors only from the frontal plane (see Figure 4-17).

Unlike the limb leads, which may be placed anywhere along an arm or leg or on the trunk near the shoulders or the groin, the precordial leads must be placed in special positions over the heart on the chest wall (see Fig. 4-17). The right anterior chest leads, V1 and V2, are close to the right atrium and the right ventricle; whereas, the left anterior chest leads, V5
and V6, are close to the left ventricle (Fig.4-17). Leads V3 and V4 are in between, i.e., they are situated over the interventricular septum. All precordial leads represent the positive pole of unipolar electrodes, so that a wave of depolarization toward any one lead will cause an upward deflection; whereas, a vector directed away from a lead will cause a downward deflection.

The small R wave normally seen in V1 and V2 (Fig.4-17) is caused by septal depolarization in an anterior direction. The same vector is seen in V5 and V6 as a small (septal) Q wave. As the main muscle mass of the ventricle depolarizes, the main vector is away from V1 and V2 and toward V5 and V6, which results in deep S waves in V1 and V2 and tall R waves in V5 and V6. Thus, in a normal ECG one expects to find a smooth progression of increasingly tall R waves as one moves from the right toward the left precordial leads (i.e., from V1 to V5). Lead V6 is a little further from the left ventricle than V5, so that the R wave is usually a little smaller in V6 than it is in V5.
Cardiac Hypertrophy
A. Atrial Muscle Hypertrophy

The right precordial leads, V1 and V2, are particularly well suited for detecting an abnormal increase in the muscle mass of the atrial wall (i.e., atrial hypertrophy), because the atria lie just below the placement of these leads on the chest wall. The right atrium is toward the front of the chest, the left atrium is more toward the back (Fig. 4-18). The right atrium depolarizes toward V1 causing an upright P wave; whereas, the left atrium depolarizes away from V1 causing an inverted P wave. These opposing vectors partially overlap in time and thus cancel each other, so that normally only a small biphasic P wave is seen in the right precordial leads.

With right atrial hypertrophy the first component of the biphasic P wave in V1 is exaggerated. Such tall, upright P waves in lead V1 (which are even more pronounced in standard lead II) are commonly seen in patients with pulmonary hypertension and are referred to as P-pulmonale. (Note that the right atrial hypertrophy is a compensatory response to the greater pressures which are required to fill the hypertrophied right ventricle. And the right ventricle is hypertrophied to provide a greater driving pressure to force blood through the abnormally high resistance in the lung).

With left atrial hypertrophy the second (inverted) component of the P wave is exaggerated in V1. Such large inverted P waves are commonly seen in patients with mitral stenosis and are referred to as P-mitrale. (Note that the left atrium hypertrophies in response to the need to generate greater pressures to force blood through a stenotic mitral valve.)
B. Ventricular Muscle Hypertrophy

The right ventricle lies below the right precordial leads. Therefore, when the muscle mass of the right ventricle is abnormally increased (i.e., hypertrophied), unusually tall R waves are seen in lead V1 and the R waves become progressively smaller (instead of taller) as the left precordial leads are approached (Fig.4-19,A). The progression of the S waves is also reversed from normal. With right ventricular hypertrophy the S wave is unusually shallow in V1, so that the ratio of R wave to S wave is greater than 1 (i.e., R/S>1). As will be discussed shortly, the mean QRS axis in the frontal plane (as measured in the limb leads) is also shifted abnormally to the right with right ventricular hypertrophy.

The left ventricle is close to the left precordial leads. When the left ventricular muscle mass is abnormally enlarged (left ventricular hypertrophy), the normal progression of R-waves from V1 through V5 is exaggerated with an unusually tall R wave in V5 (Fig.4-19,B). The same left ventricular vector, which produces a tall R wave in lead V5, produces a deep S wave in lead V1. When the voltage of the R wave in lead V5 plus the voltage of the S wave in V1 is more than 3.5 mV (or 35 mm when the EKG machine has been calibrated - as it usually is - so that 1 mV equals 10 mm) a person is said to have left ventricular hypertrophy “by voltage criteria”. In addition, many patients with left ventricular hypertrophy show a gradually downward sloping of their ST segments with T wave inversion in the left precordial leads. This so-called left ventricular strain pattern indicates subendocardial ischemia in the hypertrophied
left ventricular wall. It is seen only in those patients with left ventricular hypertrophy, who need to develop high intraventricular pressures during systole to overcome a stenotic aortic valve or to counter an increased peripheral vascular resistance in hypertension. The high intraventricular pressures in these patients compress coronary vessels more in the subendocardium than in the epicardium. This, in turn, causes T wave inversion and depression of the ST-segment. Moreover, the mean QRS axis of the heart is shifted abnormally to the left, which will be discussed next.
Mean QRS Axis
When one averages the various vectors during depolarization of the right and left ventricles, the mean resultant vector in the frontal plane (i.e., the mean QRS axis) is directed toward +60 degrees (see Fig. 4-16). There is, however, not just one normal QRS axis, but a wide range of normal values. The normal QRS axis in the frontal plane varies with age. In healthy adults over 30 years the normal mean QRS-axis falls within the range of -30 to +90 degrees (Fig. 4-20, patient A); whereas, in younger individuals the normal axis is between 0 and +110 degrees. When the mean QRS axis falls outside of these normal ranges in the counter clockwise direction (i.e., -30° to -90° in older individuals, 0° to -90° in younger individuals), left axis deviation is said to be present (Fig. 4-20, patient C). When the mean QRS axis deviates from normal in the clockwise direction (i.e., +90° to +/-180° in older individuals, +110° to +/-180° in younger individuals), right axis deviation is said to be present (Fig. 4-20, patient B).

The mean QRS axis of the heart (in the frontal plane) is determined by summing the average vectors from any two limb leads. This is most readily done with leads I and aVF (because it is easier to draw two vectors at a right angle than at angles of 30° or 60°). Plot the average QRS (or RS) vector in lead I toward 0 degrees, if the vector is positive, and (in the opposite direction) toward +/-180°, if the vector is negative. Next plot the average QRS vector for aVF toward +90°, if the vector is positive, and (in the opposite direction) toward -90°, if the vector is negative. From these two vectors determine the one result-
ing vector, which is the mean QRS axis (see Fig. 4-20). Then double check: (a) Is the greatest QRS vector seen in the limb lead closest to the calculated mean QRS axis, as it should be (e.g., lead II in Fig. 4-16)? (b) Is the QRS wave equiphasic (i.e., equal R and S waves) in a limb lead that is 90° removed from the calculated QRS axis, as it should be (e.g., lead aVL in Fig. 4-16)? (A common error made by students is to draw the vector for a positive QRS complex in aVF as an arrow directed away from the foot toward -90 degrees, instead of toward the foot at +90°.)

As is shown in Figure 4-21,A, if the QRS vector is positive (R>S) in leads I and aVF, the mean QRS axis will fall in the normal range between 0 and +90 degrees. If the QRS vector is positive in lead I (R>S) but negative in lead aVF (R<S), the mean QRS axis will fall within the range 0 to -90 degrees. If the QRS vector is negative in lead I (R<S) but positive in aVF (R>S), the mean QRS axis will fall within the range +90 to +/-180 degrees.

Fig. 4-21 Axis deviation. An easy way to assign the mean QRS axis to one of four quadrants is shown in (A) and (B). If the R wave is greater than the S wave in lead I the mean vector must be directed to the left half of the body, but if the R wave is less than the S wave in lead I, the vector must be directed toward the right half of the body (A). Similarly, if the RS complex is positive in aVF, the mean vector must be toward the lower half of the body, but if the complex is negative, the vector must be directed toward the upper half of the body. The four possible combinations of net RS vectors in leads I and aVF are shown in panel (B), i.e. the normal quadrant (0° to +90°), the right quadrant (+90° to +180°), the left quadrant (0° to -90°), and an extreme right (or left) quadrant which is virtually never seen.
In this 40 minute video-lecture Dr. Eggena considers ECG changes in Myocardial Infarction and discusses regular, irregular, and fast rhythms.
Myocardial Infarction
A. ECG Patterns of Ischemia, Injury, and Infarction

When a coronary artery is occluded, heart muscle cells become ischemic, injured, and die. Ischemic cells switch from aerobic to anaerobic metabolism causing intracellular hydrogen ion concentration to rise from accumulation of lactic acid. As these hydrogen ions move out across the membrane in exchange for sodium ions on sodium/hydrogen ion antiporters, membranes become partially depolarized and impulses travel more slowly from endocardium to epicardium, causing the ventricles to repolarize in a direction opposite from normal and resulting in inversion of T waves (see Fig. 4-12). Persistent ischemia soon causes tissue injury. Injured cells cannot bail out sodium or calcium ions that have diffused in during the action potential, because active transport requires ATPases and ATP, which mitochondria cannot synthesize without oxygen. Moreover, as potassium ions accumulate outside of ischemic and injured cells, the membrane is further depolarized because the potassium equilibrium potential [as calculated with the Nernst equation] changes from -94 mV to a more positive value. Because injured ventricular muscle cannot maintain normal resting potentials, a current of injury starts flowing between the injured patch and healthy ventricular wall. This current (and the vector associated with it) is carried away from the electrode overlying the injured patch of ventricle. This depresses the baseline below zero millivolts between successive ventricular depolarizations. The J-point is the best reference for zero millivolts, because at this point the ventricles are completely depolarized and no electrical currents are flowing. Thus, depression of the baseline below the J-point or, expressed another way, J-point elevation (or ST segment elevation) above the baseline is a sign of tissue injury in the area of the ventricle below the exploring electrode.

If injured cells do not receive oxygen, they die. Dead cells do not have resting membrane potentials nor do they depolarize when stimulated. If the full thickness of a section of left ventricular wall has been deprived of oxygen for several hours and has died (is infarcted), it is electrically silent and a lead overlying this area will record a Q wave. This is illustrated in Figure 4-22 for a transmural, lateral wall infarction recorded with standard lead I.

To explain why a deep Q wave is seen in lead I, let us pretend that we were looking at the infarcted area of the left ventricle from an angle of 0 degrees with lead I. We
would look straight through an electrically silent hole at a vector moving from endocardium to epicardium on the other (healthy) side of the ventricle. Because this vector is moving away from lead I, a downward deflection, i.e., a Q wave, would be the first wave recorded. This Q wave would be wider and deeper than the septal Q wave normally seen in lead I, because it would represent the additional vector of right ventricular depolarization. Such wider and deeper Q waves are called significant Q waves, in contrast to normal septal Q waves that are narrow and shallow (<0.04 seconds, < 25% of the succeeding R wave).

Right next to the area of infarction is an area of injury. Injured tissue does not completely repolarize and induces a current of injury that flows between healthy and injured tissues, causing ST segment elevation in leads overlying the injured area.

Between the area of injury and healthy tissue is an area of ischemia. Ischemia slows conduction (and shortens the refractory period of endocardial cells), which causes the ventricle to repolarize abnormally from endocardium to epicardium. This causes inversion of the T wave in leads overlying the area of ischemia. Add up the patterns of ischemia, injury, and infarction, and what we see in lead I is a significant Q wave, ST segment elevation, and T wave inversion. This is the picture of an acute, transmural, lateral wall myocardial infarction (Fig. 4-22).

After 3 to 4 days of rest, collateral blood flow is established, and injured tissues are repaired, but are still ischemic. Without a current of injury, the ST segments return to

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**Transmural Myocardial Infarct**

Fig. 4-22 Transmural myocardial infarction. A myocardial infarction, extending through the full thickness of the lateral wall of the left ventricle, is shown from the perspective of lead I. The patterns of infarction (Q waves), of injury (ST segment elevation) in surrounding tissues, and of ischemia (T wave inversion) are illustrated and the combined appearances and changes of these waves during the acute, subacute, and chronic phases of the infarct are shown.
baseline, but T waves remain inverted because of ischemia in the previously injured tissue. This is the picture of a **subacute myocardial infarction** (see Fig. 4-22).

As normal blood flow to ischemic tissues is restored, T waves return to their normal upright positions, but the Q waves remain for life. This is because dead myocardial tissue is replaced by electrically silent scar tissue. Thus, a significant Q wave (wider than 1 small box and/or deeper than 25% of the succeeding R wave) is a sign of a previous infarct (i.e., **chronic myocardial infarction**).

Only transmural infarcts produce significant Q waves. Lesser infarcts (**non-Q wave infarcts**), which do not involve the full thickness of the ventricular wall but only a patch of subendocardial muscle, cause ST segment depression in leads overlying the area of injury. Such small infarcts are not to be dismissed lightly, however, because they are usually followed by more serious transmural **ST-segment Elevation Myocardial Infarcts** (or **STEMI**).

**B. Localization of a Myocardial Infarction**

Although each of the twelve leads of the ECG probes the electrical vectors of the myocardium from a slightly different perspective, leads can be categorized into those which overlie the lateral wall of the left ventricle (I, aVL, V5, and V6), the inferior wall of the left ventricle (II, III, and aVF), or the anterior wall of the left ventricle and the interventricular septum (V1 through V4, see Fig. 4-23). Therefore, with a **lateral wall infarct**, Q waves are seen in leads I, aVL, V5, and V6, with an **inferior infarct** Q waves appear in leads II, III, and aVF, and
with an **anterior/septal infarct** Q waves (or QS complexes) are seen in leads V1 through V4 (see Fig. 4-23). If the infarct is acute, ST segment elevation and inversion of T waves are seen with Q waves. If it is chronic, only Q waves will be found. One would like, of course, to get a patient found to have ST segment elevation to a tertiary care center for coronary reperfusion before injured tissues dies and Q waves develop.

ST segment elevations produce mirror images (i.e., ST segment depressions) in opposite leads. Thus, in an acute lateral wall infarct the ST segment elevation in the lateral leads will be seen as ST segment depression in the inferior leads. Similarly, the ST segment elevation seen in the inferior leads with an acute inferior wall infarction produces ST segment depression in the lateral leads. There are no leads on the back with which to directly monitor posterior wall infarctions with Q waves and ST elevations. However, posterior infarcts will produce the “mirror image” of an anterior infarct. Accordingly, the QS complex and ST segment elevation seen in an acute anterior infarct in leads V1 through V4, becomes an R wave and ST segment depression (i.e., the mirror image) in these leads when the infarct is in the posterior wall (Fig.4-23).

**Fig.4-24.** Similar Patterns Between Myocardial Infarction and Normal Hearts. Similarities and differences are illustrated for normal S waves and abnormal QS complexes (A), normal (septal) Q waves and significant Q waves in transmural myocardial infarct (B), and normal ST segment elevation in early repolarization and abnormal ST segment elevation in myocardial injury (C).
C. Similar Patterns in Normal Hearts and Infarction

Chest pain is a frequent complaint. A decision for immediate hospitalization or simply reassurance of the patient often hinges upon finding Q waves and/or ST segment elevations that are significant. This can be difficult at times.

First of all, a Q wave must not be mistaken for an S wave. If there is even the smallest upward deflection (i.e., an R wave) before the downward deflection, the wave in question is an S wave rather than a Q wave. This is particularly important in lead V1, where the R wave from septal depolarization is usually quite small (Fig. 4-24,A). If the R wave in V1 is missing, because of infarction of the septum and the anterior wall of the left ventricle, a Q wave has merged with an S wave to produce a QS complex. QS complexes have the same significance as large Q waves. They signify transmural infarctions.

If a Q wave is seen, a decision must be made as to its significance. As already mentioned, a Q wave is significant, if it is wider than 1 small box (0.04 seconds) and/or is taller than about one-fourth of the succeeding R wave. Normal (septal) Q waves are sometimes seen in the lateral leads (i.e., I, aVL, V5 and V6) as the vector from early depolarization of the ventricular septum moves away from these leads. These Q waves are shallow and narrow (see Fig. 4-24,B). When is ST segment elevation significant? The ST segment elevation of myocardial injury may be confused with a phenomenon called early repolarization. Early repolarization of the ventricles is perfectly normal and is often seen in young, healthy individuals. (We see this frequently in athletic medical students who volunteer as subjects during the ECG laboratory exercise in the Physiology course.) In early repolarization, the J-point (i.e., the point where the ST segment begins) is slightly elevated, and the ST segment then slopes upward (i.e., is concave); whereas, with myocardial injury the elevated ST-segment pursues are more horizontal and downward sloping course (i.e., is convex), (Fig. 4-24,C).

The diagnosis of an acute myocardial infarction often requires serial ECGs to document an evolving infarct. For such comparisons it is important to place the precordial leads at precisely the same locations on succeeding days. This may be facilitated by marking the spots for V1 through V6 on the skin with a marker pen. In addition to documenting ECG changes, serial blood samples are taken to test for abnor-
mal levels of cardiac enzymes, which are released from injured heart muscle into the circulation. They include the myocardial band (MB) iso-enzymes of creatinine phosphokinase (CPK) and troponins I and T. A diagnosis can usually be made on the basis of ECG and troponin changes.

D. Myocardial Ischemia during Stress

Q waves are permanent (transmural infarct), ST segment elevations (injury) and T wave inversions (ischemia) are not. Many patients - but not all - are warned of an impending infarct by a characteristic chest pain, called angina pectoris. Angina is caused by coronary artery occlusion, which limits oxygen supply to heart muscle especially during exercise. The most vulnerable area of the heart is the subendocardium of the left ventricle, where blood vessels are compressed by high intraventricular pressures during systole. This subendocardial ischemia causes ST segment depression and T wave inversion in individuals with borderline coronary blood flow to the endocardium when they exercise during a stress test (Fig. 4-25,B). An exercise test is considered “positive”, if the ST segment is depressed by more than 2 mm (0.2 mV) at relatively slow heart rates, especially if these changes are associated with angina, a fall in blood pressure, or ectopic beats. If the ST depression and angina are related to effort, the ECG returns to normal and the pain subsides on resting.

Persistence of ST segment depression (along with elevations in cardiac enzymes), on the other hand, suggests subendocardial infarction (Fig.4-25,D). ST segment dep-
pression is also seen in patients taking a digitalis preparation such as digoxin (Fig.4-25,C), so that the stress test cannot be interpreted correctly in patients on this medication.

In some patients angina occurs even at rest, when a coronary artery goes into spasm. This variant form of angina is called **Prinzmetal's angina**. Since blood flow to both the endocardial and epicardial surfaces are diminished during these episodes, the ECG shows transient elevations in the ST segments rather than the typical ST segment depression seen in the usual form of angina.
Regular Rhythms
A. Measuring Heart Rates

To determine the rate at which a person’s heart is beating from an ECG record, you must know the speed at which the paper is moving past the recording pen of the ECG machine (Fig. 4-26). All ECG machines are calibrated so that the distance of one large box on the paper is 0.2 seconds. Each large box is subdivided into 5 segments of 0.04 seconds. With this information heart rates are readily calculated, as illustrated in Figure 4-26. Choose a lead that shows tall R waves (e.g., lead II) or deep S waves (e.g. lead V1) and count the number of large boxes between any two R (or S) waves. If only one box fits in between waves, the rate is 300/min (60 sec/min/0.2 sec). If two boxes fit between waves, the rate is 150/min (300/2), for 3 boxes the rate is 100/min (300/3), for 4 boxes the rate is 75/min (300/4), etc. For very slow rhythms it is more convenient to use the 3-second markers on the ECG paper. Count the number of R waves for 6 seconds (two 3-second intervals) and multiply by 10 to give the beats per minute.

B. Regular Rhythms (Sinus, AV-nodal and Ventricular Rhythms)

The rhythm of the heart is said to be regular when the distances between succeeding R (or S waves) are equal. The easiest way to test this is to place a piece of paper on the ECG tracing and mark the position of the peaks of several R waves with a
pen. Then shift the paper by one RR interval and see if all the pen marks still match with R waves. If they do, the rhythm is regular. Such a regular rhythm may originate in the SA node, the AV node, or the His-Purkinje system (Fig. 4-27).

The normal pacemaker for the heart, the SA node, generates a so-called normal sinus rhythm -- usually at a rate of 60 to 80 beats/min. However, with exercise or stress the SA node may fire well over 100 times/min. Sinus rhythm is characterized by a narrow QRS complex (<0.10 seconds) which is preceded by a P wave. When the SA node fails (as in the sick sinus syndrome), the AV node can substitute as the pacemaker. AV nodal rates are usually between 40 to 60 beats/min. AV nodal rhythms are characterized by a narrow QRS complex that is not preceded by a P wave (or by a small, inverted P wave just before or after the QRS complex). When the AV node fails to conduct impulses (as occurs with a third degree AV block), a focus in the His-Purkinje system of the ventricles usually picks up the beat. The rate of such idioventricular rhythms is, however, quite slow, usually between 20 to 40 beats/min. Idioventricular rhythms are easily identified. The QRS complexes are usually large and wide (>0.12 seconds) depending on the location of the ventricular pacemaker and occur independent of any P waves. (The P waves occur at a faster rhythm that bears no relationship to the QRS complexes.)

These differences among the intrinsic pacemaker activities of the SA node, AV node, and His-Purkinje systems are caused by different resting membrane potentials and
different rates of phase 4 depolarization (see Fig.4-27).
Irregular Rhythms
(1) Sinus Arrhythmia

An irregular (or absent) heart rhythm is called an arrhythmia. **Arrhythmias** are abnormal, unless they are caused by the cyclic changes of inspiration and expiration. The heart rate speeds up on inspiration and slows on expiration; this is **sinus arrhythmia** (see Fig.4-28,A). The QRS complexes are narrow (indicating the ventricles are rapidly depolarized by impulses conducted normally over the His-Purkinje system), and each QRS complex is preceded by a P wave. Therefore, this is a sinus rhythm (originating in the SA node). The change in rhythm (i.e., changing distances between R waves) is related to respiratory excursions. Sinus arrhythmia is expected in a young, healthy person. It is caused by a decrease in vagal tone to the SA node on inspiration.

(2) Sick Sinus Syndrome

When cells in the SA node are not functioning reliably (for instance, with diminished blood flow to this region), the SA node may fire impulses rapidly one moment and slowly the next (Fig.4-28,B). The resulting abrupt onset of tachycardia and/or bradycardia has given this condition the descriptive name **tachycardia-bradycardia syndrome**, also called the **sick sinus syndrome**. Because the AV node or His-Purkinje system cannot always be relied upon to pick up a rhythm when the SA node suddenly fails, patients with this condition are often given an artificial pacemaker.
(3) Wandering Atrial Pacemaker

The heart may also beat irregularly because of a constantly changing pacemaker focus outside of the SA node in the atrium (see Fig.4-29). This is noticed on the ECG record by irregularly spaced QRS complexes with a normal, narrow configuration. However, they are preceded by P waves that change in shape from one beat to the next. For example, when a focus close to the AV node fires, the atria depolarize in a retrograde direction, resulting in an inverted P wave (labeled as P' in Fig.4-29). A changing atrial pacemaker with a rhythm over 100 beats/min is not called a Wandering Pacemaker but is referred to as **multifocal atrial tachycardia**. This arrhythmia is frequently associated with chronic obstructive pulmonary disease.

(4) Ectopic Beats

(a) Premature Beats

Premature beats (or premature contractions) are often caused by an irritable focus in the atria (PAC), the AV node (PNC), or the ventricles (PVC). As the name implies, these beats come too early. Because a wave of depolarization from these early beats renders the heart refractory to the next scheduled beat, there is a longer pause between the premature beat and the next beat, called a **compensatory pause** (see Fig.4-30,A). Sometimes a premature beat will reset the SA node. This will change the heart rate following the premature beat.

A **premature atrial contraction** (PAC)(Fig.4-30,A) is recognized by a normal QRS complex (<0.10 seconds), preceded by a P wave. The shape of the P wave and the PR interval of the PAC vary
depending upon the site of its origin in the atria.

A **premature nodal contraction** (PNC) (Fig.4-30,B) is identified by the absence of a P wave or (more rarely) by inverted P waves just before or after a normal QRS complex (<0.10 seconds). The P wave, if seen, is inverted because the wave of atrial depolarization occurs retrograde from AV node toward the SA node. When the irritable focus is high in the AV node, an inverted P wave may be seen just before the QRS complex. When the focus is low in the AV node, an inverted P wave may be seen just after the QRS complex. Most often, the irritable focus is in the middle of the AV node and the inverted P wave is buried within the QRS complex and cannot be seen at all.

A **premature ventricular contraction** (PVC) (Fig.4-30,C) is easily recognized by its wide QRS complex (>0.12 seconds) with large R and/or S waves and the absence of a preceding P wave. The wide QRS complex reflects the slow spread of impulses via gap junctions (instead of via the Purkinje fibers) from an irritable focus in one ventricle to the other. As the two ventricles depolarize in succession - rather than simultaneously - two sequential vectors result, instead of just one summation vector (see Fig. 4-13,B). The initial vector is directed toward the leads overlying the ventricle where the ectopic beat originates, resulting in a tall R wave. The second vector is in the opposite direction and is associated with delayed depolarization of the other ventricle, resulting in a deep S wave. Sometimes PVCs arise in the interventricular septum from where impulses are more evenly conducted to right and left ventricles. These PVCs are therefore narrower than those arising, for instance, in the lateral wall of the left ventricle.

Ectopic beats can be detected by taking a person’s pulse. Premature beats are often
weak or are not felt at all, because they occur too early when the left ventricle is not completely filled. Left ventricular contraction at this lower filling volume results in a diminished stroke volume that may not generate a sufficient pulse wave to be felt at the radial artery in the wrist. However, closure of heart valves associated with the beat is readily heard with a stethoscope. The difference in the beats/min heard with the stethoscope over the heart and the beats/min felt at the wrist is called the **pulse deficit**. It is a clinical estimate of the number of premature beats. An ECG tracing is, of course, required to determine their origin (PAC, PNC, or PVC).

Ectopic beats are common in healthy young people and seem to be more frequent in tired or anxious individuals who drink coffee, smoke cigarettes, or consume alcohol. Nevertheless, such premature beats are not to be dismissed as insignificant, especially in patients with heart or lung diseases. Ectopic beats are especially significant for a patient who has been admitted to an intensive care unit for an acute myocardial infarction.

**b) Dangerous PVCs**

Certain PVCs are of concern because they may cause the ventricles to fibrillate. When

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**Fig. 4-31. Dangerous PVCs.** PVCs are considered dangerous when they (A) are multifocal, (B) fall on the T wave of the preceding beat, (C) occur in runs of more than three beats (which is considered equivalent to ventricular tachycardia), or are closely coupled as in bigemini (D) or trigemini (E). In addition, frequent (more than 6/min) PVCs require close attention (not shown).
such PVCs are noticed on a cardiac monitor, an antiarrhythmic drug may be indicated. The PVCs listed in Table 4-2 are of concern.

Any PVC that falls on the T wave of the preceding beat (R on T phenomenon) may trigger ventricular fibrillation (Fig. 4-31,B). During the T wave the ventricle is partially depolarized (endocardium) and partially repolarized (epicardium), and many cells are in states of relative refractoriness or hyperexcitability (see discussion of refractoriness). This makes the ventricle more susceptible to stimuli from PVCs, which may induce circular currents to flow around different regions of the ventricle. These repetitive circular movements of impulses may, in turn, induce ventricular tachycardia, flutter, or even fibrillation. The more frequent the PVCs, the more likely such malignant events are likely to occur.

PVCs arising from the same locus in the ventricle (unifocal PVCs with identical configurations) are less serious than PVCs arising from multiple foci (multifocal PVCs with different configurations, Fig.4-31,A) because any one of these foci of irritation may induce ventricular tachycardia. Not infrequently, PVCs are coupled directly (couplets) or with one normal beat in between (bigemini, Fig. 4-31,D) or two normal beats in between (trigemini, Fig. 4-31,E), and so forth. Such coupled beats are often seen with digitalis toxicity and may give rise to more dangerous ventricular arrhythmias. When PVCs occur in bursts of three or more, the condition is considered equivalent to a run of ventricular tachycardia (Fig. 4-31,C), and immediate measures must be taken to prevent the rhythm from deteriorating into ventricular fibrillation.

(c) Escape Beats

When the normal pacemaker in the SA node fails to depolarize, another focus usually picks up the beat (Fig. 4-32). This focus may be in the atria, the AV node, or the ventricles. Called an escape beat, this looks just like a premature beat, except that it comes later than expected.
Fig. 4-32. Escape beats. When the SA node fails to initiate an impulse (and a P wave), an escape beat is initiated by an ectopic focus located in the atria, AV node, or ventricles.
5 Fast Rhythms and Disturbances in Conduction

Movie 5.1 Fast Rhythms and AV Blocks

In this 45 minute video-lecture Dr. Eggena considers fast rhythms arising in above the ventricles, AV blocks and Potassium Imbalance.
Fast Rhythms
**Tachycardia** is defined as a heart rate of more than 100 beats/minute. Tachycardia is a useful mechanism for increasing cardiac output, but only up to a point. At very rapid heart rates, diastole is shortened more than systole and, since cardiac filling occurs during diastole, there is not enough time to adequately fill the heart with blood before it contracts during systole. Moreover, the faster the heart beats, the more oxygen (and thus the more coronary blood flow) it requires. However, blood flows through the coronaries to the left ventricle primarily during diastole because vessels in the subendocardium of the left ventricle are compressed during systole. With a shortened diastole, less blood reaches muscles that need it even more than before.

When the atria or ventricles are stimulated to contract at very rapid rates, they stop pumping blood altogether. The chambers first flutter and then fibrillate as different patches of muscle contract chaotically and the wall merely quivers. Fortunately, the ventricles are usually protected from such rapid barrages of stimuli by the AV node, which limits the number of impulses arriving at the ventricles, so that the ventricles still contract and pump effectively in patients with atrial flutter or atrial fibrillation. Therefore, supraventricular tachycardias (or atrial flutter or fibrillation) are seldom life threatening; whereas, ventricular tachycardia (or ventricular flutter or fibrillation) is and requires immediate intervention.

(1) **Sinus Tachycardia**

*Sinus tachycardia* results from increased sympathetic and decreased parasympathetic stimulation of the SA node. As discussed previously (see Fig.4-7), this raises the resting membrane potential of SA nodal cells closer to threshold (*vagolytic effect*) and speeds the upward drift of phase 4 depolarization (*sympathetic effect*). As a consequence, heart rate increases above normal to values ranging from 100 to 150 beats/min. Sinus tachycardia is seen, for example, with exercise, excitement, pain, or in patients in circulatory shock. The ECG tracing shows normal QRS complexes, each preceded by a normal P wave (see Fig.4-33,A). Sinus tachycardia is an important sign that the sympathetic nervous system has been activated, and the reason for this must be carefully sought (e.g., is the patient anemic, hypoxic, or hypotensive?) and treatment is directed at eliminating the underlying cause.

(2) **Paroxysmal Supraventricular Tachycardia (PSVT)**
(a) Paroxysmal Atrial Tachycardia (PAT)

In **paroxysmal atrial tachycardia (PAT)** the heart rate suddenly increases to a rate between 150 and 250 beats/min. The episode may terminate just as suddenly within seconds, minutes or hours. The tachycardia is often initiated by a PAC, that has an abnormally long PR interval. The QRS complexes are of normal duration, and P waves can be identified before each QRS complex - but only at the slower heart rates (4-33,B). At higher rates, the P waves become superimposed on the preceding T waves (as the duration of diastole is shortened) and P waves cannot be identified with certainty (Figs. 4-1,A and 4-33,D).

PAT is quite common in otherwise healthy individuals, but the condition is also frequently encountered in patients with aberrant conductive pathways between atria and ventricles (Wolff-Parkinson-White or Lown-Ganong-Levine syndromes). PAT can often be terminated by increasing vagal tone by the Valsalva maneuver, gagging, carotid sinus massage, or by administration of drugs such as verapamil or adenosine. A variant of this condition, **PAT with block**, is usually due to digitalis toxicity. In this situation, the atria beat between 150 to 250 times/min, but not all impulses [e.g., every other one (in a 2:1 block)] are conducted through the AV node, so that the ventricles beat slower than the atria.

(b) Paroxysmal Nodal Tachycardia

The etiology and treatment for **paroxysmal nodal tachycardia (PNT, Fig. 4-33,C)** is the same as it is for PAT. This is fortu-
nate because the two conditions cannot be distinguished at fast heart rates and are, therefore, simply referred to as paroxysmal supraventricular tachycardia (PSVT), (Fig. 4-33,D).

The approach to treating a stable, asymptomatic patient with PSVT is initially with vagal maneuvers. If vagal maneuvers don’t work, adenosine is usually tried next. Since adenosine is rapidly degraded in blood it must be injected rapidly. If adenosine does not help, a calcium channel blocker like verapamil or a beta-1-adrenergic blocker can be tried. If nothing seems to work and the patient is asymptomatic, there is time for expert cardiac consultation. If, however, the patient develops a change in mental status, hypotension and signs of shock or angina pectoris or congestive heart failure, more drastic measures such as synchronized cardioversion after sedation may be required.

(3) Atrial Flutter

The P waves in atrial flutter occur rapidly (250 to 350/min) and resemble the teeth of a saw. Not all impulses are conducted by the AV node, so the ventricular rate is slower. Thus, only every third or fourth flutter wave may be conducted to the ventricles (a 3:1 or 4:1 block [Fig. 4-33,E]).

(4) Atrial Fibrillation

In this condition the atria fibrillate above 350 times/min, and distinct P waves are replaced by small fibrillation waves. The AV node conducts only some of these impulses, so that the ventricular rate is unpredictable (Fig. 4-33,F). At times an impulse gets through early, while one of the bundle branches is still refractory and the other is not. This causes wide QRS complexes because each ventricle is depolarized sequentially rather than simultaneously. Such abnormal beats, which look like PVCs, are characteristic of atrial fibrillation. This is the Ashman phenomenon.

Atrial fibrillation is common. Even though the P waves of fibrillation may not be clear on the ECG, a diagnosis is readily made based on the completely random spacing of the QRS complexes. The QRS complexes are narrow because conduction over the Purkinje system is normal, except for the occasional Ashman beats already mentioned. Because the ventricles contract at different end-diastolic filling vol-
umes, left ventricular stroke volume and pulse pressure vary from beat to beat. This causes the pulse to be irregular with respect to both rhythm and magnitude, i.e., the pulse in atrial fibrillation is said to be irregular/irregular.

The approach to treating patients with long-standing atrial fibrillation is (a) to prevent an embolic stroke from blood clots that tend to form in the left atrial appendage and (b) to keep heart rate below 100 beats/min. To prevent clot formation patients have traditionally been placed on warfarins (i.e., coumadin) and more recently on apixaban or similar anticoagulants that do not require dietary restrictions and frequent blood tests. Heart rate is controlled by decreasing AV nodal conduction with calcium channel blockers, beta-1-adrenergic blockers, or digoxin. As mentioned earlier, all of these agents decrease the slope of phase 0 depolarization of the action potentials of AV nodal cells.

Patients with recent onset atrial fibrillation may be converted to a normal sinus rhythm with synchronized cardioversion and stabilized with amiodarone (an antiarrhythmic agents that blocks primarily potassium channels and lengthens the effective refractory period). Final correction of the underlying problem may be accomplished by surgical ablation of irritable foci in the atria that are responsible for initiating the erratic rhythm.

(5) Ventricular Tachycardia

Ventricular tachycardia consists of three or more broad (>0.12 sec.) QRS complexes that occur more frequently than 100/min (Fig.4-34,A). The arrhythmia may be tolerated well or may be associated with a change in mental status, decreased cardiac output and shock or pulmonary congestion. If the patient is unstable with the above signs and symptoms (but does have a pulse) immediate synchronized cardioversion after sedation is usually attempted. If the patient does not have a pulse (and is, therefore, unconscious) unsynchronized shocks are delivered as in ventricular fibrillation. If, on the other hand, the patient is stable with a wide QRS complex tachycardia, antiarrhythmic agents like amiodarone may be used after consultation with a cardiologist.

The atria beat independently in this condition, because the AV node is rendered refractory to conduction by retrograde depolarization from the ventricles.
In a variant form of ventricular tachycardia, **Torsade de Pointes**, the QRS complexes constantly change as if they were twisted about a point (Fig.4-34,B). This pattern may be seen in hypomagnesemia, hypokalemia, or following an overdose of antiarrhythmic agents such as quinidine that prolong the Q-T interval (i.e., prolong systole).

**6) Ventricular Flutter and Fibrillation**

A heart in **ventricular flutter** generates a rapid sequence of quite evenly spaced complexes that are rounded on top (Fig.4-34,C). Such a tracing is an ominous sign that ventricular fibrillation is soon to follow. In contrast to ventricular flutter, **ventricular fibrillation** is chaotic and disorganized (Fig.4-34,D). In this condition the ventricle quivers as different patches of ventricular wall become rapidly depolarized in a futile effort that has been likened in appearance to a bag of worms. No blood is pumped by the ventricles as they fibrillate, and within seconds a person with this condition loses consciousness. Not long thereafter, centers responsible for maintaining the respiratory rhythm fail as well, and respiratory arrest follows. The heart, deprived of oxygen, continues to fibrillate for a while - first in a coarse, erratic pattern and then in a finer, smoother pattern that ends in a flat line (**asystole**), where all traces of electrical activity have vanished from the heart.

The approach to treating a patient with ventricular fibrillation is to immediately start cardio-pulmonary resuscitation (CPR - 30 chest compressions for every 2 breaths) until unsynchronized shocks can be delivered by a defibrillator (or AED). Between successive shocks, drugs are injected --initially epinephrine or vasopressin, then amiodarone and next lidocaine. While these drugs are given intravenously, vigor-
cardio-pulmonary resuscitation must be continued.
Mechanisms of Arrhythmias
Atrial or ventricular arrhythmias may be caused by three basic mechanisms: (1) automaticity, (2) triggered activity, or (3) re-entry (see Fig. 4-35).

(1) **Automaticity** results from an increased rate in the spontaneous depolarization of one or more ectopic foci. When muscle cells in the left ventricle become ischemic, their resting membrane potentials become less negative, causing voltage-sensitive calcium channels to open and the potential to drift toward threshold during phase 4 of their action potentials (see Fig. 4-35, A). Furthermore, because myocardial ischemia is usually associated with increased circulating levels of epinephrine and because epinephrine (acting via beta-1-adrenergic receptors) increases the “open time” of calcium channels, the tendency for depolarization during phase 4 is further enhanced. In this way, coronary insufficiency may convert a normally quiescent (contractile) ventricular muscle cell to a pacemaker cell that periodically generates a PVC. If many such ischemic cells in different parts of the ventricle were to depolarize when the ventricle was not refractory, such multifocal PVCs could be partly responsible for the chaotic rhythm seen in ventricular fibrillation.

(2) **Triggered activity** may also cause ven-
tricular fibrillation or other arrhythmias. The action potentials of ventricular muscle cells, for instance, may not return to baseline during phase 3 repolarization but may instead oscillate (presumably due to an abnormal delay in negative feedback signals) close to threshold. Such after-potentials - provided they reach threshold - could induce another depolarization that would be closely coupled to the first beat. Such premature contractions (PVCs) would tend to fall within the vulnerable period of the cardiac cycle, i.e., during the T wave, when some parts of the ventricle are already repolarized while other parts are not. This imbalance in refractoriness of ventricular tissues predisposes to reentry of the impulse initiated by the PVC. The resulting circular flow of currents is probably a major cause of ventricular fibrillation.

(3) The reentry phenomenon is the most common mechanism for atrial and ventricular tachycardia, flutter, and fibrillation. The principle is illustrated for paroxysmal supraventricular tachycardia (PSVT) in Figure 4-35,C. For reentry to occur, the impulse must travel along a pathway that splits into two branches and then re-unites into a common path, thereby forming a circle by which a single impulse can reenter the original pathway over and over again to produce a burst of rapid contractions instead of just one. Reentry of the impulse into its recent path, of course, requires that the impulse must be conducted retrograde in one branch of the circular conductive pathway (branch b). Normally, this retrograde conduction does not occur because both branches (a and b) are refractory (the sodium channels are still inactivated) for a short interval after the impulse has passed. However, under certain conditions, such as ischemia, conduction in one branch (a) may be slowed, because the slope of phase 0 is decreased in ischemia, providing sufficient delay for the healthy branch (b) to repolarize before the slow impulse from the ischemic branch arrives. Since the healthy branch (b) is no longer refractory, once repolarized, the impulse arriving from the ischemic branch will now be conducted retrograde along the healthy branch and can reenter the ischemic branch (a) to be conducted once more to the ventricles. These cycles repeat over and over.
SA and AV Nodal Blocks
(1) SA Node Block

When an impulse is generated by the SA node, but the impulse is not conducted to the atria, a P wave is found to be missing from its expected position. This intermittent loss of a beat may not only be due to a temporary block but also due to failure of the SA node to depolarize (as in the sick sinus syndrome). Should the impulse from the SA node be blocked completely, then an ectopic focus, for example in the AV node, fires one or more beats or may even establish a nodal rhythm (see Fig.4-32).

(2) AV blocks

(A) First Degree AV Block
In first degree AV block conduction of impulses through the AV node is delayed, resulting in prolongation of the PR interval beyond 0.2 seconds (1 large box), (Fig. 4-36,A). This may be due to increased vagal tone, drugs (e.g., digoxin, beta-1-adrenergic blockers, calcium channel blockers) or heart disease (e.g., rheumatic fever, lyme disease).

(B) Second Degree AV Block
In second degree AV block some impulses arriving at the AV node from above are not conducted, so that only every second (2:1 block), every third (3:1 block), or every fourth (4:1 block) P wave is followed by a narrow QRS complex (Fig.4-36,C).

The second degree AV block may be variable or intermittent. Two forms are distin-
guished, **Mobitz I** (or *Wenckebach Phenomenon*) and Mobitz II (Fig.4-36,B and C). In the Wenckebach Phenomenon conduction through the AV node becomes progressively longer during a series of beats until conduction is completely stopped and a beat is lost; then the cycle repeats over and over again. This results in a clustering of beats that is readily recognized on the ECG tracing. The PR interval is progressively lengthened from one beat to the next until a P wave is not followed by a QRS complex. Mobitz I is commonly seen with digoxin overdose especially if serum potassium concentrations are low, because both digoxin and potassium ions compete for a common binding site on the sodium-potassium ATPase in AV nodal cells. Holding digoxin and adding potassium usually corrects the problem.

**Mobitz II** is also an intermittent form of AV block, but unlike Mobitz I, it occurs sporadically. In other words, every now and then, without warning, a P wave is simply not followed by a QRS complex. Mobitz II is the result of more serious and more permanent damage to the conducting system lower down in the AV node, closer to the bundle of His. Mobitz II thus serves as a warning that a complete (permanent) AV block may follow. Therefore, patients with Mobitz II are usually given artificial ventricular pacemakers.

**(C) Third Degree AV Block**

In third degree AV block (or complete AV block) no impulses from the atria are conducted through to the ventricles (Fig.4-36,D). Thus, the atria beat in a sinus rhythm and the ventricles beat at a much slower idioventricular rhythm. Consequently, there is no consistent relationship between the P waves and the QRS complexes. The QRS complexes are characteristically wide with large deflections, as is true for PVCs. Because the ventricles beat slowly, there is more time for them to fill during diastole. Stroke volumes are, accordingly, greater than normal, which is readily recognized by a bounding pulse found on physical examination. On occasion, the right atrium will contract simultaneously with the right ventricle. Because the tricuspid valve is closed at that time, blood is forced backward into the jugular veins in the neck to produce a **cannon a-wave**, i.e., a marked exaggeration of the normal jugular a-wave. Indeed, this is how a diagnosis of complete AV block was made before the ECG machine was invented. Patients with a third degree AV block usually require an artificial ventricular pacemaker.
Bundle Branch and Fascicular Blocks
Bundle Branch Blocks

When either the right or the left branch of the common bundle of His has been damaged, depolarization of the blocked ventricle is delayed because conduction occurs more slowly via gap junctions between muscle cells. This delay in depolarization results in QRS complexes that are abnormally wide, more than 0.12 seconds (> 3 small boxes) (see Fig. 4-37). With right bundle branch block (RBBB) an RR' pattern (or RSR' complex) is seen in leads V1 and V2. The R wave results from depolarization of the left ventricular portion of the interventricular septum (from left to right), the S wave (or the notch between R and R') from left ventricular depolarization (from right to left) and the R' wave (i.e., the second upward deflection) from delayed depolarization of the right ventricle (from left to right).

With left bundle branch block (LBBB) an RR' pattern (often without a notch between R and R') is seen in leads V5 and V6. In LBBB the R wave is from depolarization of the right ventricular portion of the interventricular septum (from right to left) and the R' wave from delayed depolarization of the left ventricle (from right to left). The notch between R and R' waves is due to right ventricular depolarization (from left to right), but this notch is often obscured by left ventricular depolarization, so that only a wide R wave is seen.

RBBB is commonly seen in people with normal hearts. By contrast, LBBB is either associated with heart disease (e.g., myocardial infarction) or may occur at fast
heart rates as a normal variant. Because depolarization of one ventricle is delayed with a bundle branch block, Q waves may appear in some leads even without a myocardial infarction. One must, therefore, be very cautious in making a diagnosis of myocardial infarction in patients with bundle branch blocks and rely more heavily on changes in troponin levels in blood.

(B) Fascicular Blocks

The left bundle gives rise to an anterior and a posterior branch. When either branch is blocked, the QRS complex is slightly widened (0.10-0.12 seconds), but not to the same degree as is seen with LBBB (>0.12 seconds). Block of the anterior branch (anterior hemiblock) causes left axis deviation; whereas, block of the posterior branch (posterior hemiblock) causes right axis deviation. (Fig.4-38). To make the diagnosis of a hemiblock you usually need to document a change in the QRS axis, which requires a previous ECG for comparison.

Fig. 4-38. Hemiblocks in the fascicles of the left bundle branch. Hemiblock of the posterior fascicle (A) results in right axis deviation of the mean QRS vector in the frontal plane; whereas, a hemiblock of the anterior fascicle (B) results in left axis deviation.
Aberrant Conduction
Impulses normally spread from the SA node over the atria by three specialized conductive pathways that end at the AV node. Thus, the ventricles are electrically insulated from the atria, except for impulses conducted through the AV node (Fig. 4-39,A).

**A) Wolff-Parkinson-White Syndrome**

In patients with the **Wolff-Parkinson-White syndrome** there is an abnormal accessory pathway (the bundle of Kent) from atria to ventricles (see Fig.4-39,B). Impulses by-passing the AV node via the bundle of Kent reach the ventricles a little earlier than usual, so that the PR interval on the ECG is characteristically shorter than normal (i.e., <0.12 sec). Moreover, the early arrival of the impulse pre-excites the ventricle (therefore, this condition is also called the **pre-excitation syndrome**) resulting in a slow upstroke of the R wave, which is called a **delta wave**.

Patients with Wolff-Parkinson-White syndrome have recurrent episodes of paroxysmal supraventricular tachycardia (PSVT), because impulses traveling down the bundle of Kent to the ventricle may be conducted retrograde through the AV node back to the atria in a self-sustaining circular pattern. Another potential problem with this condition is that the safety mechanism of the AV node has been by-passed. If patients with this syndrome should develop atrial fibrillation, for instance, impulses will be conducted to the ventricles via the ac-
cessory pathway at much higher rates than is usually seen in patients with atrial fibrillation. Because of these various complications, the accessory pathway is sometimes interrupted surgically in patients with Wolff-Parkinson-White syndrome.

(B) Lown-Ganong-Levine Syndrome

In patients with the Lown-Ganong-Levine syndrome one of the atrial conduction pathways by-passes the AV node to terminate at the bundle of His (Fig. 4-39,C). This accessory pathway (the James fibers) results in rapid conduction of impulses from atria to ventricles. However, pre-excitation of ventricular muscle is not seen in this condition, because impulses spread to the ventricles over the Purkinje system as usual. Thus, the ECG in this syndrome shows a characteristically short PR interval (< 0.12 seconds) and a normal QRS complex (< 0.10 seconds). Patients with this condition experience frequent episodes of PSVT, because impulses may be conducted down the James fibers and reenter a circular pathway via retrograde conduction through the AV node.
The ECG and Potassium Imbalance
In **hyperkalemia**, when the serum potassium ion concentration rises from a normal value of about 4 mEq/L to about 7 mEq/L, the PR interval is prolonged and T waves become tall and peaked (i.e., **tented T waves**; see Fig. 4-40). As potassium levels reach about 9 mEq/L, the QRS complex widens and ventricular fibrillation or cardiac standstill is imminent. In **hypokalemia**, when the serum potassium ion concentration falls from 4 mEq/L to about 2 mEq/L, T waves are flattened, and **U waves** appear. With a further decline in serum potassium, cardiac standstill or fibrillation result.

Hyperkalemia tends to depolarize myocardial cells, i.e., it moves the resting membrane potential closer to threshold; whereas, hypokalemia tends to hyperpolarize cells, i.e., it moves the resting membrane potential away from threshold. Emergency measures for hyperkalemia include administration of calcium ions, which raises the threshold of (contractile) myocardial cells, administration of sodium bicarbonate, which enhances the exchange of extracellular for intracellular potassium ions, or administration of beta-2-adrenergic agonists (e.g. albuterol), which stimulates the sodium/potassium exchange pump. Emergency measures for hypokalemia include a **very slow** infusion of a very dilute solution of potassium chloride, because raising plasma levels - even very briefly - above about 9 mEq/L will result in ventricular fibrillation.

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**Fig. 4-40. The ECG in hyperkalemia and hypokalemia.** Characteristic ECG patterns are depicted as serum potassium concentration is raised from its normal value of 4 mEq/L to 9 mEq/L or lowered to 2 mEq/L.
In this 46 minute video-lecture Dr. Eggena discusses the structure of the myocardium, the sliding filament hypothesis, excitation-contraction coupling and force-velocity relationship of cardiac muscle.
Structure of Myocardial Cells
The Basic Structure of Myocardial Cells

The walls of the atria and ventricles are made of an interlacing mesh of muscle cells. Electrical currents (carried by ions) spread through gap junctions from one muscle cell to the next (Fig. 5-1). Each cell is a muscle fiber (myofiber) consisting of bundles of many myofibrils arranged in parallel. Each myofibril, in turn, consists of a series of sarcomeres. The sarcomere is the basic contractile unit of striated muscle (i.e., both cardiac and skeletal, but not smooth muscle).

The sarcomere is surrounded by an extensive intracellular network of tubular structures called the sarcoplasmic reticulum that serves as a storage site for calcium ions. The terminal cisternae of the sarcoplasmic reticulum are in close proximity to the transverse tubules, which are invaginations of the sarcolemma (the cell membrane).

Between the bundles of myofibrils are the organelles of the cell, such as the nuclei, the mitochondria, and granules filled with glycogen. Myocardial cells are particularly rich in mitochondria, because heart muscle depends upon a continuous supply of ATP from oxidative phosphorylation to contract and relax.
Sliding Filament Hypothesis of Muscle Contraction
The Sliding Filament Hypothesis of Muscle Contraction

The sarcomere contains proteins arranged into thick and thin filaments that slide past one another as the muscle contracts (Fig. 5-2). The thin filaments are anchored to proteins in the Z-discs, which form the boundaries of the sarcomere. The thin filaments contain the structural protein actin as well as the regulatory proteins troponin and tropomyosin, which will be referred to as the troponin complex. The thick filaments contain the structural protein myosin. Part of the myosin molecule protrudes from the thick filament like a head and forms cross-bridges with binding sites on actin - provided these sites are free to bind.

While the muscle is at rest, ATP is bound to the head of myosin. During the relaxed state the binding sites on actin are covered by the troponin complex, so that the head of myosin cannot bind to actin (Fig. 5-2,1). When the muscle is stimulated, however, the binding sites on actin are uncovered, and now cross-bridges form between actin and myosin. This process is mediated by calcium ions in the following way. When the muscle is stimulated, the intracellular...
concentration of (free) calcium ions rises from a very low level of about 0.1 μM \( (10^{-7} \text{M}) \) to 1 μM \( (10^{-6} \text{M}) \) or higher. The extra calcium ions now bind to troponin C in the thin filaments, which changes the conformation of the troponin-complex and uncovers binding sites on actin.

The myosin head now binds to actin, forming an actomyosin complex, as ATP is hydrolyzed to ADP and Pi, which remain bound to myosin. Although a cross-bridge has formed between actin and myosin at this point, the filaments do not slide past one another, and the sarcomere does not shorten (or the muscle contract), until ADP and Pi dissociate from actomyosin. This dissociation reaction is catalyzed by actomyosin (which has ATPase activity), and the energy released in this step is used to induce a conformational change in the neck portion of the molecule that flexes the head. This pulls the actin molecules (and the Z-discs to which they are attached) inward, shortening the sarcomere. One such “nod” of the head of myosin produces a small contraction that is multiplied many times by repeated cycles of making and breaking cross-bridges. To return to the relaxed state, ATP must again bind to the head of the myosin molecule, and calcium ions must dissociate from troponin C.
Excitation-Contraction Coupling
Excitation-Contraction Coupling

When a ventricular muscle cell is stimulated and its sarcolemma (membrane) depolarizes to a critical threshold voltage, an action potential sweeps over the sarcolemma and through the transverse tubular system. During phase 2 of the action potential, voltage-gated slow calcium channels in the sarcolemma are open and calcium ions diffuse from extracellular fluid [where the concentration of free calcium ions is about 1 mM (10^{-3} M)] into the cytoplasm [where the concentration is about 0.1 μM (10^{-7} M)], (Fig.5-3)]. The amount of calcium entering the cytoplasm across the sarcolemma is not in itself sufficient to raise calcium ions to the critical level of about 10^{-6} M needed to initiate a contraction, but this so-called trigger-calcium causes calcium release channels in the cisternae of the sarcoplasmic reticulum to open.

Once the release channels are opened, calcium ions diffuse from storage sites in the sarcoplasmic reticulum (where the concentration of free calcium ions is above 10^{-3} M) to thin filaments, where the concentration of free calcium ions is now raised from 10^{-7} M to 10^{-6} M or higher. At the thin filaments, calcium ions interact with troponin C to uncover actin binding sites and permit cross-bridge formation between actin and myosin. The role of calcium ions in mediating these processes is known as excitation-contraction coupling.

An important aspect of excitation-contraction coupling in myocardial cells (in contrast to skeletal muscle) is that the
force of contraction is regulated by the cytoplasmic concentration of free calcium ions. For example, at $10^{-6}$ M calcium the muscle will generate a smaller force than at $10^{-4}$ M calcium, because fewer troponin C molecules will be saturated at the lower concentrations, and, therefore, the rate of cross-bridge formation will be less. For this reason, agents that increase cytoplasmic calcium concentrations, such as epinephrine or digoxin, will increase the force of myocardial contraction. Such drugs are said to have a **positive inotropic action**. On the other hand, agents that decrease cytoplasmic calcium concentrations, such as calcium channel blockers (e.g., verapamil) or beta-adrenergic antagonists (e.g., propranolol) are said to have **negative inotropic actions**.
Myocardial Muscle Relaxation
Myocardial relaxation depends upon the removal of calcium ions from troponin C (Fig.5-4A). The process starts when slow channels in the sarcolemma and calcium leak channels in the sarcoplasmic reticulum close at the end of phase 2 of the action potential, which stops influx of calcium ions into the cytoplasm. Removal of calcium ions from the cytosol is accomplished by three mechanisms: (1) a high capacity calcium pump (ATPase) in the tubular portion of the sarcoplasmic reticulum, (2) a low capacity calcium pump (ATPase) in the sarcolemma, and (3) a sodium/calcium ion exchanger in the sarcolemma. Of these three mechanisms, the high capacity (and high affinity) calcium pump in the SR is most important in rapidly removing calcium ions and thus caus-
ing rapid relaxation of muscle. This pump must operate against a very steep (10,000-fold) calcium ion concentration gradient across the SR. The activity of this pump is stimulated by epinephrine.

Rapid relaxation of ventricular muscle immediately following systole is as important as a forceful contraction during systole. If the ventricle did not relax immediately after systole (at the beginning of diastole) when most of ventricular filling is accomplished, the end-diastolic volume would be substantially less, and the volume ejected during systole (the stroke volume) would be decreased accordingly. This is especially true when heart rate is increased which reduces the duration of diastole relatively more than the duration of systole. Fortunately, as the heart rate increases with sympathetic stimulation, epinephrine not only increases the speed of contraction during systole but also the speed of relaxation during diastole.

The actions of epinephrine to facilitate both contraction and relaxation of heart muscle are explained as follows (Fig. 5-4B). Epinephrine increases intracellular cyclic AMP after binding to beta-1-adrenergic receptors at the cell surface and activating adenylate cyclase in the sarcolemma. Cyclic AMP, in turn, activates a protein-kinase that phosphorylates (1) calcium channels in the sarcolemma, (2) troponin I in the thin filament, and (3) phospholamban, a protein that is closely associated with the calcium pump on the inside of the SR. First, the phosphorylated calcium channel facilitates calcium entry and cross-bridge formation between thin and thick filaments. Second, the phosphorylated troponin I complex decreases calcium binding to troponin C, which prevents further cross-bridge formation and facilitates relaxation. Third, the phosphorylated
phospholamban complex facilitates the operation of the calcium ion pump, which removes calcium ions from the cytosol into the SR and facilitates relaxation.

Relaxation also requires energy in the form of ATP. Without an adequate supply of ATP (from oxidative phosphorylation), calcium ions are not sequestered in the SR or removed from the cell by calcium ion pumps, ADP is not replaced on the myosin heads by ATP, and cross-bridges between actin and myosin are not broken fast enough. This mechanism may be responsible for the diminished **ventricular wall compliance** (i.e., its increased stiffness) when the left ventricle becomes ischemic or even infarcted following a reduction in coronary blood flow. In the more extreme situation of generalized ATP depletion when a person dies, muscle cannot relax, and the sustained contraction of skeletal muscle results in the stiffening of trunk and limbs known as **rigor mortis**. The sequence of events involved in myocardial contraction and relaxation is summarized in Figure 5-5.
Papillary Muscle Contraction
A. Function of Papillary Muscle

Up to now we have discussed how single ventricular muscle cells (or single muscle fibers) develop a force by cycling cross-bridges between actin and myosin. Let us next consider how a papillary muscle, which has many such fibers, behaves when stimulated to contract. The papillary muscles are anchored to the wall of the left (or right) ventricle and are attached (via the chordae tendinae) to the leaflets of the mitral (or tricuspid) valve. During systole, the papillary muscles contract simultaneously with the ventricular wall to prevent the mitral valve leaflets from prolapsing into the atria as pressure rises in the ventricle. When a papillary muscle (or the chordae tendinae or the valve leaflets) is stretched (or malformed), the valve becomes incompetent toward the end of systole, and the turbulent reflux of blood produces an end-systolic murmur, which may be preceded by a clicking sound. This condition is known as mitral valve prolapse. It is very common; its incidence in young (healthy) women has been reported as high as 15%. Mitral valve incompetence may also occur suddenly when a papillary muscle is infarcted along with a section of ventricular wall.

Fig. 5-6. Isometric and isotonic contractions of papillary muscle. A 5 g weight is suspended from a cat papillary muscle at rest (A), which lengthens the individual sarcomeres and produces a resting tension (Tr). The muscle is then stimulated to contract, and although cross-bridges form between thin and thick filaments, the active tension (Ta) developed in the muscle is just equal to the resting tension (Tr) so that the weight cannot be lifted. Because the Z-discs do not move inward and the muscle does not shorten, this is called an isometric contraction (B). When the muscle is stimulated a little more intensely so that its active tension (Ta) just exceeds the resting tension (Tr), the sarcomeres and the muscle shorten. Because the tension remains constant during contraction, this is called an isotonic contraction (C).
B. Isometric and Isotonic Contractions in an Isolated Papillary Muscle

The contractile properties of a cat’s papillary muscle are considered in Figure 5-6. The muscle has been suspended from a bar on one end and a load (weighing 5 g) has been attached to its other end. The weight will stretch the muscle fibers until the resting tension develops in elastic elements (primarily connective tissue fibers that are arranged in parallel to the sarcomeres) to the point where it just balances the load. The muscle will now be at its resting length for this particular load, and this will be reflected by the increased distance between the Z-discs of the individual sarcomeres of the myofibrils (Fig.5-6,A). When the muscle is now stimulated, cross-bridges form and active tension in the myofibrils mounts. However, the muscle does not shorten (and the weight is not lifted) unless the active tension from muscle contraction exceeds the resting tension from muscle stretching. When the muscle contracts without shortening, it is said to contract isometrically (Fig.5-6,B). When it contracts and shortens, it is said to contract isotonically (Fig.5-6,C) because muscle tension remains the same as the weight is being lifted. The work performed by the muscle is equal to the load multiplied by the distance that the load is moved. Thus, if the muscle shortens by 5 cm while lifting a load of 5 g, the work performed by the muscle equals 5 g x 5 cm = 25 g x cm.

C. Force and Velocity of Papillary Muscle Contraction

The force generated by cross-bridge cycling can be used for developing tension or for shortening the muscle. The curve in Figure 5-7 describes all the possible combinations of tension and (initial) velocity of shortening for a papillary muscle that has been stretched to a certain length and then weighted down with various loads. The principle depicted in the force-velocity curve is simply this: the heavier the load, the slower the muscle will shorten. If the load is zero, the muscle will shorten at its maximum velocity (V_{max} in Fig.5-7,A). If the load is too heavy to be lifted, then the muscle will develop its maximum tension (T_{max}) without shortening at all.

The ability of a papillary muscle to generate force is regulated in two ways: (1) when it is stretched more (within limits), it will contract more when stimulated (line B,
Fig. 5-7: Force-velocity relationship of papillary muscle. Various loads are suspended from a papillary muscle and the initial velocity of shortening is measured upon stimulation. The maximum velocity of shortening ($V_{\text{max}}$) occurs when the load is zero. The maximum tension ($T_{\text{max}}$) is found when the load cannot be lifted so that the velocity of shortening is zero. When the papillary muscle is stretched before stimulation, its velocity of shortening is increased at any given load (B). Similarly, exposing the papillary muscle to norepinephrine before stimulation increases its velocity of shortening for any given load (C). The mechanism for increased force generation in B is shown to result from increased cross-bridge formation; whereas, in C an increased cycling rate of cross-bridges is suggested as the underlying mechanism.

Fig. 5-7) and (2) when it is exposed to norepinephrine (epinephrine or other positive inotropic agents) it will contract more when stimulated at any length (C). Stretching a muscle aligns actin and myosin filaments in a more favorable position for cross-bridges to form (see B); whereas, norepinephrine increases the force of contraction by increasing the cycling rate of cross-bridges at any given length (see C).
In this 49 minute video-lecture Dr. Eggena discusses the LaPlace equation, ventricular compliance, the Frank-Starling law of the heart, homeometric regulation of cardiac contraction, and volume-pressure changes during the cardiac cycle, preload and afterload.
LaPlace Equation
1. Relationship between Tension, Pressure, and Volume (Laplace's Equation)

When the cross-bridges cycle in the many sarcomeres of a papillary muscle, they generate a force (measured in dynes) and produce tension (measured in dynes/cm) throughout the length of the muscle fiber (Fig. 5-8). This tension in the papillary muscle fibers prevents the pressure (measured in dynes/cm²) in the ventricle from prolapsing the mitral valve leaflets during systole. The same tension that is experienced by the papillary muscles during systole is also present in the muscle fibers of the ventricular walls, where the term wall stress is sometimes used instead of wall tension. The tension (T) in these fibers (in dynes/cm) is equal to the intraventricular pressure (P, in dynes/cm²) multiplied by one-half the radius (R/2, in cm) of the fluid space (which is assumed to be spherical). This is Laplace's equation for a sphere, where

\[ T = P \times \frac{R}{2} \]

Thus, for a given intraventricular pressure, ventricular wall tension will increase in proportion to the increase in radius. This increase in wall tension, when the ventricular chamber becomes enlarged (e.g., heart failure), leads to hypertrophy of the ventricular wall, which reduces stress on each muscle fiber by distributing the tension among many fibers.
Ventricular Compliance
**Ventricular Compliance**

If one wants to measure the elasticity of a rubber band, one measures the force it takes to stretch it. For a rubber balloon (or a ventricle) one could measure the pressure it takes to distend it to a given volume. The relationship between volume and pressure is a measure of ventricular compliance (which is the inverse of elastance). Just as a rubber band has a higher compliance (or lower elastance) the more readily it stretches, so a ventricle that fills at a lower pressure is more compliant. Accordingly,

\[ C = \frac{\Delta V}{\Delta P} \]

the compliance (C) equals the difference in volume (\( \Delta V \)) divided by the difference in diastolic filling pressure (\( \Delta P \)). The stiffer the ventricle, the lower its compliance. As shown in Figure 5-9, compliance is not constant over all ranges of volumes, but decreases in the higher volume ranges. Thus, an increase in end-diastolic volume from 100 ml to 150 ml requires only an additional 5 mmHg filling pressure, but an additional 20 mmHg filling pressure is required to further increase end-diastolic volume from 150 ml to 200 ml (see Fig. 5-9). The increasing difficulty in expanding the ventricle at higher end-diastolic volumes is, presumably, owing to elastic fibers that resist being stretched beyond a certain limit, just

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**Fig. 5-9. Compliance of the left ventricle.** (A) When ventricular volume is plotted as a function of ventricular filling pressure (or pulmonary artery wedge pressure, [PAWP]), the slope of the curve (\( \Delta P/\Delta V \)) is the ventricular elastance. The inverse of the ventricular elastance is the ventricular compliance (\( \Delta V/\Delta P \)). Note that ventricular compliance is not constant, but decreases at higher end-diastolic volumes (or elastance increases at higher end-diastolic volumes). Pulmonary edema occurs when PAWP exceeds the plasma oncotic pressure. (B) PAWP is increased at all end-diastolic volumes when the compliance of the left ventricle is decreased because of hyper-trophy or ischemia. These conditions are, therefore, frequently associated with pulmonary edema.
as a rubber band requires more force when stretched beyond a certain length.

Ventricular compliance is typically reduced with hypertrophy or with myocardial ischemia and infarction (see Fig.5-9). Such changes in ventricular compliance are rarely documented in patients, because this would require inserting a catheter via the aorta into the left ventricle for pressure measurements and two-dimensional echocardiographic (or cine-magnetic resonance imaging [MRI]) studies for simultaneous measurement of end-diastolic volumes. In practice, left ventricular filling pressures are usually estimated from measurements of the pulmonary artery wedge pressure (PAWP) with the Swan-Ganz catheter which will be considered later. The PAWP, however, is only a reliable estimate of left ventricular filling pressure if resistance to blood flow between the catheter tip and the left ventricle is not abnormally increased, as it is in mitral stenosis, for instance. Moreover, even if PAWP reliably reflects left ventricular filling pressure, without a simultaneous estimate of end-diastolic filling volume, no conclusions about ventricular compliance can be reached.
Ventricular Contraction
A. Preload and Afterload

For the left ventricle to eject blood into the aorta during systole, obviously, its muscle fibers must shorten. Before shortening, however, the sarcomeres must first develop sufficient force to balance the resting tension. Then they must raise the tension (and intraventricular pressure) even further to a level where the aortic valve will snap open (a pressure just above the diastolic blood pressure in the aorta at the end of the previous beat) before blood can escape into the aorta. The preload, which is responsible for the resting tension in the ventricular wall, is the load on the myocardial fibers just before they contract in systole. According to the Laplace equation the preload (T) is proportional to the end-diastolic volume [i.e., one-half the radius of the ventricular chamber (R/2)] times the ventricular pressure (P), (T = P x R/2). As the ventricle contracts and wall tension rises to a level equal to the preload, ventricular muscle still cannot shorten and eject blood because of an additional load, the afterload, that impedes blood from flowing into the aorta during systole. This impedace (the afterload) is initially caused by a closed aortic valve and later (after the aortic valve has opened) by resistance to blood flow in the peripheral circulation.

Thus, the afterload equals the intraventricular pressure that must be generated to open the aortic valve (i.e., the diastolic blood pressure, if the aortic valve is normal) and force blood into the aorta during systole. This increase in pressure is generated by an increase in wall tension that, in turn, is generated by contraction of muscle fibers in the ventricular wall. The increase in wall tension (T) leads to a proportional increase in pressure (P) when ventricular volume and radius (R) remain constant (T = P x R/2) before the aortic valve opens.

As cross-bridges in ventricular sarcomeres cycle (are made, broken, and made again) during systole, they create a force. This force is used either to raise tension and increase intraventricular pressure or to shorten muscle fibers and eject blood. When force is used to generate pressure without muscle shortening or ejecting blood, the contraction is said to be an isometric (or isovolumic) contraction. When force is used to shorten muscle fibers (at constant tension), the contraction is said to be an isotonic contraction. During early systole, ventricular muscle contracts (and raises pressure) without (appreciably) shortening. This period is, therefore,
called the **isovolumic phase of systole**. Once intraventricular pressure rises sufficiently to open the aortic valve, ventricular muscle shortens, and blood is ejected into the aorta. This period is, therefore, called the **ejection phase of systole**.

**B. Maximum Force Generated by Left Ventricle**

The maximum force that the left ventricle can generate during systole is most readily measured in an experimental preparation where the aorta is clamped so that ventricular muscle cannot shorten as the ventricle contracts (Fig. 5-10). In this way, the force from ventricular contraction is converted into tension and pressure (see $T_{max}$, in Fig. 5-7) rather than into movement. Such experiments were originally carried out by Frank on isolated frog hearts and later by Starling in a heart-lung preparation on dogs.

The maximum tension that the ventricle can exert during systole depends upon (1) the degree to which it is stretched before contraction and (2) the degree to which it is stimulated by the sympathetic nervous system (or agents that have a positive inotropic action on the heart). These are, of course, the same factors responsible for

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**Fig. 5-10.** Isovolumic contractions of the left ventricle at various preloads. In this simulation, the left ventricle is filled with different end-diastolic volumes (or preloads) and then stimulated to contract. Muscle shortening is prevented by clamping the aorta so that blood cannot be ejected. Therefore, all contractions are isovolumic or isometric, and a maximum pressure (or tension) is generated for each preload. The increased capacity of the left ventricle to raise intraventricular pressure as the preload increases is thought to be primarily due to a more favorable alignment (i.e., less overlap) of thin and thick filaments with stretching. Following sympathetic stimulation, the maximum pressure curve is shifted upward so that a greater pressure (or tension) is generated for any given preload. The compliance curve shows the diastolic filling pressure (PAWP) required for each preload given.
the force-velocity relationship of contraction of the isolated papillary muscle discussed earlier (Fig.5-7).

(1) Effect of Increasing Preload on Ventricular Contraction

In the simulation in Figure 5-10, the left ventricle was filled with end-diastolic volumes of 100, 150, or 200 ml, and intraventricular pressures were then measured during isovolumic contractions. As can be seen in the figure, the larger the end-diastolic volume (or preload), the greater the intraventricular pressure generated during systole. In other words, the more the ventricle is distended during diastole, the more forcefully it will contract during systole.

This phenomenon is thought to result primarily from an improved alignment of thin and thick filaments of sarcomeres with stretching (Fig.5-10). At low volumes (100 ml), the ends of adjoining thin filaments are shown to overlap, which presumably interferes with optimal cross-bridge formation between actin and myosin. When the sarcomere is stretched, such geometric restraints are no longer present, and cross-bridge formation is enhanced. In addition to such geometric considerations, there is evidence to suggest that stretching somehow (perhaps by stretch-activated calcium channels) increases the availability of calcium ions or the sensitivity of the contractile apparatus to calcium ions, which would, in turn, increase the cycling rate of the extra cross-bridges formed by stretching.

(2) Effect of Sympathetic Stimulation on Ventricular Contraction

Sympathetic stimulation (or exposure of the ventricle to agents or drugs that have a positive inotropic action) increases the tension or pressure that the left ventricle can generate at any given end-diastolic volume (or preload). Thus, the maximum pressure curve in Figure 5-10 is shifted upward. This increase in myocardial contractility results from an increased membrane permeability to calcium ions, which makes more calcium ions available for cross-bridge formation at any given degree of stretch.
Volumes and Pressures during the Cardiac Cycle
Left Ventricular Volume and Pressure During the Cardiac Cycle

The force produced during ventricular contraction at any given end-diastolic volume is used for generating pressure and for ejecting blood, as illustrated in Figure 5-11 for a typical beat. Diastole starts at point 1 in the diagram. The left ventricle has just relaxed at the end of systole and intraventricular pressure has fallen below the pressure in the left atrium (about 10 mmHg), causing the mitral valve to open (1), and the ventricle starts to fill. The ventricle is not empty at this time, but still contains about 42 ml of blood left over from systole, the end-systolic volume. The pressure head of about 10 mmHg in the left atrium (estimated by the PAWP) forces about 83 ml into the left ventricle, increasing its volume to 125 ml at the end of diastole, which is the end-diastolic volume.

Diastole comes to an end with the onset of ventricular contraction. As left ventricular pressure rises above left atrial pressure (2), the mitral valve closes. Because blood is now trapped between a closed mitral valve and a closed aortic valve, contraction of the ventricle raises intraventricular pressure without (noticeably) changing blood volume. This phase of the cardiac cycle (from 2 to 3) is, therefore, referred to as the period of isovolumic (or isovolumetric)
contraction. As the intraventricular pressure exceeds the diastolic blood pressure in the aorta, the aortic valve opens (3), and blood is ejected from the ventricle into the aorta (3 to 5). In the absence of aortic stenosis, the peak intraventricular pressure (4), which is similar to the systolic blood pressure, is slightly (1-2 mmHg) above the peak aortic pressure during systole.

As the ventricular volume declines during the period of ejection, the capacity of the left ventricle to generate pressure decreases along the maximum pressure curve (4-5). When the ventricle relaxes at the end of systole and intraventricular pressure falls below the pressure in the aorta, the aortic valve closes (5), and intraventricular pressure falls to near zero mmHg (1), before another cardiac cycle is initiated.

A normal ventricle (at rest) will usually eject about two-thirds of its end-diastolic volume, e.g., 125 ml - 42 ml = 83 ml, which is called the stroke volume (between points 1 and 2 in Fig. 5-11). The ratio of the stroke volume to the end-diastolic volume (2) is called the ejection fraction, which is normally 0.67 (two-thirds). The work of a single beat, the stroke work, is given by the area enclosed by the pressure volume loop (1-2-3-4-5-1).
Regulation of Stroke Volume
A. Regulation of Stroke Volume by Changes in Preload (Frank-Starling Mechanism or Heterometric Autoregulation)

The ventricles have the inherent capacity to automatically adjust their stroke volumes to the amount of filling during diastole (i.e., the extent to which cardiac fibers are stretched, their preload). This phenomenon is known as the **Frank-Starling effect**, which is illustrated in Figure 5-12. Three heartbeats are shown with progressively increasing end-diastolic volumes (or preloads). For each of these beats the diastolic blood pressure (the afterload) and ventricular contractility (the end-systolic volume-pressure relationship) are kept constant. Note, that the progressive increase in end-diastolic volume is associated with a proportional increase in stroke volume. The mechanism responsible for this increase in stroke volume is a more optimal alignment and enhanced calcium sensitivity of sarcomeres with stretching, as previously illustrated in Figure 5-10. Because autoregulation of stroke volume by the Frank-Starling mechanism is due to a change in length of ventricular fibers, the phenomenon is also called **heterometric autoregulation**.

![The Frank-Starling Effect](image)

**Fig.5-12.** The Frank-Starling Effect. Three beats at progressively increasing end-diastolic volumes (preloads) are illustrated. The more the ventricle is filled during diastole, the more it ejects during systole (the greater the stroke volume). Note that the three beats are confined by the end-systolic volume-pressure curve at the time of aortic valve closure (ESVPC) above and the diastolic volume-pressure curve (DVPC) below. ESVPC is a measure of ventricular contractility, whereas DVPC is a measure of ventricular compliance.

The primary function of the Frank-Starling mechanism is rapidly to adjust the stroke volumes of the right and left ventricles so that their outputs match - not for each beat, but on average over a number of
beats. For example, when you breathe in, the right ventricle fills more than the left, and, accordingly, the stroke volume ejected by the right ventricle is greater than that ejected by the left ventricle. A few beats later (during expiration), the extra blood reaches the left ventricle, which now becomes more distended and contracts more forcefully to eject a larger stroke volume, and the balance in the cardiac output of the right and left sides of the heart is restored.

B. Regulation of Stroke Volume by Changes in Myocardial Contractility (Homeometric Regulation)

When the ventricle contracts more forcefully (at any given preload) its contractility is said to have increased. When it contracts less forcefully than normal, contractility is diminished. Contractility of ventricular muscle is increased by sympathetic stimulation or by norepinephrine, epinephrine, or drugs that have a positive inotropic effect, such as digoxin or dobutamine.

In contrast, drugs, such as the calcium channel blockers or beta-adrenergic blocking drugs, that decrease myocardial contractility are said to have a negative inotropic effect. In addition to side effects of drugs, hypoxemia and acidosis are quite frequent causes of diminished myocardial contractility.

In ventricular hypertrophy, the force developed by the ventricle increases independently of changes in contractility of individual myofibrils. Thus, the left ventricular hypertrophy in a long distance runner, for example, provides the power for the increased cardiac output; whereas, the left ventricular hypertrophy in a patient with long-standing hypertension (increased aortic blood pressure) provides the power for a normal stroke volume despite an increased afterload. In contrast, a decreased force of contraction is seen with loss of muscle mass, as is true for patients who have had a myocardial infarct.

When the left ventricular contractility is increased and blood is ejected at a higher velocity than usual, a greater volume than usual will be ejected during systole. This increase in stroke volume, of course, must result in less blood being left at the end of systole, so that the end-systolic volume is diminished. The slope of the end-systolic volume-pressure curve (ESVPC) is, therefore, an indirect measure of myocardial contractility. This is illustrated in Figure 5-13, where pressure-volume loops have been plotted for a normal heart (A) and for
hearts that exhibit increased contractility (B, sympathetic stimulation) or decreased contractility (C, heart failure). Because stroke volume has changed without a change in end-diastolic ventricular muscle length, the phenomenon is called **homeometric regulation**.

In exercise sympathetic stimulation of ventricular muscle increases contractility (ESVPC is rotated to the left and up) so that the stroke volume increases and a greater fraction of the end-diastolic blood volume is ejected with each beat (Fig. 5-13,B). The increase in stroke volume for subsequent beats requires that ventricular filling is also increased. This is accomplished by contraction of muscles which enhances blood flow back to the heart.

In heart failure myocardial contractility is diminished (ESVPC is rotated to the right and down) and a smaller fraction of the end-diastolic blood volume is ejected with each beat (Fig.5-13,C). Although stroke volume is reduced for the first beat illustrated in Figure 5-13,C, the stroke volume will usually return to normal for subsequent beats, for the following reasons. When ventricular contractility is reduced and more blood than usual is left in the ventricle at the end of systole, the ventricle fills to a greater volume during diastole. This, in turn,

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**Fig. 5-13. Left Ventricular Contractility.** A. The end-systolic volume-pressure curve (ESVPC) at the time of aortic valve closure is a measure of ventricular contractility. B. When contractility is increased (e.g., by sympathetic stimulation), the slope of the ESVPC is increased and the curve is rotated to the left. This increases the stroke volume and the ejection fraction. C. When contractility is decreased (e.g., ventricular failure), the slope of the ESVPC is decreased and the curve is rotated to the right. This decreases the stroke volume and the ejection fraction.
stretches the ventricle and increases the stroke volume by the Frank-Starling mechanism. Unfortunately, the large end-diastolic volume increases pulmonary capillary pressure (see Fig. 5-9), which may cause fluid to leave the capillaries and result in pulmonary edema (congestive heart failure).

C. Evaluation of Left Ventricular Contraction

The ability of the left ventricle to contract depends on the ventricular muscle mass and the ability of individual myofibrils to generate force. The most reliable index of myocardial contractility is the maximum change in ventricular pressure ($\Delta P$) as a function of time ($\Delta t$), i.e., the $\Delta P/\Delta t_{\text{max}}$, measured during the isovolumic phase of systole with a catheter inserted in the left ventricle.

Another method of evaluating left ventricular contractility is to measure the end-systolic volume and pressure at the point in time when the aortic valve closes for various afterloads (see Fig. 14B). The slope of this end-systolic volume-pressure curve (ESVPC) is an indirect measure of myocardial contractility.

The most practical and usual method for estimating myocardial contractility is to measure the ventricular ejection fraction, i.e. stroke volume/end-diastolic volume. The ejection fraction can be estimated by measuring ventricular volumes at the end of systole and diastole by two-dimensional echocardiography or by cine-magnetic resonance imagining (cine-MRI).

The ejection fraction (normally about 66%) will decrease when a person’s heart fails to eject a normal stroke volume because myocardial contractility ($\Delta P/\Delta t_{\text{max}}$) is decreased. As a consequence of this inability to rapidly generate an increase in intraventricular pressure, the relative proportion of the stroke volume ejected early in systole will be less than usual. Thus, in a normal heart, about two-thirds of the stroke volume is ejected during the first third of systole (phase of rapid ejection); whereas, in the failing heart, ejection will be more evenly distributed throughout systole. Because of the decrease in cardiac output (in relationship to the capacitance of the vascular bed) the velocity of blood flowing through the circulation is decreased and, therefore, (the circulation time) is prolonged in patients with heart failure. The circulation time measures the velocity of blood flow between two points in the circulation. One way physicians (many years ago) used to measure the circulation time is to inject a bitter-tasting substance into
an arm vein and to note the time when the bitter taste is first detected, which is called the **arm-to-tongue time**. Another method is to inject a small (non-harmful) dose of cyanide into an arm vein and note the time for a sudden increase in the rate and depth of breathing when the carotid bodies are stimulated by the bolus of cyanide, which is called the **arm-to-carotid body time**. Prolonged circulation times are characteristically seen in patients with heart failure and, indeed, the periodic respiration pattern occasionally seen in patients with congestive heart failure (**Cheyne-Stokes respiration**) is a reflection of the increased circulation time between central chemoreceptors for respiration in the brain and the lung. The circulation time is no longer used to diagnose congestive heart failure, because better methods are now available.

**D. Effect of an Increased Afterload on Left Ventricular Stroke Volume**

There are basically two ways to increase the afterload on the left ventricle: (1) by increasing the resistance in the aortic valve (**aortic stenosis**) and (2) by increasing the systemic vascular resistance (**hypertension**). A person is said to have hyperten-

**Fig. 5-14. Left ventricular response to increased afterload (hypertension).** A. The pressure-volume loop of a normal heart beat. B. Pressure-volume loops with normal (a) and increased (b) afterloads (i.e., diastolic blood pressures). Note the increased intraventricular pressure required to open the aortic valve, which decreases the stroke volume and the ejection fraction. C. Compensation for the increased afterload via the Frank-Starling mechanism. Note, that more blood was left over from beat b, so that the ventricle filled more before beat c. Increased muscle stretch causes a more forceful contraction, which returns stroke volume to normal. D. Compensation for the increased afterload with sympathetic stimulation. Note, that sympathetic stimulation increases myocardial contractility, rotating the ESVPC to the left and thereby increasing the ejection fraction of beat d. This returns the stroke volume to normal without a need for sustaining the high preload. E. Compensation for an increased afterload with muscle hypertrophy. Note, that as left ventricular muscle hypertrophies, the ESVPC is rotated to the left, replacing the need for continuous sympathetic stimulation. Unfortunately, hypertrophy decreases ventricular compliance (DVPC rotates to the left) and increases filling pressure which may cause pulmonary edema.

**ESVPC** = end-systolic volume-pressure curve at aortic valve closure; **DVPC** = diastolic volume-pressure curve.
sion when on at least 3 separate occasions in a quiet, relaxed environment he/she is found to have a blood pressure in excess of 140/90 mmHg (systolic/diastolic blood pressure). In Figure 5-14B the effect of a sudden increase in diastolic blood pressure on stroke volume is illustrated in beat b. Although systole for beat b starts with the same preload, the stroke volume is reduced. The reason is that a greater proportion of the force during ventricular contraction must now be expended to raise intraventricular pressure above diastolic blood pressure so that the aortic valve will open and allow blood to be ejected from the ventricle into the aorta. As a consequence, less force is available for muscle shortening during the ejection phase of systole, which reduces the stroke volume of beat b. Although the stroke volume is reduced, the stroke work, which is the area enclosed by the pressure-volume loop, remains unchanged.

(1) Compensation for an Increased Afterload by the Frank-Starling Mechanism

After raising the afterload, more blood is left in the ventricle at the end of systole (beat b, Fig. 14,B and C). Therefore, when the normal stroke volume from the right ventricle arrives on the left side and starts filling the left ventricle during diastole, the left ventricle will now fill to a greater volume. This increase in the preload stretches muscle fibers and increases the force of contraction via the Frank-Starling mechanism, returning stroke volume to normal, despite the increased afterload (beat c, Fig. 14,C).

The left ventricle will be more distended if it continues to function at a higher than normal end-diastolic pressure. Although a dilated ventricle (within limits) will contract more forcefully because of the Frank-Starling mechanism, the stress on the ventricular wall increases with an increase in the radius of the intraventricular chamber, according to the Laplace equation. To overcome this wall stress (or tension), more force is required, so that a dilated heart consumes more oxygen.

(2) Compensation for an Increased Afterload by Sympathetic Stimulation

When possible, the left ventricle will compensate for an increase in its afterload (e.g., arterial hypertension) by increasing its contractility. This is accomplished initially by sympathetic stimulation (Fig. 5-14,D) and later by hypertrophy of ventricular muscle (Fig. 5-14,E). Sympathetic stimulation rotates the end-systolic volume-
pressure curve to the left (Fig. 14,D), so that a greater fraction of the end-diastolic volume is ejected during systole and the left ventricle returns to its original end-systolic volume, despite the persistent increase in afterload (beat d).

(3) Compensation for an Increased Afterload by Left Ventricular Hypertrophy

A persistent increase in afterload (such as untreated hypertension) causes the number of myofibrils in each muscle cell to increase, resulting in a greater muscle mass in the left ventricle (hypertrophy). As left ventricular muscle strength increases with time, the need to increase contractility by sympathetic stimulation gradually subsides, i.e., the ESVPC is rotated to the left (Fig.14,E) by the increased force generated by the hypertrophied muscle.

The hypertrophied muscle makes the left ventricle stiffer, i.e., its compliance decreases (the DVPC is rotated to the left). This increases the diastolic filling pressure and the pulmonary capillary pressure, which may cause pulmonary edema and difficulty breathing.

A beneficial effect of ventricular hypertrophy is that the increase in wall thickness distributes the tension over a greater number of muscle fibers and thus diminishes wall stress. Wall thickness is not taken account in the Laplace equation, so cardiologists sometimes modify the equation in the following way:

\[ T = \frac{PR}{2H} \]

where T is the tension (or stress), P the pressure, R the radius, and H the wall thickness. It follows from these relationships that, if wall thickness increases in parallel with an increase in radius, wall tension will remain constant.

Thus, the concentric hypertrophy of the left ventricle in patients with untreated hypertension diminishes wall tension and increases the ability of the thickened ventricle to contract. But the contractility of individual myofibrils in the hypertrophied ventricle is less than normal, and the hypertrophied heart consumes relatively more oxygen (and needs more coronary blood flow) for the extra work it does. With persistent (untreated) hypertension, the hypertrophied heart starts to dilate and, thereby, once again must call upon the Frank-Starling mechanism to increase stroke volume. Although the sarcomeres are stretched and contract more forcefully with an increase in the end-diastolic volume, the basic structure of the individual sar-
comeres is not really changed in the failing heart. In other words, the individual sarcomeres are not overstretched; the myofibrils alone are displaced by sliding over one another in parallel.

As already mentioned, the hypertrophied left ventricle requires a higher filling pressure (see Figs. 5-9B and 5-14,E). This not only causes pulmonary edema and hypoxemia, but also increases the impedance to right ventricular ejection, and, as the afterload on the right ventricle increases, the right ventricle, in turn, is stimulated to contract more forcefully and hypertrophies. But eventually the ejection fraction of the hypertrophied right ventricle declines and end-diastolic volume increases to compensate. As the right ventricle fails and its compliance decreases, the filling pressure of the right ventricle (the CVP) also increases which, in turn, raises capillary pressure and causes peripheral edema.
Work of the Heart
A. The Left Ventricular Stroke Work Index

The work of a single heart beat is given by the area enclosed by the pressure-volume loop (see Fig. 5-11). In clinical practice such pressure-volume loops are not available, so that the stroke work is estimated by multiplying the stroke volume by the mean blood pressure minus the pulmonary artery wedge pressure. Moreover, since stroke volume varies from person to person depending on their height and weight, stroke volume is normalized to body surface area (which is determined from standard charts for height and weight). Stroke volume normalized to body surface area is called the stroke index.

For example, a person with a surface area of 1.7 m$^2$ has a blood pressure of 140/80 mmHg, a mean systemic arterial pressure (MSAP) of 100 mmHg, a pulmonary artery wedge pressure (PAWP) of 15 mmHg, and a stroke volume (SV) of 100 ml/beat. Her stroke index (SI) is, therefore, 100 ml/1.7 m$^2$ = 59 ml/m$^2$; and her stroke work (SW) is 59 ml/m$^2$ x 85 mmHg = 5,015 ml x mmHg/m$^2$. This value is usually multiplied by a factor of 0.0136 to convert units to g x m/m$^2$, which yields the left ventricular stroke work index (LVSWI) of 68 g x m/m$^2$. These units imply that left ventricular muscle performs work for each beat equivalent to lifting a load of 68 g over a distance of 1 m (or a load of 680 g over a distance of 10 cm) for each square meter of body surface area.

B. The Right Ventricular Stroke Work Index

Although the stroke volumes of the right and left ventricles are the same (when averaged over a minute), the ventricular stroke work index is considerably lower on the right than on the left side of the heart. Assume that the right ventricle ejects the same stroke volume as the left ventricle in the above example (i.e., SV = 100 ml, SI = 59 ml/m$^2$), that the afterload for the right ventricle is 16 mmHg (the mean pulmonary artery pressure, MPAP), and that the right ventricular filling pressure (the central venous pressure, CVP) is 5 mmHg. Accordingly, the right ventricular stroke work index (RvSWI) will be

$$\text{RvSWI} = \text{SI} \times (\text{MPAP} - \text{CVP}) \times 0.0136 \text{ g x m/m}^2$$

$$= 59 \times 11 \times 0.0136$$

$$= 9 \text{ g x m/m}^2$$

Thus, the right ventricle ejects 100 ml with a SWI of 9 g x m/m$^2$; whereas the left ventricle ejects the same stroke volume with a SWI of 68 g x m/m$^2$. The reason for the increased work load of the left ventricle is, of...
course, that resistance is much higher in the peripheral than in the pulmonary circulation. To carry out the greater work load, the muscle mass of the left ventricle is considerably greater and its oxygen consumption accordingly higher than the right ventricle.
Cardiac Metabolism
The heart is not particularly selective in choosing what to metabolize, although, shortly after a meal, it will usually metabolize relatively more glucose, lactate, and pyruvate; whereas, during fasting more free fatty acids and ketones tend to be used.

**A. Synthesis of ATP**

The heart cannot store energy or function anaerobically (and accrue an oxygen debt) to the degree that skeletal muscle can. The heart, therefore, depends upon a constant supply of oxygen to continuously synthesize new ATP molecules in the many mitochondria typically found in cardiac muscle. Under aerobic conditions, for every mole of glucose metabolized, 36 moles of ATP are synthesized and for every mole of fatty acid, 130 moles of ATP are formed. Under anaerobic conditions, by contrast, one mole of glucose yields only 2 moles of ATP, which emphasizes the importance of providing heart muscle cells with a continuous supply of oxygen. Some ATP is also synthesized from high energy bonds in phosphocreatine, but stores of this compound in the myocardium are limited and no substitute for aerobic metabolism.

**B. Utilization of ATP**

The heart uses considerably more ATP during systole than it does during diastole. It has been estimated that about 25% of the total ATP used in a single cardiac cycle is expended during diastole and the remaining 75% during systole. Most of the ATP (about 50%) expended during systole is used during the isovolumic phase of ventricular contraction. This reflects the increased energy cost of performing pressure versus volume work. In other words, volume work (e.g., the type of cardiac work performed by a long distance runner) is more efficient and requires less oxygen and fewer ATP molecules than pressure work (e.g., the type of cardiac work performed by a person with hypertension). For example, if the afterload were doubled and the stroke volume reduced to keep the stroke work identical, ATP utilization by the heart would just about double. These considerations indicate that the area of the pressure-volume loops (or stroke work indices) are poor predictors of ATP utilization and myocardial oxygen consumption.

Because most ATP is utilized during the isovolumic and early ejection phases of systole, the oxygen requirements of the heart increase with an increase in heart rate. Thus, it is more efficient for the heart...
to beat slowly with a large stroke volume, than rapidly with a smaller stroke volume. For instance, if a cardiac output of 5 liters/minute is required at rest, this can be accomplished either with a stroke volume of 67 ml and a heart rate of 75 beats/min (67 ml/beat x 75 beats/min = 5,000 ml/min) or with a stroke volume of 83 ml and a heart rate of 60 beats/min (83 ml/beat x 60 beats/min = 5,000 ml/min). The latter arrangement is more efficient and is usually seen in well conditioned individuals who have large stroke volumes and slow resting heart rates.

At present, the simplest and most practical predictor of ATP utilization and oxygen consumption by the heart is the product of systolic blood pressure and heart rate, which is called the pressure-rate product. For this reason, a reduction in arterial pressure and in heart rate are among the first therapeutic considerations in a patient with angina pectoris, which is the cardiac pain experienced when oxygen consumption by the heart exceeds oxygen supply.

The pressure-rate product is usually determined during the stress test where the patient’s systolic blood pressure and pulse are taken while running on a treadmill. Knowing the patient’s pressure-rate product at a point in time when the patient first experiences chest pain or dizziness or when ST-segment depressions or PVCs are first noted on the ECG is important for documenting changes in exercise tolerance due to treatment, such as coronary stenting.

C. Oxygen Consumption

Oxygen delivery to the various tissues and organs of the body, including the heart, is a major function of the left ventricle, and, indeed, the cardiac output is ultimately adjusted to meet the overall needs of the body for oxygen and nutrients.

1. Oxygen Consumption by the Heart

The oxygen consumption ($\dot{V}O_2$, in ml/min) of a single organ is equal to the product of its blood flow ($Q$, in ml/min) and the amount of oxygen it extracts from arterial blood, i.e., the difference between its arterial and venous oxygen content ($CaO_2-CvO_2$, in ml O$_2$/dL blood):

$$\dot{V}O_2 = Q \times (CaO_2 - CvO_2)$$

The heart receives about 4% of the cardiac output (e.g., 5 liters/min), so that blood flow to the heart ($Q$) amounts to about 200 ml/min at rest. Heart muscle extracts about 50% of the oxygen from blood flowing through it. Assuming a nor-
mal hemoglobin concentration (15 gm/dL) and normal arterial oxygen saturation (97.5%), the arterial oxygen content of blood (CaO₂) entering the heart via coronary arteries will be 20 ml O₂/dL blood, and the venous oxygen content of blood (CvO₂) leaving the heart via coronary veins will be 10 ml O₂/ dL. The oxygen consumption of the heart will be accordingly,

\[ \dot{V}O_2 = 200 \text{ ml/min} \times (20 \text{ ml O}_2/\text{dL} - 10\text{ml O}_2/\text{dL}) \]

= 20 ml O₂/min

This value will, of course, depend on the size of the person and whether or not he or she is at rest or exercising. Somewhat surprising is the fact that with exercise neither the percentage of the cardiac output (4%) that perfuses the coronaries nor the percentage of oxygen extracted from coronary blood (50%) is substantially increased over what it is at rest. Yet oxygen consumption of the heart increases markedly on exercise. Obviously, then, oxygen consumption of the heart increases in direct proportion to the increase in cardiac output seen during exercise. Thus, if cardiac output increases threefold, i.e., from 5 to 15 liters/min, during exercise, oxygen consumption of the heart will also increase threefold, i.e., from 20 to 60 ml O₂/min.

2. Oxygen Consumption of the Body

Similarly, the oxygen consumption of the whole body is equal to the product of the cardiac output (CO) and the difference between the arterial oxygen and mixed venous (e.g., right atrial) oxygen content of blood, i.e.,

\[ \dot{V}O_2^{(\text{total})} = CO \times (\text{CaO}_2 - \text{CvO}_2) \]
Assuming a cardiac output of 5 liters/min at rest, an arterial oxygen content \((\text{CaO}_2)\) of 20 ml \(\text{O}_2/dL\) blood, and a mixed venous oxygen content \((\text{CvO}_2)\) of 15 ml/dl blood (i.e., 25% extraction of oxygen on average by all the organs and tissues),

\[
\text{\(\overline{V}\)O}_2 = 5 \text{ liters/min} \times (20 \text{ ml } \text{O}_2/dL - 15 \text{ ml } \text{O}_2/dL) = 250 \text{ ml } \text{O}_2/\text{min}
\]

The total body oxygen consumption can be measured by spirometry. A person breathes air from a water-sealed air space under an inverted bell, which moves up and down in the water as he inspires 500 ml of air (the tidal volume), and then expires a slightly smaller volume. The up-and-down movement of the bell is recorded on a moving sheet of paper to graph changes in lung volume (Fig. 5-15). The difference in volume of inspired and expired air (after the expired carbon dioxide has been absorbed by a lime canister) is a measure of oxygen uptake by the lungs. As oxygen is removed from the air space, the volume of air under the bell declines, e.g., by 250 ml during a one-minute test period in the example in Figure 5-15. In the steady state, oxygen uptake by the lungs is equal to the oxygen consumption of the body as a whole, i.e., \(\text{\(\overline{V}\)O}_2 \text{ (total)} = 250 \text{ ml/min}\) in Figure 5-15.

An oxygen consumption of 250 ml/min is a normal average value for a person at rest. During exercise, however, oxygen consumption increases markedly and, indeed, increases proportionally more than the increase in cardiac output. The reason for this is that skeletal muscle (unlike cardiac muscle) extracts very little oxygen from arterial blood at rest, but extracts virtually all oxygen during exercise. As a consequence, the oxygen content of mixed venous blood \((\text{CvO}_2)\) falls well below the usual 15 ml \(\text{O}_2/dL\), which increases total oxygen consumption \((\text{\(\overline{V}\)O}_2)\) beyond that attributable to an increase in cardiac output with exercise.
8

The Cardiac Cycle

Movie 8.1 The Cardiac Cycle

In this 41 minute video-lecture Dr. Eggena discusses cardiac output, hemodynamic monitoring in the ICU, and Pressure changes during the cardiac cycle.
Measuring Cardiac Output
A. Cardiac Output by the Fick Principle

After measuring the oxygen consumption of the whole body ($\bar{V}O_2$ (total)), the cardiac output is readily measured by rearranging equation (2):

$$CO = \frac{\bar{V}O_2 \text{(total)}}{(CaO_2-CvO_2)}$$

(Fick Principle)

For example (see Fig.5-16), assuming a total oxygen consumption of 250 ml O_2/min at rest, an arterial oxygen content of 20 ml O_2/dL blood, and a mixed venous oxygen content of 15 ml O_2/dL blood,

$$CO = \frac{250 \text{ ml O}_2/\text{min}}{(20-15) \text{ ml O}_2/\text{dL}}$$

CO = 5,000 ml blood /min

You need to know the following data to calculate the cardiac output by the Fick principle: (1) the oxygen consumption (VO_2), (2) the arterial oxygen content (CaO_2), and (3) the mixed venous oxygen content (CvO_2). To determine CaO_2, the hemoglobin (Hb) concentration and the partial pressure of oxygen in arterial blood (PaO_2) must be known. The percentage saturation of hemoglobin (SaO_2) for different values of PaO_2 are derived from the hemoglobin dissociation curve. To determine CvO_2, the partial pressure of oxygen in mixed venous blood (PvO_2) and mixed venous blood saturation (SvO_2) must be known. Note that the mixed venous blood sample cannot be taken from an arm vein but must be collected at (or close to) the right atrium, whereas the arterial sample may be collected from any artery.

Fig.5-16. Cardiac output (CO) can be calculated by the Fick equation if the following data are provided: (1) The oxygen consumption (VO_2), (2) the arterial oxygen content (CaO_2), and (3) the mixed venous oxygen content (CvO_2). To determine CaO_2, the hemoglobin (Hb) concentration and the partial pressure of oxygen in arterial blood (PaO_2) must be known. The percentage saturation of hemoglobin (SaO_2) for different values of PaO_2 are derived from the hemoglobin dissociation curve. To determine CvO_2, the partial pressure of oxygen in mixed venous blood (PvO_2) and mixed venous blood saturation (SvO_2) must be known. Note that the mixed venous blood sample cannot be taken from an arm vein but must be collected at (or close to) the right atrium, whereas the arterial sample may be collected from any artery.

(SO_2) or its oxygen tension (PO_2) must also be known.
Figure 5-16 shows how to calculate cardiac output by the Fick principle. The hemoglobin concentration is 15 g/dl with a PaO₂ of 100 mmHg, so that hemoglobin is 97.5% saturated (SaO₂ = 97.5%). Since each g of hemoglobin binds 1.34 ml of oxygen when fully saturated, 1 dL of arterial blood contains (CaO₂) 15g/dL x 1.34 ml/g x 0.975 = 20 ml oxygen/dL blood. On the other hand, a mixed venous blood sample from the right atrium has a PvO₂ of 40 mmHg with an SvO₂ of 75%, so that the oxygen content of mixed venous blood (CvO₂) is:

\[
CvO₂ = 15g/dl \times 1.34 \text{ml/g} \times 0.75 \\
= 15 \text{ml oxygen/dL blood}
\]

Therefore, each 100 ml (or 1 dL) of arterial blood flowing through the peripheral tissues and organs has delivered 5 ml of oxygen, which must be added back to venous blood as it flows through the lungs. Knowing from spirometry measurements for this case (Fig. 5-16) that 250 ml of oxygen are being taken up by mixed venous blood every minute, it follows that 50 dL of blood - each taking up 5 ml O₂ - must be flowing through the pulmonary circulation each minute. The amount of blood ejected over a minute from the right ventricle into the pulmonary circulation is, of course, equal to the amount of blood ejected by the left ventricle into the peripheral circulation, the cardiac output.

Cardiac output depends on body size and is therefore normalized with regard to body surface area, which is determined from a normogram that takes into account a person’s weight and height. This normalized value is called the **cardiac index** (CI).

**B. Cardiac Output by the Thermodilution Principle**

Although the measurement of cardiac output by the Fick principle is the standard and most reliable method, a more commonly used method for measuring cardiac output at the bedside is by the thermodilution principle. With a Swan-Ganz catheter in the pulmonary artery and a thermistor (a thermo-sensitive probe) near its tip, 10 ml of cold (either at 0 or 21°C) saline is injected proximal to the thermistor into the right atrium via one of several ports in the catheter. The cold saline dilutes the warmer blood (37°C) and lowers its temperature in proportion to the blood flowing into the pulmonary artery, which equals the cardiac output. The thermistor is connected to a computer that (after careful calibrations) converts the rate of temperature change into values for cardiac output.
Hemodynamic Monitoring
Hemodynamic (or cardio-pulmonary) monitoring is commonly used for seriously ill patients on intensive care units, where knowledge of cardiac output, pulmonary artery wedge pressure (PAWP), and oxygen saturation (or tension) of mixed venous blood is considered of sufficient importance in guiding therapy that it warrants the risks associated with inserting a Swan-Ganz catheter into the external jugular vein and advancing it into the right heart. Usually, an arterial cannula is inserted at the same time to monitor systolic, diastolic, and mean arterial blood pressure, as well as to have ready access to arterial blood samples to measure arterial oxygen saturation (or tension). In addition, the electrical activity of the heart is continuously monitored in these patients, because insertion of the Swan-Ganz catheter may be associated with cardiac arrhythmias that must be promptly recognized and, if necessary, treated.

A. Swan-Ganz Catheterization

(1) Central Venous and Right Atrial Pressures

The Swan-Ganz catheter has a balloon near its end that, when inflated, tends to float with the flow of blood and carry the catheter tip into the right atrium, right ven-

Fig. 5-17. Hemodynamic monitoring. A balloon-tipped Swan-Ganz catheter is inserted into a jugular (or subclavian) vein and advanced into the superior vena cava (1), the right atrium (2), the right ventricle (3), the pulmonary artery (4), and wedged in a branch to the lower lobe of the lung (5). Pressure changes are recorded on a monitor as the catheter is advanced. A computer calculates cardiac output based on changes in temperature when the catheter is in the pulmonary artery and cold saline is injected by one of several ports (thermodilution technique for measuring cardiac output). A, c, and v waves and the x- and y-descents are seen when the Swan-Ganz catheter is introduced into the internal jugular vein and advanced into the right atrium. Similar waves that are seen when the catheter is wedged in a branch of the pulmonary artery are caused by pressure changes in the left atrium during the cardiac cycle.

A radial (or femoral) artery is cannulated for monitoring systolic and diastolic pressures and calculating a mean systemic artery pressure (MSAP), which is equal to the diastolic pressure plus one third of the pulse pressure. The arterial and Swan-Ganz catheters (in the unwedged position) are also used to collect blood samples for blood gas analysis, as indicated in Table 5-3.
tricle, and through the pulmonic valve into the pulmonary artery and to one of its major branches (Fig.5-17).

The catheter is usually inserted into an external jugular or a subclavian vein and then advanced toward the heart while observing changes in venous pressure on a monitor. When the catheter tip reaches the superior vena cava in the chest, venous pressure is seen to fluctuate with respirations. This is the central venous pressure (CVP), which should normally be less than 10 mmHg and is usually about 5 mmHg (see Table 5-3). As the catheter is advanced (with the balloon now inflated) into the right atrium, the right atrial pressure is found to be similar to the CVP. Closer scrutiny reveals not just one pressure but a series of changing pressure waves, which can also be detected without the Swan-Ganz catheter, simply by carefully inspecting the side of the neck over the external jugular vein. Comparing the appearance of these waves with the ECG monitor overhead, one notices that the tallest of these waves, the a wave, immediately follows the onset of the P wave on the ECG (see Fig.5-17). Accordingly, the a wave is a pressure wave due to atrial muscle contraction. The next wave crest is called the c wave. The c wave comes right after the QRS complex on the ECG and is due to the pressure wave caused by bulging of the tricuspid valve into the atrium as the right ventricle contracts during its isovolumetric phase of systole. Right atrial pressure declines after the a and c waves (x1- and x2-descent), which is caused by the downward movement of the base of the heart during ventricular contraction. The v wave is the last of the three crests. It occurs toward the end of ventricular systole and is due to atrial filling. Right atrial pressure rapidly falls after the v wave, which is called the y-descent. This fall in pressure occurs when the tricuspid valve opens at the beginning of ventricular diastole and blood empties from the right atrium into the ventricle.

(2) Right Ventricular and Pulmonary Artery Pressures

As the catheter is now advanced across the tricuspid valve into the right ventricle, large fluctuations are noted between systole and diastole, with the right ventricular systolic pressure rising to about 23 mmHg and the right ventricular diastolic pressure falling to around 4 mmHg (see Fig.5-17). With a twist, the balloon now carries the catheter tip through the pulmonic valve and into the pulmonary artery, where the pulmonary artery systolic pressure is
similar to the right ventricular systolic pressure (about 22 mmHg), but the **pulmonary artery diastolic pressure** (about 10 mmHg) is much higher than the diastolic pressure in the right ventricle. The reason for the higher diastolic pressure in the pulmonary artery is as follows. When the right ventricle ejects its stroke volume into the pulmonary artery during systole, only part of the stroke volume is immediately transmitted to the left atrium, the rest remains in the pulmonary artery and its branches, which are stretched to accommodate the volume. When the right ventricle relaxes during diastole and intraventricular pressure falls below pulmonary artery pressure, the pulmonic valve snaps shut, and the pulmonary vessels now generate a recoil pressure (the diastolic pressure) which gradually forces the remainder of the stroke volume in the direction of the left atrium during diastole.

**B. Arterial Cannulation**

Following insertion of a cannula into a radial or femoral artery, characteristic pressure changes are recorded during left ventricular systole and diastole, as shown in Figure 5-17. The peak pressure is the systolic blood pressure, e.g., 120 mmHg. The lowest pressure, which is seen at the end of diastole, is the diastolic blood pressure, e.g., 80 mmHg. The difference between the systolic and diastolic pressure is the **pulse pressure**, e.g., 40 mmHg. The **mean pressure** is the average pressure during systole and diastole. It is usually estimated by adding one third of the pulse pressure to the diastolic pressure, e.g., 80 mmHg + 40 mmHg/3 = 93 mmHg.
The Cardiac Cycle
1. Atrial and Ventricular Pressure Changes During the Cardiac Cycle

When the sino-atrial node depolarizes, a wave of depolarization sweeps over the atria, inscribing a P wave on the electrocardiogram (Fig. 5-19). Shortly thereafter the atria contract, and the increase in atrial pressure results in an a wave which, for the right atrium, can be observed in the jugular venous pulse on physical examination.

When the ventricles depolarize, a QRS complex is inscribed on the electrocardiogram. Shortly thereafter, the ventricles contract, and the increase in ventricular pressure causes the mitral and tricuspid valves to shut in the left and right ventricles, respectively. The vibrations from closure of these valves produce the first heart sound.

Systole starts with the period of isovolumic contraction during which intraventricular pressure rises without significant changes in volume. During this period the c wave may be observed in the jugular venous pulse. It is caused by bulging of the tricuspid valve into the right atrium. Pressure then declines in the atria as the base of the heart is pulled downward during ventricular systole (the x₂-descent in the jugular pressure tracing). When intraventricular pressure exceeds the diastolic arterial pres-
sure, the semi-lunar valves open, and blood is ejected at a high velocity during the period of rapid ejection.

When the ventricles repolarize, a **T wave** is inscribed on the electrocardiogram. Shortly thereafter the ventricles relax. When left ventricular pressure falls below aortic pressure, the aortic valve closes, and when right ventricular pressure falls below the pulmonary artery pressure, the pulmonary valve closes. The vibrations from closure of these valves produces the **second heart sound**, which marks the end of systole. When ventricular pressure falls below the pressure in the atria at the peak of the **v wave**, the mitral and tricuspid valves open and blood rushes into the ventricles causing atrial pressure to fall (the **y-descent**) in early diastole.

### 2. Ventricular Volume Changes During the Cardiac Cycle

A normal ventricle ejects about two thirds of its the end-diastolic filling volume during systole, i.e., the normal ejection fraction is 0.67 at rest (Fig. 5-19). The volume of blood ejected during systole is, of course, the stroke volume. About two-thirds of the stroke volume is ejected in the first one-third of systole, the **period of rapid ejection**. Thus, when the duration of systole is shortened as heart rate increases, for instance, during exercise, stroke volume is only minimally affected. Moreover, sympathetic stimulation simultaneously increases myocardial contractility (and thus the ejection fraction) so that stroke volume is not only maintained, but actually is increased during exercise.

About two-thirds of ventricular filling is accomplished early in diastole during the period of rapid filling. This time interval coincides with the y-descent following the v-wave in the atrial pressure tracing. Turbulence from the rapid flow of blood during early diastole may cause a third heart sound. Ventricular filling then slows (**diastasis**), until the atria contract during atrial systole. The turbulent flow of blood resulting from atrial contraction may cause a fourth heart sound. Because a fourth heart sound depends upon atrial contraction, it is never heard in patients with atrial fibrillation.

Just as ventricular ejection adapts well to increasing heart rates, so ventricular filling is facilitated when the heart is stimulated to beat faster. The reason is that shortening of diastole at higher rates impinge - at least initially - on the period of diastasis when filling is slow. The relatively minor
loss in filling by shortening the period of diastasis is offset by actions of norepinephrine and epinephrine (1) to facilitate ventricular relaxation, which enhances filling in early diastole and (2) to increase atrial contractility, which enhances filling in later diastole.

Despite these adaptations, at very high rates (i.e., above 180 beats/min in a normal heart) ventricular filling will diminish and so will stroke volume. Because atrial contraction plays an increasingly important role in ventricular filling as heart rate increases, patients with atrial fibrillation and fast heart rates often experience symptoms of insufficient cardiac output. Their condition is often markedly improved - not by reverting the fibrillating atria back to normal - but simply by decreasing the heart rate below about 100 beats/minute. This is usually accomplished by administering a beta-1-adrenergic blocker or digoxin, which delays conduction of impulses from the fibrillating atria through the A-V node to the ventricles.
Heart Sounds

Movie 9.1 Heart Sounds and Murmurs

In this 43 minute video-lecture Dr. Eggema discusses and listens to heart sounds and the murmurs of mitral and aortic stenosis and mitral and aortic insufficiency in Dr. Eggema’s multimedia Authorware computer program.
Auscultation
1. Auscultation

**Auscultation** is listening to sounds from within the body - usually with the aid of a stethoscope. Heart sounds are caused primarily by vibrations of heart valves as they are forced shut. Sounds arising from the tricuspid or mitral valves are usually heard best along the left sternal border (4th intercostal space) or at the cardiac apex (5th intercostal space, midclavicular line), respectively (Fig. 5-20). Sounds arising from the semilunar valves are projected in the direction of blood flow across the valve, so that sounds from the pulmonic valve are best heard in the second intercostal space just to the left of the sternum; whereas, sounds from the aortic valve are usually best heard in the second intercostal space just to the right of the sternum as well as over the carotid arteries in the neck (see Fig. 5-20). Heart sounds can be displayed as a function of time on an oscilloscope after placing a special transducer on the chest wall at the locations where heart sounds are best heard with a stethoscope. Such **phonocardiograms** allow precise timing of heart sounds and murmurs and facilitate their correlation with other events of the cardiac cycle, such as the electrocardiogram and pressure readings obtained from cardiac catheterization.

Fig. 5-20. Auscultation of the heart. The listening areas on the anterior chest wall for sounds arising from the A-V valves and semilunar valves are indicated and the timing of heart sounds related to an ECG tracing. The first heart sound (S1) occurs just after the QRS complex; its first component is due to closure of the mitral valve (Mc); its second component from closure of the tricuspid valve (Tc). Shortly after S1, the pulmonic (Po) and aortic (Ao) valves open without a sound (normally). The second heart sound (S2) occurs just after the T wave on the ECG; its first component (A2) is from closure of the aortic valve (Ac) and its second component (P2) from closure of the pulmonic valve (Pc). Shortly after S2, the tricuspid (To) and mitral (Mo) valves normally open without a sound. A third heart sound (S3) is occasionally heard during ventricular filling in early diastole, and an abnormal fourth heart sound (S4) is occasionally heard during atrial contraction (shortly after the P wave of the ECG).
2. The First Heart Sound

As already mentioned, the first heart sound (S1) occurs as the tricuspid and mitral valves are forced shut as the ventricles contract at the beginning of systole (Fig. 5-20). S1 is usually heard as a single sound, but when it is split in two, the first component is from closure of the mitral valve and the second component from closure of the tricuspid valve. The first sound is usually loudest at the cardiac apex. Its intensity is increased when the A-V valves are wide open as they are suddenly slammed shut by ventricular contraction. This occurs with a short P-R interval (decreased time for atrial relaxation), with exercise (increased ventricular filling and contractility), and with mitral stenosis (from stiff valve leaflets with slow ventricular filling).

3. The Second Heart Sound

The second heart sound (S2) occurs when the semi-lunar valves close at the end of systole. The second heart sound is loudest at the base of the heart and characteristically has two components: The first component is due to closure of the aortic valve (A2), the second component is due to closure of the pulmonic valve (P2), (Fig. 5-20). Closure of the aortic valve is louder and more widely heard over the chest than is the sound of closure of the pulmonic valve, which is usually heard only at the second intercostal space just left of the sternum.

The intensity of A2 is often increased in systemic hypertension; whereas, the intensity of P2 is increased in pulmonary hypertension. This, presumably, is caused by a more forceful closure of semi-lunar valves with high pressures in the aorta or pulmonary artery. On the other hand, when blood flows slowly across semi-lunar valves that are narrowed, scarred, and stenotic, the intensity of the second heart sound usually diminishes.
Splitting of Second Heart Sound
A. Physiological Splitting of the Second Heart Sound

The pulmonic component of the second heart sound (P2) is normally delayed during inspiration, so that the second heart sound becomes more widely split (Fig. 5-21,A). This is called **physiological splitting of the second heart sound**. It is particularly pronounced in children and is perfectly normal. Physiological splitting of S2 results primarily from delayed closure of the pulmonic valve when venous return to the right ventricle increases during inspiration. During inspiration the more subatmospheric pressure in the chest distends the heart, which allows more blood to flow from peripheral veins, where pressure is higher, into the right atrium and the right ventricle and, thereby, to increase right ventricular end-diastolic volume. As a consequence, right ventricular ejection takes a little longer than usual, so that closure of the pulmonic valve is slightly delayed. At the same time, the aortic valve (A2) closes a little earlier than usual. The reason is that blood pools in the lungs on inspiration, and the left ventricle is, therefore, filled with a smaller end-diastolic volume, which requires less time than usual to eject. Thus, an early A2 and a late P2 are responsible for normal splitting of the second heart sound on inspiration.

B. Fixed Splitting of the Second Heart Sound

In certain pathological conditions, ejection of the stroke volume by the right ventricle is delayed not only during inspiration, but also during expiration. Under such circumstances, the second heart sound is split both on inspiration and on expiration (although it is more widely split on inspiration), which is called **fixed (or wide) splitting**.
ting of the second heart sound (Fig. 5-21,B). Fixed splitting of the second heart sound is seen, for instance, when impulse conduction to the right ventricle is delayed by a right bundle branch block, when ejection is slowed by an increased afterload in stenosis of the pulmonic valve, or when the preload of the right ventricle is increased by reflux of blood from the left atrium into the right atrium through an atrial septal defect.

C. Paradoxical Splitting of the Second Heart Sound

Pathological conditions that slow emptying of the left ventricle cause an abnormal delay in closure of the aortic valve so that A2 occurs after P2. This is opposite from normal. During expiration, when left ventricular stroke volume and ejection time are increased, wide splitting of the second heart sound is now heard. However, during inspiration, when right ventricular stroke volume and ejection time are prolonged, only a single second heart sound is heard. This abnormal inversion of the second heart sound during the respiratory cycle is called paradoxical (or reversed) splitting of the second heart sound (Fig. 5-21,C). It is seen, for instance, when impulse conduction to the left ventricle is delayed by a left bundle branch block, when left ventricular ejection is slowed by an increased afterload in stenosis of the aortic valve, or when left ventricular contractility is substantially reduced as it is, for instance, following a myocardial infarction.
Third and Fourth Heart Sounds
The **third heart sound** (S3) is produced toward the end of the period of rapid ventricular filling (see Fig. 5-19). This sound is normal in young individuals or during exercise. But beyond age 40 a third heart sound is abnormal and is associated either with a high cardiac output state (e.g., anemia, thyrotoxicosis, or late pregnancy) or with a dilated ventricle (e.g., heart failure). The third heart sound in left ventricular failure is a low-pitched sound that is best heard with the bell of the stethoscope at the cardiac apex when the patient is in the left lateral position and has breathed out, bringing his heart closer to the chest wall.

A **fourth heart sound** (S4) is produced during atrial systole when blood is injected into a ventricle that has a low compliance. Thus, an abnormal fourth heart sound is often heard in patients with left ventricular hypertrophy or from a scarred and stiffened left ventricle following a myocardial infarction. Sometimes one can hear an abnormal fourth heart sound during an acute episode of angina pectoris. As mentioned earlier, the fourth heart sound - often present for years in patients with aortic stenosis and hypertrophy of the left ventricle - disappears when the patient develops atrial fibrillation. The fourth heart sound (like the third heart sound) is low-pitched and best heard with the bell of the stethoscope at the cardiac apex and the patient in the left lateral position.

The extra third and fourth heart sounds produce the cadence of a galloping horse called a gallop rhythm. The word Tennessee captures the rhythm produced by a fourth heart sound; whereas, Kentucky is a useful mnemonic for the gallop rhythm produced by a third heart sound. At rapid heart rates third and fourth heart sounds may fuse to produce a **summation gallop**.
Heart Murmurs
Characterization of Murmurs
Heart murmurs arise when blood flow across valves becomes turbulent. This occurs most often when a valve has been damaged so that it is unable to open wide (stenosis) or to close completely (insufficiency or incompetence). The resulting vibrations produce sounds that last longer than a third or a fourth heart sound, for instance, but otherwise heart murmurs are indistinguishable from heart sounds.

The intensity of murmurs is graded on a scale of I to VI, where a grade I/VI murmur is barely audible and a grade VI/VI can be heard with the stethoscope just removed from the chest wall. Abnormal vibrations from murmurs can sometimes be felt over the heart as a thrill, a sensation similar to touching a purring cat.

The location where a murmur is best heard is important to note. Thus, the murmur of aortic stenosis, for instance, is best heard in the second intercostal space just to the right of the sternum, and the sound is projected along the carotids into the neck. The murmur of mitral insufficiency is not heard very well at the base of the heart, but is loudest near the apex of the heart in the fifth intercostal space at about the mid-clavicular line.

The pitch of the sound is another characteristic of a murmur. The high-pitched murmur of aortic stenosis, for example, is best heard with the diaphragm of the stethoscope; whereas, the low-pitched, rumbling sound of mitral stenosis is more readily detected with the bell of a stethoscope. The high-pitched Still's murmur has a musical quality; it is a harmless murmur. Musical terminology is used to describe murmurs of increasing (crescendo) or decreasing (decrescendo) intensities. Thus, the murmur of aortic stenosis, for instance, is a crescendo-decrescendo murmur because its intensity first increases and then decreases.

The timing of the murmur is another important characteristic: Does the murmur occur during systole or diastole? Diastolic murmurs usually indicate heart disease; whereas, systolic murmurs - especially if they occur in early systole - are often functional (or innocent) flow murmurs associated with rapid ejection of blood across normal semilunar valves. The duration of murmurs may be long or short. For example, the murmur of mitral insufficiency starts with the first heart sound and ends with the second heart sound. It is, therefore, a pansystolic (or holosystolic) regurgitant type murmur. The murmur of aortic stenosis, on the other hand, starts shortly...
after the first heart sound and ends before the second heart sound. It is, therefore, a mid-systolic ejection murmur.

Murmurs are often difficult to hear, so special maneuvers are often used to intensify the murmur, and to distinguish between similar sounding murmurs of different origins. Such maneuvers are aimed at increasing the preload or afterload on the right or left ventricles and include positional changes (such as sudden standing or squatting), isometric hand-grip exercises, the Valsalva maneuver, and leg raising. These maneuvers are used to distinguish the systolic murmur of hypertrophic obstructive cardiomyopathy from innocent flow murmurs which are frequently heard in athletes with perfectly normal hearts.
Mitral Stenosis
In mitral stenosis the mitral valve leaflets are thick and stiff from fibrous tissue and calcium deposits and often fused with one another leaving a smaller than normal opening through which blood can pass. As a result of this increased resistance a large pressure gradient develops across the mitral valve during diastole (Fig. 5-24). The left atrial pressure tracing shows a prominent a-wave as the left atrium contracts against a stenosed mitral valve. As the mitral valve opens at the beginning of diastole, blood flows slowly into the ventricle with a shallow y-descent in the left atrial pressure tracing. In the normal heart this is the period of rapid ventricular filling. The left ventricular pressure tracing is perfectly normal in mitral stenosis because the work load of the left ventricle is not affected.

Mitral stenosis is more common in women and is usually a late consequence of rheumatic fever in childhood. The disease progresses slowly and may go unnoticed until the need for an increase in cardiac output arises as, for example, in the third trimester of pregnancy. In late pregnancy, large amounts of blood flow through low resistance vessels in the placenta increasing venous return to the right ventricle. The increase in preload, in turn, increases the right ventricular stroke volume and cardiac output. Keeping pulmonary capillary pressure from rising (and the lungs free of fluid) requires rapid filling of the left ventricle during diastole which is not possible when the mitral valve is stenosed. The resulting pulmonary edema in mitral stenosis interferes with oxygen transport and makes breathing difficult. Moreover, the high pressure in the pulmonary circulation ruptures blood vessels causing hemoptysis, which is the frightening experience of coughing up blood. With the decrease in preload of the left ventricle, cardiac output declines causing fatigue and dizzy spells.

On physical examination the patient with mitral stenosis may appear cyanotic from diminished oxygen transfer because of pulmonary edema, and crackles (rales) may be heard on auscultation of the lungs. The external jugular veins may be distended and peripheral edema may be present as the right ventricle fails because of its increased afterload, i.e., pulmonary hypertension.

On listening to the heart - with the bell of the stethoscope in the fifth intercostals space, mid-clavicular line and with the patient lying partly on the left side (i.e., in the left lateral decubitus position) – one hears two murmurs, both in diastole. The first murmur occurs in early diastole, during the period of “rapid” filling. It is a low pitched,
rumbling murmur, preceded by an **opening snap** as the stiff leaflets of the mitral valve suddenly open (Fig. 5-24). The second murmur is at the end of diastole when the left atrium contracts forcing blood across the stenotic mitral valve. This second murmur ends suddenly when the mitral valve shuts with a loud first heart sound at the beginning of systole. This pre-systolic murmur, which depends upon atrial contraction, disappears when the patient develops atrial fibrillation, as is often the case in the late stages of mitral stenosis.

The ECG in mitral stenosis shows signs of left atrial hypertrophy, i.e., a biphasic P-wave in lead V1 with an accentuated second (downward) component (Figs. 5-24 and 4-18). The increased afterload on the right ventricle causes it to hypertrophy with tall R-waves appearing in lead V1 (Figs. 5-24 and 4-19). Right ventricular hypertrophy eventually causes right atrial hypertrophy with tall (upright) P-waves in leads V1 and II (Figs. 5-24 and 4-18).

Once the diagnosis of mitral stenosis is established, patients are usually given a daily dose of penicillin as prophylaxis for β-hemolytic streptococcal infections which cause rheumatic fever and endocarditis and further damage the mitral valve. How-

Fig. 5-24. Mitral stenosis. The time course of left ventricular, left atrial, and aortic pressure changes during the cardiac cycle are illustrated and compared with heart sounds and murmurs heard on auscultation. Typical features include: a high pressure gradient across the mitral valve during diastole, a gradual y-descent in the atrial pressure curve (due to slow ventricular filling), an opening snap of the mitral valve followed by early and late diastolic murmurs. ECG shows a biphasic P wave in lead V1 with early signs of left atrial hypertrophy (P-mitrale) and later signs of right atrial hypertrophy (P-pulmonale) as pulmonary hypertension develops. As the right ventricle hypertrophies, the height of the R wave in V1 exceeds the depth of the S wave.
ever, once the orifice of the mitral valve has decreased from its normal area of about 5 cm$^2$ to about 1 cm$^2$, the valve leaflets must be forced apart with a balloon catheter (valvuloplasty), or the valve must be replaced (valvotomy).
Mitral Insufficiency
In mitral insufficiency the mitral valve leaflets and ring are hard and distorted and the chordae tendinae are shortened so that the valve does not close properly allowing blood to leak from the left ventricle back into the left atrium during systole. This increases the end-diastolic volume and results in an unusually large v-wave in the left atrial pressure tracing (Fig. 5-25). The increased preload of the left ventricle increases the stroke volume, which often compensates for the back leak. However, when the back leak is substantial, cardiac output is diminished which gives rise to symptoms of fatigue and weakness. As the left ventricle hypertrophies and becomes less compliant, pulmonary capillary pressure increases, which causes pulmonary edema and dyspnea.

On physical examination a thrill may be felt at the cardiac apex if the turbulence from back flow of blood during systole is substantial. A thrill, if present, is associated with a loud holosystolic (or pansystolic) murmur that starts with the first heart sound and extends slightly beyond the second heart sound, i.e., during the period of isovolumic relaxation (Fig. 5-25). The large preload of the left ventricle may be associated with a third heart sound (S3), best heard along the left sternal boarder. Mitral insufficiency is usually a consequence of rheumatic fever in childhood and is treated with prophylactic antibiotics. With severe regurgitation the valve is replaced.

With the availability of penicillin for treating streptococcal infections, rheumatic fever and mitral insufficiency are no longer common problems. A much more common form of mitral insufficiency today is mitral valve prolapse, particularly in young women. In this condition the chordae tendinae are too long (rather than too short), which allows the mitral valve leaflets to prolapse into the left atrium during systole.
The resulting back leak of blood is usually insignificant. On auscultation a **systolic click** may be heard at the cardiac apex as the prolapsing leaflets are suddenly stopped by the elongated chordae tendinae. This click is followed by a **high-pitched murmur late in systole** as blood leaks backward though an incompletely closed valve. This murmur becomes louder with maneuvers that decrease ventricular volume such as sudden standing or during the Valsalva maneuver, and the murmur becomes less intense when ventricular volume is increased as in leg-raising. The regurgitation in mitral valve prolapse is usually insignificant and requires no treatment other than possibly antibiotics to prevent endocarditis.
Aortic Stenosis
In **aortic stenosis** the aortic valve cusps are distorted by calcification or rheumatic fever so that the valve cannot fully open during systole. This increases the pressure gradient across the aortic valve during systole (Fig.5-26). The intraventricular pressure may rise above 200 mmHg during systole, while the aortic (and brachial artery) pressure is usually less than normal. The increase in afterload causes left ventricular hypertrophy which increases contractility and relieves wall stress by distributing tension over a larger number of muscle fibers. The increased muscle mass requires more coronary blood flow which is, however, decreased for several reasons: (1) The pressure in the aorta at the entrance to the coronaries is diminished. (2) Abnormal currents in the vicinity of the coronary openings due to distorted valve cusps slow blood flow into the coronary arteries. (3) Coronary vessels in the subendocardium are compressed by the high intraventricular pressure during systole. As a consequence of the imbalance in oxygen supply and oxygen demand, myocardial ischemia and infarction are common complications in patients with aortic stenosis.

Common complaints are dyspnea, chest pain, and dizziness. Dyspnea is due to pulmonary edema which results from the high pulmonary capillary pressure required to move blood into the noncompliant, hypertrophied left ventricle. Chest pain is due to

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**Fig. 5-26.** Aortic stenosis. The time course of left ventricular, left atrial, and aortic pressure changes during the cardiac cycle are illustrated and compared with heart sounds and murmurs heard on auscultation. Typical features include: a high pressure gradient across the aortic valve during systole, slow aortic pressure rise, a mid-systolic ejection murmur, and a fourth heart sound. ECG shows signs of left atrial and left ventricular hypertrophy with left ventricular strain pattern.
myocardial ischemia. Dizziness is due to diminished cerebral perfusion.

On physical examination the blood pressure is low with a small pulse pressure and a weak pulse. On palpating the radial artery with three fingers one can feel the pulse wave moving slowly from one finger to the next, which is called **pulsus tardus**. This results from the prolonged systolic ejection time due to the stenotic aortic valve. Similarly, on palpation of the carotid artery the pulse wave can be felt to rise more slowly, which is called a **plateau** or **anacrotic pulse**.

On listening at the right second intercostal space with the patient sitting and leaning forward one hears a harsh **mid-systolic, crescendo-decrescendo (diamond-shaped) murmur** which often radiates up into the neck and down the left sternal border to the cardiac apex. A pre-systolic gallop (4th heart sound) is usually heard, which is consistent with a noncompliant left ventricle. The second heart sound is split on expiration (paradoxical splitting) because of the prolonged left ventricular ejection time (Fig.5-21).

Most patients (usually men) with symptomatic aortic stenosis require surgical valve replacement. In children with congenital aortic stenosis the narrow opening is sometimes expanded by balloon valvuloplasty.
Aortic Insufficiency
In **aortic insufficiency** (or **aortic regurgitation**) the aortic valve does not close properly at the end of systole so that a fraction of the stroke volume leaks back into the left ventricle during diastole. This raises the end-diastolic volume (i.e., the preload) which automatically increases the stroke volume via the Frank-Starling mechanism, so that cardiac output is maintained. The increased wall tension of the distended left ventricle (see the Laplace equation, Fig. 5-8) causes hypertrophy with more demand for oxygen and nutrients. Oxygen supply is, however, diminished due to the low driving pressure for coronary blood flow during diastole. As a consequence, the left ventricle becomes ischemic and stiff which results in a greater filling pressure in the pulmonary capillaries. This causes pulmonary edema with difficulty in breathing, especially upon exertion.

On physical examination one can feel a bounding pulse, a so-called **Corrigan** or **water hammer pulse**, which is due to the large pulse pressure (i.e., the great difference in systolic and diastolic blood pressures). Another characteristic finding is a high-pitched **early diastolic decrescendo murmur** which starts with the second heart sound (Fig.5-27). This murmur is best heard in the second intercostal space just to the left of the sternum with the patient sitting up, leaning forward, and holding the
breath at the end of expiration. Sometimes a secondary (functional) murmur, the *Austin Flint murmur*, is heard in late diastole. This low-pitched pre-systolic murmur is similar to the murmur of mitral stenosis but, in this case, the mitral valve is not damaged. When the aortic regurgitation is substantial, the anterior leaflet of the mitral valve is closed by a jet of blood from the leaky aortic valve which impedes ventricular filling and creates turbulence when the left atrium contracts at the end of diastole.

Aortic insufficiency is more common in men than in women. Tertiary syphilis and rheumatic fever were once common causes before penicillin therapy became available. Patients are given prophylactic antibiotics until they develop symptoms from congestive heart failure at which time the aortic valve is usually replaced.
In this 54 minute video-lecture Dr. Eggena discusses pressures and blood volumes in the circulation, laminar and turbulent blood flow, Poiseuille's equation, resistance in the circulation, and measurement and determinants of blood and pulse pressures.
Anatomic Considerations
The muscle mass of the two ventricles differs considerably. The right ventricle pumps blood through the lungs where resistance to blood flow is low, so that the right ventricular wall requires relatively little muscle. In contrast, the left ventricle has a much greater muscle mass because it must force blood against the much higher resistance of the peripheral circulation. The aorta must withstand the high blood pressures generated by the left ventricle; its walls are reinforced by strands of elastic fibers and bands of smooth muscle. As the aorta gives rise to its major arteries and these, in turn, divide and subdivide to form arterioles, elastic tissue decreases progressively, and more smooth muscle now takes its place in the vessel wall. Thus, the walls of arterioles are almost entirely smooth muscle. Because this muscle contracts or relaxes in response to an increase or decrease in sympathetic stimulation which alters resistance to blood flow, the arterioles are sometimes referred to as resistance vessels. It is here that the total peripheral resistance, which we will discuss a little later, is primarily regulated.

Each arteriole gives rise to many capillaries. Blood flow into the capillaries is controlled by smooth muscle in the walls of terminal arterioles. In some tissues (i.e., the mesenteries), a cuff of smooth muscle on terminal arterioles forms a sphincter (a precapillary sphincter) that constricts or relaxes depending upon the metabolic needs of the tissue. When one looks at a capillary bed (in live tissue) under a microscope, one notices red blood cells lined up in columns which are either stagnant or moving rapidly through capillaries across the visual field. It appears that constriction of the precapillary vessels does not just slow movement, but brings all movement to a complete halt. Then, just as suddenly as the movement had stopped, it starts up again as precapillary vessels relax. This constriction and relaxation of precapillary vessels, which had caused sudden movements of red blood cells, are referred to as vasomotion. In the resting state only a fraction of all capillaries are open. This is especially true for skeletal muscle. The capillary walls have neither elastic tissue nor muscle - just a single layer of endothelial cells. This permits rapid transfer of gases, fluids, and nutrients between blood and interstitial fluid; for this reason capillaries are called exchange vessels.

Blood leaving capillaries enters venules, the larger veins, the vena cava and then flows into the right atrium. Valves in the larger veins create relatively short hydrostatic columns of blood and allow blood to
move in only one direction - toward the heart, instead of flowing backward with the pull of gravity. Veins are much less muscular than are arteries, and their walls also have less elastic tissue. Veins are, therefore, more compliant than arteries, which gives veins a greater capacity for storing blood at lower pressures. The larger veins are, therefore, sometimes referred to as capacitance vessels. The smooth muscle in the walls of these capacitance vessels is innervated by sympathetic nerves. When these nerves are stimulated, as they are, for example, in exercise or hemorrhage, the veins become less compliant and cannot hold the usual amount of blood. This, in turn, shifts blood from these venous reservoirs toward the heart, from where it is pumped into the large arteries to sustain blood pressure.
Distribution of Blood and Cardiac Output
An average person weighing 75 kg has a **plasma volume** of about 3 liters and a **blood volume** of about 5 liters, considering that **whole blood** is about 60% plasma and 40% red blood cells. Most of this blood (about 65%) is on the venous side of the circulation in the peripheral veins and the venous reservoirs in the spleen and liver. About 15% is in arteries and arterioles, and another 15% is in the heart and pulmonary vessels (see Fig.6-2). Only 5% of the blood volume is in capillaries because they are very short (only a few millimeters) and, therefore, hold relatively little blood despite their large numbers.

A normal **cardiac output** at rest is about 5 liters/minute, so that the entire blood volume of 5 liters is moved through the circulation once every minute. About 15% of the cardiac output perfuses the brain, 25% the gastrointestinal system (including spleen and liver), 20% the kidneys, 4% the coronaries, and the rest goes to the musculoskeletal system and skin (see Fig.6-2). During exercise cardiac output increases to 15 liters/minute or more, and a much greater fraction of the cardiac output now goes to skeletal muscle and a significantly lesser fraction to the kidneys and gastrointestinal tract.
Velocity of Blood Flow
It is important to keep in mind that the heart can only pump the amount of blood that is returned to it from the various organs and tissues. In other words, venous return must equal cardiac output. Therefore, when the cardiac output is 5 liters/min, 5 liters of blood will pass through the aorta, the arterioles, the capillaries, the veins, and enter the right atrium within the span of one minute. Although the same volume of blood flows each minute through the various sections of the circuit (measured in liters/min), blood will flow at different linear velocities in each section (measured in meters/second).

The **linear velocity of blood flow** is inversely related to the mean cross-sectional area of the vessels through which blood is moving (see Fig.6-3, A and B). The cross-sectional area of the vascular system increases from the aorta to the capillary bed because as arteries and arterioles branch they give rise to a greater number of smaller blood vessels. Let us pretend that we could focus on a single red blood cell (RBC) as it moves through the circulation. When the RBC is first ejected by the left ventricle into the aorta, its linear velocity will be maximal because the aorta has the smallest total cross-sectional area (about 3 cm²). As the RBC leaves the aorta and moves through the arteries and arterioles to enter the capillaries, its velocity decreases progressively and reaches minimum speed in the capillaries where the mean cross-sectional area is greatest (about 3,000 cm²). Slow flow of blood through the capillaries is essential to allow enough time for gases and nutrients to diffuse across the capillary wall. As the RBC leaves the capillaries, its velocity increases.
again in the venules and veins as the cross-sectional area progressively decreases to about 9 cm² in the vena cava.
Pressures in the Circulation
Let us next take a look at pressures in different parts of the circulation (see Fig.6-3,C). Left ventricular pressure rises to about 120 mmHg during systole and falls to between 5 and 10 mmHg during diastole. As intraventricular pressure rises during systole and exceeds aortic pressure, the aortic valve opens and blood is ejected into the aorta. Because the aortic valve normally offers little resistance to blood flow, the pressure in the aorta is only slightly lower than it is in the left ventricle in early systole. In late systole pressure in the aorta is slightly higher than in the left ventricle as a result of kinetic energy imparted to the blood during rapid ejection. During diastole, however, aortic pressure is substantially higher than intraventricular pressure.

During systole the left ventricle forces its stroke volume of roughly 80 ml (at rest) into the aorta. Because of the viscosity of blood and the resistance to flow in the periphery, the stroke volume is not instantaneously forced through the circuit. Only part of the stroke volume moves out of the aorta and the major arteries to the muscles and various organs during systole - perhaps one-third. The remainder is stored in the aorta and large arteries, and these structures, of course, expand to accommodate the increased volume. During diastole the elastic fibers, which have been stretched in systole, recoil and gradually push the rest of the stroke volume through the circuit. As blood runs off into capillaries during diastole, pressure in the large arteries declines toward zero mmHg. However, long before this level is reached, the left ventricle contracts again and forces a new stroke volume into the arteries. The lowest pressure that is reached before the next ventricular contraction occurs is, of course, the diastolic blood pressure.

The difference between the peak (or systolic) blood pressure and the diastolic blood pressure is called the pulse pressure. This pulse pressure increases slightly as one proceeds from aorta to the large muscular arteries, but then declines to a very low value in the capillaries (see Fig.6-3,C). The reason for the slight increase in pulse (and systolic) pressure in the large arteries is that the pressure wave is reflected in the periphery and combines with waves spreading toward the periphery. This summation is thought to be similar to the formation of larger waves observed when waves reflected from a pond's edge meet those spreading toward it.

A steady, nonpulsatile flow is seen in capillaries when pressures have been damp-
ened by arteriolar constriction. When arteri-oles are dilated, however, or when the pulse pressure in the aorta is abnormally high - as it is, for instance, in aortic insuffi-ciency or in severe anemia (case 6), the pulse wave will be transmitted all the way to the capillary bed, which can be seen on physical examination. If you apply pres-sure on the end of a fingernail, you will see that the outer part of the nail bed blanches while the inner part remains red. Now look at the borderline between white and red and you can see that the borderline moves with each heart beat, illustrating pulsatile flow in these capillaries.

Despite differences in pulse (and systolic) pressure, the mean blood pressure in the aorta is very similar to what it is in the brachial artery, where blood pressure is usu-ally measured (see Fig.6-3,C). The mean arterial pressure is not the average pres-sure between the systolic and diastolic pressure, but rather an average value under the pressure curve throughout systole and diastole. This mean pressure value can be approximated by adding one-third of the pulse pressure to the diastolic pres-sure (note that the pressure during diastole is weighted more heavily because diastole is usually much longer than systole). Thus, for a person with a systolic pressure of 120 mmHg and a diastolic pressure of 80 mmHg, the pulse pressure is 40 mmHg, and the mean arterial pressure is 93 mmHg.

The mean pressure in arterioles is between 40 and 60 mmHg and declines in capillar-ies to between 20 and 40 mmHg. Capillary pressures will depend on the pressure transmitted through arterioles, on whether the precapillary vessels are constricted or relaxed, and on pressures in the postcapil-lary venules. An increase in venous pres-sure is readily transmitted backward to the capillaries because postcapillary venules do not constrict.

The pressure in the peripheral veins is about 10 mmHg and decreases to about 5 mmHg in the vena cava and the right atrium. The central venous pressure (CVP) can be estimated on physical exami-nation in the following manner: With the pa-tient in a semi-recumbent position look for a distended external jugular vein. Adjust the patient’s position so that the meniscus of the blood column falls between the clavi-cle and angle of the jaw. Measure the verti-cal distance between the meniscus and the tricuspid valve, which serves as a zero reference point and is located at the fourth intercostal space in the midaxillary line. The CVP, measured in cm H₂O, can be con-
verted to mmHg by dividing by the specific gravity for mercury, which is 13.5 g/ml.
Types of Blood Flow
The movement of blood through the circulatory system is essentially of two types: (1) laminar flow or (2) turbulent flow (Fig.6-4). In **laminar flow**, the thin layer (or lamina) of water molecules in direct contact with the vessel wall is stationary. But as second, third, and fourth, etc. concentric layers of water slide over each other (by breaking hydrogen bonds between water molecules), movement increases progressively toward the center of the blood vessel so that water moves as a spike through a tube. In **turbulent flow**, on the other hand, the lamina fall apart and small aberrant currents form as the fluid travels as a front, rather than a spike, through the vessel.

Laminar flow is the most efficient type of flow in the sense that the least amount of driving pressure yields the most volume flux. Laminar flow is also referred to as **Newtonian flow** and is characterized by **Poiseuille's equation**,

\[ Q = \frac{(\Delta P \times \pi r^4)}{(8 \times l \times \eta)} \]

where \( Q \) is the amount of fluid flowing through a tube in liters/min, \( \Delta P \) is the driving pressure across the tube, \( r \) is the radius of the tube, \( l \) is the length of the tube, and \( \eta \) is the viscosity. This equation predicts, for instance, that doubling the tube length will decrease flow by one-half, but that halving the radius of the tube will decrease flow by a factor of 16! Thus, relatively minor changes in the diameter of vessels (e.g., constriction or relaxation of arterioles) can lead to profound changes in blood flow. In case 6 in response to anemia, autoregulation dilated resistance vessels, increasing blood flow by the fourth power of the radius. The decrease in hematocrit from 45% to 20% reduced viscosity
by almost one-half, which should have increased flow almost twofold, according to the Poiseuille equation.

The circulatory system, however, does not behave exactly as water flowing through the straight glass tubes on which Poiseuille based his conclusions about laminar flow. Laminar flow is seen only in small, straight tubes where flow is slow, as in the arterioles and capillaries. In these vessels we would expect to see a fall in resistance and enhanced flow in the man in case 6. Where velocity is high, where tubes are large, or where there are irregularities in the tube, blood flow is turbulent (see Fig. 6-4).

In the larger vessels, and particularly in the chambers of the heart, a decrease in blood viscosity actually increases resistance and tends to slow blood flow. When flow occurs at a high velocity (as it does in the heart and large vessels) a decrease in viscosity changes blood flow from laminar to turbulent flow, which is much less efficient and no longer obeys the Poiseuille equation. Therefore, we cannot predict changes in total peripheral resistance from viscosity measurements of blood alone.

In turbulent flow energy is wasted in the form of heat and sound. The sound waves generated by turbulent flow around a plaque or constricted artery are called bruits. Heart murmurs are caused by turbulent blood flow through stenotic or incompetent valves. A functional or hemic murmur is caused by a decrease in viscosity and/or an increase in velocity of blood flow in an otherwise normal heart. Functional murmurs are loudest during the early part of systole when ejection of blood is rapid. They are never heard in diastole when blood flow is slow. The functional murmur of anemia disappears following a blood transfusion.

The tendency for flow to become turbulent is given by Reynolds's number ($R_e$). This is a dimensionless number that takes into account all the factors that contribute to turbulent flow:

$$R_e = \frac{\text{velocity} \times \text{diameter} \times \text{density}}{\text{viscosity}}$$

When Reynolds's number exceeds a value of 2,000, laminar flow will deteriorate into turbulent flow even in a straight, smooth vessel. However, in the presence of irregularities in the vessel wall or at points where the vessel branches, turbulence will be seen at much lower values than 2,000. This equation predicts, for instance, that turbulent flow is more likely in the aorta,
where the velocity of blood flow is high and the vessel diameter is great, than in a capillary, where the velocity is low and the diameter small. Moreover, the equation helps explain why severe anemia often causes functional heart murmurs from reduced blood viscosity and increased velocity of flow from high output.
Blood Viscosity
Newton was first to measure viscosity of liquids. He studied the slippage of concentric layers of liquids as he stirred them in a drum with a central rotor. He observed that the layer closest to the rotor moved fastest with a progressive decline in circular motion as the wall of the drum was approached. We now know that this slippage between portions of water is due to rupture of hydrogen bonds and, in deed, the strength of the hydrogen bond has been estimated from measurements concerning temperature-dependent changes in water viscosity.

1. Effects of Hematocrit and Protein-Concentration on Blood Viscosity

The relationship between hematocrit (Hct) and blood viscosity is shown in Figure 6-5. Plasma is about twice as viscous as water, and whole blood, in turn, is about twice as viscous as plasma. The Hct in healthy men and women ranges between 40% and 50%, with women tending toward the lower end of the range. Viscosity rises sharply when the Hct rises above 50% and is about twice normal at an Hct between 60% and 70%.

Individuals with such abnormally high concentrations of red blood cells are said to have polycythemia. To keep the flow of blood constant with twice normal viscosity would require twice the normal driving pressure, according to Poiseuille's equation, if there were no compensatory change in the diameter of resistance vessels. Thus, one might expect patients with polycythemia to have systemic blood pressures in excess of 200 mmHg. However, on physical examination most patients with polycythemia are found to have only

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**Fig. 6-5.** Effects of hematocrit on blood viscosity. The hematocrit (percentage of red blood cells in whole blood) is plotted as a function of viscosity (relative to the viscosity of water, which is taken to equal 1). Normal hematocrit for females is 40-48% and for males 42-50%. Hematocrit values significantly above or below the normal range are termed polycythemia or anemia, respectively. (Values for blood viscosity are from J.Physiol. (Lond.), 1933:78:338.)
slightly elevated blood pressure because arterioles compensate for the increased blood viscosity by dilating and, moreover, blood flow to tissues is reduced.

Polycythemia may be caused by a primary abnormality in red cell proliferation (e.g., polycythemia vera or excessive erythropoietin production by a renal tumor) or it may be caused by a secondary (adaptive) response to hypoxemia that is seen in people who live at high altitudes (e.g., in the mountains of Peru or Nepal) or in patients with chronic heart or lung conditions. In individuals with secondary polycythemia, the increase in oxygen carrying capacity is a useful compensatory response to diminished oxygen loading of blood in the lungs - but only up to an Hct value of about 60%. Above this value, blood simply becomes too viscous (tending to clump and form rouleaux (stacks of donut-shaped red blood cells, see Fig. 6-6). However, changes in protein concentration are much less important than changes in Hct in altering blood viscosity.

2. Flow Dependent Changes in Blood Viscosity

The viscosity of blood changes not only with the hematocrit and protein concentration, but also as a function of the velocity of blood flow and the geometry of the vessels through which blood is flowing. These flow-dependent changes are not real changes in blood viscosity - they cannot be measured with a viscosity meter in a test tube - so they are categorized as apparent changes in viscosity. These apparent changes in viscosity are primarily due to the fact that blood does not behave as a Newtonian fluid, such as water, because of suspended particles and their changing distribution during flow.

As blood flows at high velocity, red cells take on streamlined, bullet-like, shapes and accumulate in the center of the stream.
to form an **axial core**. This greatly diminishes frictional resistance between blood and the vessel wall which now interacts essentially with the plasma portion of blood. When flow is sluggish, as it is in the postcapillary venules, red blood cells leave the axial core, form **rouleaux**, and increase viscosity (Fig. 6-6). This increase in blood viscosity due to **sludging** of red blood cells is a major determinant of resistance and rate of blood flow in the immediate postcapillary region of the circulation.

The increase in the apparent viscosity of blood in the postcapillary region is offset by a decrease in the apparent viscosity of blood in the precapillary region. When blood flows through arterioles with diameters less than 0.5 mm (but greater than the diameter of a red blood cell), blood behaves as if it were thinner, i.e., flow is greater than expected for a given driving pressure. This phenomenon, the **Fahraeus-Lindqvist effect**, is thought to result from a flow-dependent decrease in the Hct in microvessels (Fig. 6-6). What apparently happens is this: The red blood cells line up in the axial core of the stream and, therefore, move more rapidly than the plasma in the outer lamina close to the vessel wall. Thus, blood leaving the capillaries would have a higher Hct, were it not for the fact that the spacing between individual red blood cells increases as blood flows through small arterioles and capillaries. This preserves the normal ratio of blood cells to plasma as blood leaves the microcirculation; yet, at any one point in a small vessel, the Hct is lower than normal (e.g., one-half normal in Fig. 6-6) and viscosity is accordingly reduced.

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**Fig. 6-6.** Flow-dependent changes in blood viscosity. The flow of blood from arterioles via the capillaries into venules is shown. The apparent viscosity of blood in small (less than 0.5 mm diameter) arterioles and capillaries is decreased (Fahraeus-Lindqvist Effect) due to increased spacing between red blood cells as they move at higher velocity in the axial core. Note that red blood cells also become more bullet-shaped in small vessels. In the postcapillary venules the apparent viscosity of blood increases due to sludging and formation of rouleaux.
Radius of Vessels
1. Driving and Distending Pressures in Vessels

According to Poiseuille’s equation resistance to blood flow changes with the fourth power of the radius, so that increasing or decreasing the radius of an arteriole by altering sympathetic tone to vascular smooth muscle will have marked effects on blood flow through the arteriole (Fig. 6-7,A). For example, if the radius is reduced by a factor of 2, flow will diminish by a factor of 16. Moreover, for any given radius, flow increases in direct proportion to the increase in driving pressure. This is illustrated in Figure 6-7,B for a lead pipe. However, arterioles are different from rigid lead pipes or glass tubes in that changes in the driving pressure are associated with changes in the radius.

We have a tendency to think of blood pressure as providing a driving force that is applied only to moving blood through the circulation and forget that this same pressure also pushes the vessel wall out and keeps the vessel distended (as described by the Laplace equation, Fig. 6-7,A). Flow and driving pressure in arterioles are, therefore, not related linearly (see Fig.6-7,B).

2. Aneurysms

The relationship between vessel radius, the distending pressure, and the wall ten-
Tension is given by the **Laplace equation**, which (for a cylinder) states that wall tension (T) equals pressure (P) times radius (r):

\[ T = P \times r \]

One can predict from this relationship that wall tension (measured in dynes/cm) is much greater in a large vessel, such as the aorta, than in a small vessel, such as a capillary - not only because of the higher pressure (measured in dynes/cm\(^2\)) in the aorta, but primarily because of its much larger radius (measured in cm). Indeed, the wall tension in the aorta is about a ten thousand-fold greater than in a capillary. To prevent this increase in tension (the linear force exerted on muscle strands and elastic fibers) from rupturing the vessel wall, the aorta needs considerable elastic and muscle fiber support. In contrast, the capillary wall can withstand the considerably lower tension without any extra collagen fibers or muscle, so its wall consists of only a single layer of endothelial cells.

Let us briefly consider the series of events that take place in the aorta when the wall cannot withstand the arterial pressure generated by the left ventricle. When the wall of the aorta has been weakened - perhaps by calcific plaques in atherosclerosis or by clogging the vasa recta by chronic inflammation in tertiary syphilis - the wall bulges outward in the area of damage (see Fig.6-8). This, in turn, increases the radius of the vessel at that point. Assuming that blood pressure remains constant, this increase in radius leads to an increase in wall tension which, in turn, leads to further

**Fig. 6-8.** Aortic aneurysm. An aneurysm of the abdominal aorta is shown in an early and late stage of expansion. With the maximum pressure in the left ventricle and aorta at a constant value (P), an increase in the radius of the aortic lumen (r1 to r2) leads to an increase in wall tension (T), according to Laplace’s equation. The increased wall stress may, in turn, rupture more elastic support fibers in the wall of the aorta and lead to still further expansion of the aneurysm by a positive feedback mechanism, eventually resulting in a blow out.
bulging of the wall at that point with a further increase in the radius, etc. This positive feedback loop rapidly terminates in a blow-out, just as a tire first bulges and then ruptures at a point where the rubber has worn thin. Such abnormal dilations in vessels are called aneurysms.

Aortic aneurysms are usually due to atherosclerosis and are most common in the lower aorta below the origins of the renal arteries. Such aneurysms are seldom painful although they may produce a pounding sensation in the abdomen. On physical examination a pulsatile mass is palpated and its size is measured by ultrasound or x-ray techniques. The risk of rupture and sudden death from an abdominal aneurysm of the aorta is considerable when its diameter exceeds 6 cm or when it is found to be expanding on serial examinations, in which case surgical excision with graft replacement is usually recommended.
Resistance to Blood Flow
1. Total Peripheral Resistance

The overall resistance of blood as it flows from the left ventricle through the peripheral organs and tissues and returns again to the right ventricle is called the **total peripheral resistance**. The total peripheral resistance is equal to the pressure gradient between the aorta and the vena cava, divided by the amount of blood that flows in response to that gradient, which is the cardiac output:

\[ \text{TPR} = \frac{\text{MSAP} - \text{CVP}}{\text{CO}} \]

For example, if the mean systemic arterial pressure (MSAP) is 93 mmHg, the central venous pressure (CVP) is 3 mmHg, and the cardiac output (CO) is 5 liters/min, the total peripheral resistance (TPR) will equal 18 mmHg/L/min. The units for TPR are often converted from mmHg/L/min to dynes x sec x cm\(^{-5}\) by multiplying by 80, i.e., 18 mmHg/L/min x 80 (dynes x sec x cm\(^{-5}\))/ (mmHg/L/min) = 1,440 dynes x sec x cm\(^{-5}\).

Because it is now possible to measure all of the above variables simultaneously on patients in intensive care units, this information is important for making decisions on the use of agents that increase CO or reduce TPR. For clinical purposes, TPR is a good estimate of the afterload of the left ventricle. For example, patients with congestive heart failure and markedly elevated values for TPR often respond to vasodilator treatment with an increase in cardiac output and increased tissue perfusion.

2. Parallel and Series Resistances

The total peripheral resistance is the sum of all the individual resistances in different parts of the circulation. These resistances are arranged either in series (for example, the resistances of arteries, arterioles, capillaries, venules, veins) or in parallel circuits (for example, the resistances of the kidneys, the gastrointestinal tract, muscles, skin, brain, etc.). The **total resistance** (R\(_{\text{total}}\)) of three individual resistances (R\(_1\), R\(_2\), and R\(_3\)) arranged in series is simply the sum of the individual resistances, i.e., R\(_{\text{total}}\) = R\(_1\) + R\(_2\) + R\(_3\) (Fig. 6-9,A). The total resistance of individual resistances arranged in parallel circuits is obtained by adding conductances, where the **conductance** equals 1/resistance. Thus, the total conductance or 1/R\(_{\text{total}}\) equals 1/R\(_1\)+1/R\(_2\)+1/R\(_3\) (Fig. 6-9,B).

When circuits are arranged in series, the individual resistances are always less than the total resistance. However, when circuits are arranged in parallel, the individual
resistances are always greater than the total resistance. Consider, for example, the resistance to the kidneys. The pressure gradient across the kidneys (between renal artery and renal vein) is about 90 mmHg, and about 1 L/min of blood flows through the kidneys (20% of cardiac output), so that the renal resistance is 90 mmHg/L/min, which is five times greater than the total peripheral resistance. The obvious advantage of this arrangement is that the resistance to any one organ can be increased by selective arteriolar constriction without increasing the TPR and, thereby, the work load of the left ventricle.

Not all organs are arranged in parallel circuits. The pulmonary circulation is arranged in series with the peripheral circulation. Were it not for the right ventricle that pumps blood only through the lungs, the pulmonary circulation would place an inordinate strain on the left ventricle. Consider for a moment what would happen if the booster function of the right ventricle were lost: the pressure in the central veins would now have to be high enough to force blood through the pulmonary vasculature. In other words, central venous pressure (CVP) would have to rise to the level of the pulmonary artery pressure (about 20 mmHg), and the capillary pressure in the peripheral tissues would have to be even higher for blood to flow towards the heart. This high capillary pressure would, in turn, cause peripheral edema. We normally do not have these high venous pressures and peripheral edema because the right ventricle keeps the CVP much lower than the
pulmonary artery pressure. But when the right ventricle fails to pump normally, we do observe an increase in CVP and the characteristic symptoms of peripheral edema.
Measurement of Blood Pressure
Everyone has had their blood pressure taken at one time or another. A cuff is placed around the upper arm and inflated to a pressure well beyond the systolic pressure, i.e., 30-40 mmHg above the expected systolic pressure (Fig. 6-10). You then listen over the brachial artery with a stethoscope for Korotkoff’s sounds, which are heard when the brachial artery under the cuff is partially obstructed so that blood flow becomes turbulent distal to the cuff. When the cuff pressure is above the systolic pressure in the brachial artery, the artery is completely occluded, no blood flows distally in the artery and, therefore, no sounds are heard on auscultation. As the cuff is now gradually deflated, a pressure is reached where some blood rushes through the brachial artery during the peak of systole and hits the column of stagnant blood distal to the cuff and produces a sound. The pressure reading when the sound is first heard is the systolic blood pressure. As the cuff pressure is gradually lowered further the intensity and duration of the sound increases and then becomes muffled and fades away when a pressure is reached at which the brachial artery under the cuff is always open, during systole as well as during diastole. The pressure at which the sound first becomes muffled is usually taken as measurement of the diastolic blood pressure (see Fig. 6-10). Measuring blood pressure with the sphygmomanometer by auscultation and palpation. A cuff is placed around the arm and pumped to a pressure of 160 mmHg, in this example. At this point the brachial artery under the cuff is completely occluded, no blood flows distally, and no sounds are heard. As the cuff pressure is gradually lowered (by opening the valve to the cuff), a pressure is reached where a small jet of blood rushes under the cuff at the peak of systole and creates turbulence distal to the cuff where it can be heard by auscultation with a stethoscope (Korotkoff’s sounds) or palpated as a small pulse wave. This is the systolic pressure. Sounds are heard at increasing intensity as cuff pressure is lowered below systolic pressure. Sounds then become muffled and disappear when cuff pressure reaches diastolic blood pressure, at which time the brachial artery is no longer occluded and blood flow again becomes laminar.
When blood pressure is low - as it is, for instance, in patients in circulatory shock - turbulence is minimal and Korotkoff’s sounds may not be heard. In such situations, the systolic (but not the diastolic) blood pressure can usually be estimated by palpating the pulse in the brachial artery and then noting the pressure at which the pulse disappears when the cuff is gradually inflated.

Blood pressure can also be measured at the ankles. In the supine position, ankle and arm blood pressures are normally similar. A significant reduction in ankle blood pressure relative to pressure in the arms suggests obstruction of blood flow in the aorta, ileacs, and/or femoral arteries, most commonly due to the presence of atherosomatous plaques. Such patients are at increased risk for having a heart attack or a stroke, and are likely to benefit from preventive measures, e.g., aspirin, exercise, weight reduction, and lowering blood cholesterol with diet and drugs.

Automated blood pressure machines are now in common use, especially by patients with hypertension which allows them to monitor the response to (or need for) treatment by themselves at home.
Determinants of Blood Pressure
Blood pressure, in clinical usage, refers to pressure in the brachial artery. This pressure is similar in value to pressures in the other major arteries, including the aorta, assuming that all pressure readings are taken at the same level to avoid differences due to gravity. For instance, when a person is standing, blood pressure in the femoral artery will be greater than in the brachial artery. Blood pressure depends upon two variables: (1) the volume of blood in the large arteries and (2) the compliance of large arteries. Unfortunately, neither of these variables can be measured in life.

The volume of blood in the large arteries depends upon how much flows in and how much flows out. In other words, the volume and pressure \( P \) in the large arteries depend upon (1) the cardiac output \( CO \) and (2) the total peripheral resistance \( TPR \). \( P = TPR \times CO \), which is the same relationship discussed earlier for the measurement of total peripheral resistance. Accordingly, blood pressure will increase when the total peripheral resistance increases and/or when cardiac output increases. Although we can measure \( CO \), \( TPR \), and \( P \), we cannot measure the volume of blood in the large arteries nor the elastic properties of these vessels, which are responsible for the observed blood pressure.

The compliances of large arteries (such as the aorta) have been measured at autopsy by filling the vessels with various volumes of fluid and measuring the associated pressure changes (see Fig. 6-11). The slope of the volume-pressure curve \( \Delta V/\Delta P \) is the compliance. The compliance of large arteri-
ies decreases with advancing age and/or with atherosclerosis. This is sometimes referred to as hardening of the arteries. Because the arteries of older people are stiffer than normal, they can hold a normal volume of blood only at a higher than normal pressure and this accounts, in part, for the increased blood pressure so often seen with advancing age.

The compliance of large arteries is also slightly diminished by sympathetic constriction of vascular smooth muscle, which tends to raise blood pressure. Much more important is that sympathetic constriction increases peripheral resistance so that less blood flows out of the aorta and large arteries into arterioles and capillaries. This leaves a greater blood volume in the large arteries and increases blood pressure even without any change in large vessel compliance.

The compliance of large vessels in a given individual (young or old) is not a constant value, but decreases as pressure rises (see Fig. 6-11). This is presumably due to an elastic limit that is reached by fibers in the vessel wall as they uncoil and become excessively stretched. Therefore, a person with hypertension and a high diastolic blood pressure will experience a greater rise in blood pressure (i.e., a greater pulse pressure) than a person with a normal diastolic blood pressure for the same left ventricular stroke volume.
Pulse Pressure
The compliance of the aorta and large arteries and the volume of blood in these vessels cause the changes in blood pressure that are measured in the brachial artery. There are many volumes and many pressures during the cardiac cycle. The peak pressure, the systolic pressure, is seen only for the short moment when the large arteries reach a peak volume during the period of rapid ejection (see Fig. 6-12). As blood runs off through the arterioles and volume in the large arteries declines, pressure falls. The pressure associated with the smallest volume in the large arteries is the diastolic pressure. The difference between the systolic and diastolic pressures is the pulse pressure.

Although we can measure systolic and diastolic pressures, the blood volumes and vessel compliance responsible for these pressure changes cannot be measured. Nevertheless, there is some minimal (unmeasured) volume in the large arteries (Vd) when diastolic blood pressure (Pd) is measured (see Fig. 6-12). As the left ventricle ejects its stroke volume into the large arteries during systole, their volume increases to a maximum volume (Vs), which is associated with a maximum pressure (Ps). The pulse pressure, Ps - Pd, will therefore depend upon the compliance and the maximum volume changes in the large arteries.

Fig. 6-12. Relationship between pulse pressure and large artery compliance. The relative volume of blood contained within the aorta and large arteries of a normal subject (a) and a patient with atherosclerosis (b, low compliance) is plotted as a function of pressure within these vessels. The pressures associated with minimal volumes are the diastolic pressures (Pd), whereas the pressures associated with maximum volumes are the systolic pressures (Ps). The pulse pressure (PP) is the difference between systolic and diastolic pressures. In this graph, the assumption has been made that both subjects (a) and (b) have the same diastolic blood pressure of 75 mmHg and that the aorta and large arteries are filled with the same volume of blood during systole (i.e., approximately equal stroke volumes). The systolic blood pressure of (b) will rise to a much higher value (175 mmHg) than it will in (a) (125 mmHg), so that the pulse pressure (PP) in (b) is 50 mmHg higher than it is in (a). Accordingly, pulse pressure is proportional to stroke volume divided by aortic and large vessel compliance.
Vs-Vd. The difference between Vd and Vs depends on the stroke volume, the velocity of left ventricular ejection (\( \Delta P/\Delta t_{\text{max}} \)), and the total peripheral resistance. When the total peripheral resistance and velocity of ejection are constant, the pulse pressure (PP) is proportional to the stroke volume (SV) divided by large vessel compliance (C):

\[ \text{PP} \approx \frac{\text{SV}}{C} \]

Thus, the pulse pressure increases as arterial compliance decreases. This is seen with advancing age or in patients with atherosclerosis. As mentioned earlier, patients with hypertension also have high pulse pressures because compliance (even of normal arteries) is decreased in the high pressure ranges. The pulse pressure also increases with an increase in the stroke volume. One sees this frequently in individuals with bradycardia or in patients with aortic regurgitation, for example.

The pulse pressure is closely related to the pulse you feel at the patient's wrist on physical examination. You do not sense the actual flow of blood through the radial artery but rather a pulse wave that is initiated by radial stretch of the aorta during ejection of the stroke volume. This wave travels about 100 times faster along the arteries than blood actually flows. The velocity of the pulse wave is inversely related to the compliance of the arterial tree. Therefore, the pulse wave travels faster along noncompliant, atherosclerotic vessels than along normal, flexible arteries.

Taking a person's pulse is an important part of the physical examination. The radial pulse not only provides useful information about cardiac and circulatory function but also communicates your concern for the patient's well-being. Therefore, you must not rush when taking a pulse. Place the three middle fingers along the radial artery and sense the amplitude of the pulse wave, its force, its velocity, its rhythm and its rate, and note any changes during inspiration and expiration. A weak and thready pulse, which one may encounter in a patient who is in circulatory shock, is called pulsus parvus. A sluggish, biphasic pulse of low velocity, which one may encounter in left ventricular outflow obstruction, is called a **bifid pulse** or **pulsus tardus**. A bounding, strong pulse is seen with high pulse pressures in anemia or in aortic insufficiency and is called a **water hammer** or **Corrigan pulse**.

In a patient with cardiac tamponade the intensity of the pulse decreases substantially during inspiration (see Fig. 6-13). This is
called **pulsus paradoxus**. Pulsus paradoxus is said to exist when the systolic blood pressure falls by more than 10% on inspiration. The mechanism for pulsus paradoxus is as follows: During inspiration more blood is returned to the right ventricle. The right ventricle normally accommodates the increased volume by bulging outward into the pericardial space. However, when the pericardial space is filled with fluid (**cardiac tamponade**) the right ventricle cannot expand outward and, instead, bulges into the left ventricular chamber, diminishing left ventricular filling. The resulting decrease in left ventricular stroke volume, in turn, decreases systolic blood pressure, which can be palpated at the patient’s wrist when the decrease is excessive. Cardiac tamponade is a medical emergency requiring rapid removal of fluid from the pericardial space.

The intensity of the pulse may vary from one beat to the next (Fig. 6-14, A). This is called **pulsus alternans**. It is a sign that the left ventricle is unable to eject similar stroke volumes from one beat to the next and usually signifies severe left ventricular failure.

An irregular pulse may be due to an **ectopic beat** (e.g., a premature ventricular contraction [PVC]). This beat may occur prematurely at a time when the left ventricle has not had sufficient time to fill, so that the stroke volume may be insufficient.
to induce a pulse wave that can be felt at the wrist in the radial artery (Fig.6-14, B). However, the contraction of the ventricle and closing of heart valves will be heard with the stethoscope. The difference in beats/min heard at the heart and beats/min felt at the wrist is called the **pulse deficit**. It is a measure of the number of ectopic beats per minute. Such ectopic beats are quite common in young medical students and are no cause for alarm. They are often caused by a lack of sleep, smoking, drinking coffee, or anxiety before or after an examination. However, in a patient with a history of coronary artery disease, ectopic beats take on special significance.

**Fig. 6-14. Dropped beats and pulsus alternans.** A. In pulsus alternans a large pulse wave alternates with a small pulse wave. This phenomenon is characteristic of severe left ventricular failure. B. The ECG is compared with a tracing of arterial pressures in the brachial artery. An early premature ventricular contraction (PVC) causes only a small increase in brachial artery pressure which may not be palpated but is heard on auscultation, resulting in a dropped beat (or pulse deficit). The PVC is followed by a compensatory pause during which left ventricular filling is augmented, so that the next QRS complex triggers a larger than usual pulse wave (postectopic potentiation).
In this 52 minute video-lecture Dr. Eggena discusses the Starling-Landis principle, autoregulation of blood flow and Raynaud’s disease, neural regulation, the baroreceptor reflex, orthostatic hypotension, and the Cushing phenomenon.
Fluid Exchange across Capillaries
1. Filtration and Reabsorption of Fluids in Capillaries

The primary function of the circulation is to deliver oxygen and nutrients to cells and to remove carbon dioxide and metabolic waste products. This exchange of gases and solutes between cells and blood occurs in the capillaries. There is also a constant flow of water from the capillaries into the interstitium primarily on the arterial end, and back again into capillaries primarily on the venous end. The driving force for this filtration and reabsorption of water across the capillary endothelium is provided by the balance of hydrostatic and plasma oncotic pressures in the plasma and the interstitium. We have considered this phenomenon (i.e., the Starling-Landis principle) previously in the context of body fluid balance; we now return to this subject for a closer look at how transcapillary fluid movements are regulated.

The hydrostatic pressure in capillaries is regulated by the arterioles that supply the capillaries with blood. When the arterioles are dilated (e.g., decreased sympathetic nerve stimulation), hydrostatic capillary pressure declines and less fluid is filtered into the interstitium. The hydrostatic pressure is not a constant value throughout the length of a capillary (except for the glomerular capillary in the kidney). Pressure declines from the arterial to the venous end because of the frictional resistance encountered by blood as it flows through a channel that is about equal in diameter to a red blood cell. Therefore, in the capillary bed depicted in Figure 7-2, the hydrostatic pressure is shown to decline from 30 mmHg on the arterial end to 15 mmHg on the venous end. The **hydrostatic pressure** that tends to filter fluid out is offset by the **plasma oncotic pressure** that tends to draw fluid back into the capillary. The plasma oncotic pressure depends upon the concentration of plasma proteins. When plasma protein concentration is normal (about 1 mM), the plasma oncotic pressure equals 27 mmHg (see the Gibbs-Donnan equilibrium, Figure 3-5).

The exchange of fluids across the capillary wall depends not only on the hydrostatic and oncotic pressures in the capillary, but also upon similar (albeit much smaller) forces in the interstitial fluid compartment surrounding the capillaries. The oncotic pressure of interstitial fluid varies markedly in different organs, depending upon pro-
tein concentration. Although it is true that capillaries are much less permeable to proteins than to water and small salt molecules, protein molecules do slowly diffuse out of capillaries. Some capillaries, such as capillaries in the lungs or liver, are more permeable to proteins. Moreover, proteins diffuse more readily into the interstitium when the capillary endothelium has been damaged or made more permeable by the release of vasoactive compounds such as the prostaglandins, the kinins, and histamine. Many proteins serve important functions in the interstitium, as for example, the antibodies that fight viruses and prevent infection.

Proteins in interstitial fluid have no means of returning directly to blood by diffusion, because the concentration gradient favors diffusion in the opposite direction (i.e., out of capillaries). Therefore, once protein molecules have entered the interstitial space, the only way back into blood is via the lymphatic system. There is always some protein in interstitial fluids that tends to pull water from capillaries into the interstitial fluid compartment (e.g., an interstitial fluid oncotic pressure of 5 mmHg in Figure 7-2). The hydrostatic pressure within the interstitial fluid compartment is usually equal to 0 mmHg (i.e., equal to atmospheric pressure), except in the lung, where the hydrostatic pressure is usually -2 to -4 mmHg. (Another exception is edema, when the hydrostatic pressure of interstitial fluid becomes a positive value.)

Adding up the capillary and interstitial oncotic and hydrostatic pressures in Figure 7-2, there is a net force of 8 mmHg favor-
ing filtration on the arterial side of the capillary and a net force of 7 mmHg favoring re-absorption of fluid on the venous side. Therefore, fluids are primarily filtered from capillaries to interstitium on the arterial side and reabsorbed back into capillaries on the venous side, which is known as the Starling-Landis principle (see Fig.7-2).

What is not picked up by capillaries enters the lymphatics (along with proteins) and is transported via the thoracic duct back to the circulation. The view that a single capillary accomplishes both filtration and reabsorption is probably not always true. Some capillaries with dilated precapillary vessels and high hydrostatic pressures may filter fluids for their entire lengths, while others with constricted precapillary vessels and low hydrostatic pressures may only reabsorb fluids. Our concepts of fluid movement in the interstitial spaces around cells also need modification as more becomes known about extracellular matrixes. The interstitial space is apparently not filled with water, like a bag, but instead consists of a gel-like substance through which movements of water and solutes are more restricted than in free solution.

2. Edema

Edema develops when the delicate balance between filtration and absorption of fluids in the capillaries (and by lymphatics) has been upset, so that excessive fluid accumulates in the interstitium. Sudden weight gain as well as painless swelling
and pitting in the ankles (for an ambulatory patient) or in the presacral area (for a patient confined to bed) are signs of edema.

Edema may be caused by an increase in the hydrostatic pressure in capillaries, a decrease in the plasma oncotic pressure, blockage of lymphatics, or an increased permeability of capillaries to proteins (Fig. 7-3).

A. Increased Hydrostatic Pressure

An increase in hydrostatic pressure at the arterial end of capillaries occurs when arterioles supplying a given capillary bed relax. This often happens when a person eats salty food and then drinks water to quench his thirst. Because the kidneys are slow in excreting a salt water load into urine, this fluid (essentially 0.9% saline) is deposited in the blood vessels. The resulting increase in the circulating blood volume is sensed by low pressure baroreceptors in the subendocardium of the atria (and in large vessels in the lung), which relay this information to the medulla (via vagal afferents). The vasomotor center in the medulla responds by diminishing impulse traffic over sympathetic nerves to arterioles which, in turn, dilate. This allows more of the hydrostatic pressure head generated by the left ventricle to be transmitted to capillaries. The increased capillary hydrostatic pressure causes more fluid to be filtered into the interstitium. The extra fluid will not be enough to cause edema in a healthy person, but it will cause an increase in weight. However, in a person with poor kidney function, a persistent increase in salt intake will not only lead to weight gain, but the increased fluid in the interstitium will also be detected on physical examination as edema. Another common cause of edema is an increase in venous pressure. The hydrostatic pressure at the venous end of capillaries cannot be lowered - as it may on the arterial end by constriction of arteriolar smooth muscle. Thus, an increase in central venous pressure is transmitted back to capillaries, resulting in edema. Capillary pressure must rise whenever central venous pressure rises in order to keep blood flowing from tissues back to the heart. An increase in central venous pressure is seen with right ventricular heart failure. Such patients typically have swollen feet and complain of tenderness in the right upper quadrant of the abdomen from a congested liver. They may also feel nauseated and have difficulties with digestion because the tissues in the wall of their gastrointestinal tract are congested and swollen with excess interstitial fluid.
Because of gravity, venous pressure is higher in the feet than elsewhere in the body in the upright position; for this reason the presence of edema is first detected in the feet and ankles. Venous pressure is normally kept low in the feet by contraction of leg muscles when we walk, which squeezes the column of blood from one valve to the next in the direction of the heart. When a person stands perfectly still or when the venous valves are incompetent (as they are for instance in people with varicose veins), venous pressure will rise in the feet and legs and more fluid will be filtered into the interstitial compartment and, if excessive, may cause edema.

**B. Decreased Plasma Oncotic Pressure**

The plasma oncotic pressure normally draws fluid from the interstitium back into capillaries with a force of about 27 mmHg, depending on the concentration of proteins in the plasma. Therefore, edema may result from a decrease in the concentration of proteins in the plasma that is seen with diminished protein intake (protein malnutrition [Kwashiorkor]), with protein loss in urine (in the nephrotic syndrome) or in the gastrointestinal tract (protein-losing gastro-enteropathy), and with diminished protein synthesis (liver disease).

**C. Increased Capillary Permeability**

When the capillary membrane becomes more permeable to proteins (as may occur, for example, in tissues infected by bacteria, in response to toxins, following burn injuries, or during an allergic reaction), proteins are lost into the interstitial space. This diminishes the forces favoring reabsorption of fluids and causes edema. (Although capillary injury also increases water permeability, this is not the cause for the increased water movement, because water permeability is always very high, even in intact capillaries.) Edema in such instances is often localized, as in hives (urticaria), where an allergic reaction leads to histamine release from mast cells. Histamine not only increases capillary permeability to proteins (which decreases the net oncotic reabsorptive force), but also dilates arterioles (which increases the net hydrostatic filtration forces).

**D. Lymphatic Blockage**

Considerable edema may be seen when the lymphatic drainage is inadequate. This is seen, for example, in lymph node resection for breast cancer or following chronic inflammatory changes and blockage of lymphatic vessels by nematodes in filariasis, which may lead to massive swelling of a
leg, called **elephantiasis**. The lymphatic system is the only way by which proteins that have leaked from capillaries into the interstitium can be returned to blood. When lymph drainage is compromised or the system is overwhelmed by excessive filtration, protein concentration rises and the associated increase in oncotic pressure draws more fluid into the interstitial space.

**E. Limits of Edema**

Edema occurs only when the lymphatic system is overwhelmed. Then the only mechanism left to limit edema is the hydrostatic pressure in the interstitium. If the compartment in which fluid is accumulating and in which pressure is rising is surrounded by tissues that resist being stretched (e.g., the tendons in the wrist), swelling will be minimal. But, if the compartment is surrounded by loose tissues (e.g., around the eyes), edema fluid will keep accumulating and cause massive swelling until interstitial fluid pressure rises to a level that counters filtration of more fluids into the space. In burn injuries there is no skin to contain the fluid that leaks from damaged capillaries and there is no way to generate an effective interstitial fluid pressure that can limit further fluid loss. For this reason, burn injuries are commonly associated with plasma volume depletion, which may cause circulatory shock unless fluids that have been lost are replaced promptly.
Autoregulation
1. Short-term Regulation of Blood Flow

Let us consider how flow through capillaries is regulated by carrying out an experiment in which we cannulate the artery and vein of a muscle and then measure the volume of blood that flows from artery to vein through the capillaries each minute as we change the arterial pressure (Fig. 7-4). If we increased the perfusion pressure, blood flow would increase, but only for a short time. Very soon blood flow would return to its original level, despite the continued increase in perfusion pressure. If we now decreased the perfusion pressure below normal, flow would first diminish, but only for a short while. Then, very rapidly, flow would be reestablished to near normal levels.

Recall that flow ($Q$) equals pressure ($P$) divided by resistance ($R$), ($Q=\frac{P}{R}$). It follows that, to maintain a constant rate of blood flow at varying perfusion pressures, resistance must increase at high perfusion pressures and decrease at low perfusion pressures. These compensatory changes in vascular resistance are caused by dilation or constriction of precapillary vessels. Experiments that measure blood flow at different perfusion pressures have found similar results for most tissues. The process by which each tissue regulates (within limits) blood flow by changing its vascular resistance is called autoregulation.

Two major theories have been proposed to account for autoregulation: (A) the myogenic hypothesis and (B) the metabolic hypothesis.

(A) The myogenic hypothesis suggests that vascular smooth muscle contracts in response to sudden stretching. Thus, a sudden surge in blood pressure would automatically increase vascular resistance and adjust blood flow back to its normal level. This hypothesis is appealingly simple and supported by observations that smooth muscle does, indeed, contract when suddenly stretched. However, smooth muscle (for instance in the urinary bladder or in the uterus) will not contract when gradually stretched or when the increased pressure is sustained. Thus, the myogenic hypothesis is only feasible in situations where temporary fluctuations in blood pressure require rapid and transient adjustments in blood flow. The myogenic mechanism of autoregulation appears to be important in the kidneys. Not all of the two million nephrons in the kidneys are perfused with the same pressure head, so that glomerular capillaries of nephrons exposed to higher than average pressure
tend to filter more fluid (i.e., have higher single nephron glomerular filtration rates, \([\text{SNGFR}]\)) than nephrons exposed to lower pressures. Nephrons that are filtering too much fluid (which may ultimately be lost in urine) are adjusted by constriction of afferent arterioles. Thus, autoregulation of SNGFR by the myogenic hypothesis appears to be responsible for matching glomerular blood flow and SNGFR for the many nephrons in the kidney, despite differences in perfusion pressure.

B. The metabolic hypothesis of autoregulation suggests that blood flow to tissues is regulated by vasodilator substances that are released from cells and cause relaxation of vascular smooth muscle in precapillary sphincters, metarterioles, and arterioles (see Fig. 7-4). These vasodilator substances accumulate locally when blood flow is too slow to wash them away immediately. Such vasodilator substances include increased levels of carbon dioxide, lactic acid, extracellular potassium ions, adenosine, or increased fluid osmolarity. Such conditions prevail when tissues are hypoxic. In addition, a low oxygen tension may directly relax smooth muscle in precapillary vessels, because without oxygen there is no ATP in cells for a contractile response. While every organ has this inherent capacity to regulate its own blood flow according to its metabolic needs, not all vasodilators are of equal importance in different organs. In the brain, for example, carbon dioxide is a particularly powerful...
vasodilator and too little carbon dioxide causes brain vessels to narrow. Everyone has experienced the light-headedness that one feels on blowing up an air mattress or hyperventilating for some other reason. The decrease in arterial carbon dioxide tension (PaCO$_2$) of blood perfusing the brain constricts vessels and limits the amount of oxygen and glucose that can be supplied to brain cells, causing light-headedness. Although carbon dioxide may also play a role in autoregulation of blood flow to the heart, adenosine appears to be more important in dilating coronary vessels.

Autoregulation of blood flow is more closely linked to metabolism in some organs than in others. In the kidney, for example, blood flow is not regulated by the metabolic needs of kidney cells as much as it is by the overall requirement of the body to maintain a normal salt and water balance and to get rid of metabolic waste products generated by other organs. In a way, the kidney's physiologic function is not directly linked to its rate of metabolism and, indeed, blood flow to the kidney is far in excess of what is needed for kidney cells to carry out their transport functions. For this reason, the kidney regulates its blood flow by non-metabolic (i.e., myogenic) mechanisms.

In skeletal muscle, on the other hand, metabolic mechanisms for autoregulation of blood flow are very important. At rest, most muscle capillaries are closed and blood flows through low resistance thoroughfare pathways from arterioles to venules. During exercise, however, muscle cells produce more vasodilator substances that relax smooth muscle in precapillary vessels and markedly increase blood flow through capillaries. This increase in blood flow upon exercise is called active hyperemia. When blood flow to a muscle is temporarily interrupted by occluding a major artery, blood flow will be increased well beyond pre-obstruction levels upon removal of the obstruction. This physiological reaction to occlusion of an artery is known as reactive hyperemia. You can readily demonstrate this phenomenon on yourselves (see Fig. 7-5). Obstruct the brachial artery with a blood pressure cuff by raising the pressure above systolic and leaving it there for about 5 minutes. Your hand will turn white from lack of blood. When the cuff pressure is released your hand turns red, feels warm, and the veins on its dorsal surface become maximally distended with blood flowing from the hand. This sequence of events is explained as follows: During the period of obstruction, vasodilator substances accumulate, causing relaxa-
A common example of reactive hyperemia is seen when you lean on an arm and compress a patch of skin. When you release the pressure you will note that the skin that had been under pressure has turned red and is warm from the increased amount of blood flowing through it. While you leaned on your arm and obstructed blood flow, vasodilators accumulated that, in turn, enhanced blood flow to the area following the obstruction. A similar, but more pronounced, form of reactive hyperemia is seen with Raynaud's phenomenon. In this condition vascular smooth muscle in the fingers (and toes) goes into spasm when exposed to cold or in response to emotional stress. The fingers first turn white. Then, as vasodilators build up, the spasms in venules are overcome and the fingers turn blue (cyanosis) as unoxygenated blood refluxes into the fingers. Finally, the fingers turn red and throb painfully as vasodilators relax arterioles, and capillaries are flooded with oxygenated blood (Fig. 7-6).
2. Long-Term Regulation of Blood Flow

We have given examples of rapid autoregulation of blood flow by constriction or relaxation of precapillary vessels. If the deficit in blood flow to an organ continues for a prolonged time, the vascular bed is remodelled to increase the number of vessels to the affected tissues. Thus, if an artery is occluded, collateral vessels will develop that will allow blood to flow around the point of obstruction. If, on the other hand, blood flow through a capillary bed is excessive, the density of capillaries will gradually be reduced. This remodeling of capillary beds is an ongoing process that occurs more rapidly and efficiently in younger people. Some of these restructuring processes appear to depend upon wall tension and/or upon the oxygen content of blood, and to involve special substances that stimulate vessel growth (angiogenic factors). Following is a tragic example of this phenomenon.

There was a period in the 1950s when it was customary to place infants in respiratory distress in tents with 100% oxygen. The retinal vessels perceived the high oxygen tension of blood as a sign that blood flow was excessive, and regulatory mechanisms diminished the number of retinal vessels accordingly. When these infants were subsequently removed to a normal oxygen environment, the retinal vessels perceived this change as oxygen deprivation and sprouted new vessels that extended into the vitreous humor of the eye. These extra vessels prevented light rays from passing through the vitreous humor to the retina so that these infants were (irreversibly) blind. This condition is known as retrolental fibroplasia.

Fig. 7-6. Raynaud's phenomenon. The three stages of his phenomenon and the underlying mechanisms are shown.
Neural Regulation
Short-term and long-term autoregulation of blood flow is usually sufficient to meet the metabolic demands of the various organs and tissues. There are occasions, however, when blood is not plentiful and when the vasomotor center in the medulla and pons must decide how to distribute a diminished cardiac output appropriately. Thus, in hemorrhage, for instance, autoregulation of blood flow to the kidneys, gut, skin, and muscle is overruled in order to shunt this blood to the brain and to the coronary vessels of the heart. This redistribution of blood flow is mediated by the sympathetic nervous system that we will consider next, and by hormones that we will consider a little later.

1. The Vasomotor Center

Situated in the lower pons and upper medulla is a bilateral area that when stimulated electrically causes an increase in sympathetic neuronal outflow and an increase in blood pressure. This area has, therefore, been called the vasopressor area. Just medial to it is an area that when stimulated electrically causes a fall in blood pressure. This area has, therefore, been called the vasodepressor area. The vasodepressor area is closely associated with the vagal nuclei so that stimulation of the vagus nerve activates the vasodepressor area and lowers blood pressure. There are abundant interconnections between the vasodepressor and the vasopressor areas arranged in negative feedback loops, so that when one center is active the other is inhibited. Therefore, the vasodepressor and vasopressor areas function as a single center with a variable output, the vasomotor center (Fig. 7-7). Impulses from the vasomotor center travel along preganglionic sympathetic neurons to sympathetic chain ganglia (where acetylcholine serves as the neurotransmitter) and from there impulses travel along postganglionic neurons to vascular smooth muscle where release of norepinephrine causes arteriolar constriction after interacting with alpha-1-receptors at the surface of smooth muscle cells.

2. Activation of the Sympathetic Nervous System

The sympathetic nervous system is activated in a number of circumstances. Plasma volume depletion (e.g., in hemorrhage [Figs. 3-16] or diarrhea [Fig. 3-14]) is a good example. In this condition the increase in sympathetic outflow to the arterioles increases their resistance and diminishes blood pressure in the capillaries. The low pressure in capillaries results in reabsorption of fluid from the interstitium. Contraction of smooth muscle in capacitance
vessels starts slightly ahead of arteriolar constriction and results in a decrease in venous compliance and in an increase in venous pressure that forces more blood into the right ventricle. As a result, the right ventricular end-diastolic pressure increases, causing an increase in the stroke volume of the right ventricle and then in the left ventricle (Frank-Starling law of the heart—Fig. 5-12).

Sympathetic fibers also influence the heart rate and stroke volume directly; however, epinephrine released from the adrenal medulla upon sympathetic stimulation has a greater effect on heart rate and cardiac contractility. A preganglionic fiber goes directly to the medulla where acetylcholine triggers the release of epinephrine (see Fig. 1-4). Epinephrine increases the slope of phase 4 depolarization of the sino-atrial node (i.e., chronotropic effect - Fig.4-7) and increases the contractile force of the heart (i.e., homeometric regulation or inotropic effect (see Fig. 5-13). Thus, the heart beats faster and the stroke volume increases even further. Clearly, the increased heart rate times the increased stroke volume results in an increase in cardiac output (HR × SV = CO).

Blood pressure has also been raised because the increased stroke volume delivered into the aorta and large arteries will not run off to the kidneys, skin, gastrointestinal tract, or muscles as usual because the arterioles to those organs have been constricted by sympathetic impulses. In other words, the total peripheral resistance (TPR) has been increased. This leaves more blood in the aorta and large arteries and raises blood pressure (BP), i.e., BP = CO × TPR. This increase in pressure results in improved perfusion of the heart and brain.

The generalized increase in sympathetic outflow to various organs and tissues does not cause constriction of cerebral vessels, which would be counterproductive. Constriction of these vessels is avoided by a sparse sympathetic innervation so that the brain can readily accept the blood that has been diverted from other organs in the periphery during this emergency. The coronaries have a fairly extensive sympathetic innervation compared to brain vessels, but autoregulatory vasodilator substances— notably adenosine—usually override the tendency for neuronal vasoconstriction. Nevertheless, sympathetic inputs (both α and β) do contribute to modulation of coronary blood flow.

The above scheme is an oversimplification that implies that an increase in sympa-
thetic outflow from the central nervous system will increase cardiac output (CO) and mean systemic arterial blood pressure (MSAP). This is not always so because the increase in total peripheral resistance (TPR) following intense sympathetic stimulation may actually reduce venous return (VR) and cardiac output (CO) if the increase in TPR is not offset by an increase in BP, because \( VR = CO = \frac{MSAP}{TPR} \). The heart - no matter how fast or how powerfully it is stimulated to pump - cannot pump more blood than is being returned to it, so that cardiac output must equal venous return.

The primary purpose of sympathetic activation is to raise blood pressure and, thus, increase blood flow to the brain even if this means decreasing blood flow to peripheral tissues and organs.

3. The Sympathetic Vasodilator System

There are times when it is necessary to shunt blood to the heart and to the brain and still preserve full muscle capability as, for instance, during exercise. In such situations a specialized network is activated. This system of nerves is neither quite cholinergic nor quite sympathetic (they are cholinergic fibers traveling with sympathetic nerves), so these nerves are referred to as sympathetic-cholinergic nerves or sympathetic vasodilator nerves. Impulses traveling along these nerves to skeletal muscle have their origin in the premotor cortex in proximity to neurons responsible for initiating movement. In anticipation of exercise, impulses travel from the premotor cortex via the midbrain to emerge from the spinal chord and travel over preganglionic and postganglionic fibers to muscle where acetylcholine, instead of norepinephrine, is released. Acetylcholine triggers dilation of thoroughfare vessels, which are low-resistance channels that supply capillaries with increased amounts of blood if precapillary vessels are dilated and otherwise serve to conduct blood rapidly from arterioles to veins. In addition, low levels of circulating epinephrine dilate skeletal muscle arterioles by binding to beta-2-adrenergic receptors. As exercise is initiated and muscles contract, vasodilator substances are released (e.g., \( CO_2 \), adenosine, lactic acid, potassium ions) that cause precapillary vessels to dilate. As the exercise intensifies and more and more capillaries are recruited, an ample supply of blood now flows through thoroughfare vessels upon which capillaries can draw.

Vasodilation of skeletal muscle during exercise offsets the vasoconstriction in other
vascular beds, such as the kidneys and gut, so that the total peripheral resistance is typically decreased during exercise. The decrease in total peripheral resistance during exercise results in an increase in venous return and an increase in cardiac output. Mean blood pressure is usually slightly increased during exercise. That is, the tendency for a decrease in total peripheral resistance (TPR) to lower blood pressure is offset by the tendency for an increase in cardiac output (CO) to raise mean blood pressure (MSAP), i.e., MSAP = CO x TPR.

4. Depression of the Sympathetic Nervous System

Let us next consider what happens when sympathetic outflow from the central nervous system is depressed. First of all, it is important to bear in mind that there is a certain basal vasomotor tone - that is, a continuous discharge of sympathetic impulses that maintains a resting or basal level of vascular smooth muscle contraction. This basal muscle tone is greater in arterioles than in veins, which are already almost completely relaxed in the basal state. Therefore, when sympathetic outflow diminishes below basal levels, little additional blood is stored in capacitance vessels, but total peripheral resistance falls and blood flow is markedly enhanced in arterioles. The increased capillary pressure enhances filtration of fluid out of capillaries into the interstitium. With a reduction in sympathetic nervous impulses (and epinephrine) to the heart, the heart rate slows and its contractile force decreases, which usually results in a reduction in cardiac output and blood pressure.

A good example of a generalized decrease in sympathetic outflow from the vasomotor center is during administration of a general anesthetic. Without sympathetic nerve impulses to maintain a basal peripheral resistance, blood pressure would fall to about 50 mmHg and the patient would lapse into neurogenic shock, were it not for an intravenous drip of an alpha adrenergic receptor agonist, i.e., compounds related to norepinephrine, which act on alpha-1-receptors of vascular smooth muscle, causing arteriolar constriction.

Neurogenic shock may also result from other conditions that interfere with the vasomotor center or the sympathetic nervous system. This occurs, for instance, in patients with spinal cord injuries or ischemia of the vasomotor center when blood flow to the medulla and pons is inadequate. Moreover, severe and persistent -- rather than acute -- pain leads to a de-
crease in sympathetic outflow from the central nervous system, which is a frequent cause for neurogenic shock in soldiers wounded in battle. Morphine, for pain, and alpha adrenergic agonists are used to treat this type of circulatory shock.

5. Reflex Regulation of Blood Pressure

We have considered how the medullary vasomotor center plays a central role in maintaining normal blood pressure. But how does the vasomotor center know when to increase or decrease sympathetic outflow to peripheral organs and tissues? How does it receive the necessary information to regulate its output? The answer to these questions is that the central nervous system is surrounded by a number of detectors that signal the vasomotor center to make the appropriate adjustment when the circulation to the brain is threatened.

A. Baroreceptors

The most important regulator of blood pressure - at least for responding to sudden changes in body position - are the baroreceptors in the carotid sinuses and in the wall of the aortic arch. Baroreceptors send impulses to the medulla via the glossopharyngeal nerve from the carotid sinuses and

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**Fig. 7-7. Circulatory Adjustments To Standing.** The sequence of events (in numerical order) are depicted for a person who suddenly stands after lying in bed. Gravity causes pooling of blood in the limbs and a decreased venous return and cardiac output. This leads to a fall in blood pressure and decreased stretch of baroreceptors in the carotid sinuses. Fewer impulses over the glossopharyngeal nerve to the vasomotor center cause a decrease in reflex impulse traffic over vagal efferent nerves to the sino-atrial node, causing tachycardia. Simultaneously, the vasomotor center increases sympathetic outflow, which tenses venous capacitance vessels and constricts arterioles in the gut, kidneys, skin, muscle, and bone. The increased cardiac output (CO) and increased total peripheral resistance (TPR) return blood pressure (BP) to normal, i.e., \( BP = CO \times TPR \).
via the vagus nerve from the wall of the aortic arch. These stretch receptors are tonically active and very sensitive. Indeed, if we monitored the impulse traffic along the glossopharyngeal nerve, we would observe more impulse traffic at the peak pressure of systole than during the lower pressures of diastole. Thus, when arterial baroreceptors are stretched by an increase in blood pressure, they send impulses to the medulla that result in slowing of the heart and a decrease in blood pressure.

(1) Normal Response to Sudden Standing

When a person stands suddenly, gravity causes blood to pool in the large veins of the legs and, because venous return to heart decreases, cardiac output and blood pressure decline (Fig. 7-7). This decreases stretch on the baroreceptors, which triggers a decrease in impulse traffic toward the medulla, resulting in a reflex decrease in impulse traffic via vagal fibers from the medulla to the sino-atrial (SA) and atrio-ventricular (AV) nodes of the heart. As discussed previously, the vagus nerve is part of the parasympathetic nervous system that uses acetylcholine as a neurotransmitter at target cells. The SA node is tonically inhibited by acetylcholine (see Fig. 4-7). When less than the usual amount of acetylcholine is released (with a decrease in impulse traffic along the vagus), the SA node is released from tonic restraint and heart rate increases. Keep in mind that the parasympathetic system is more powerful than the sympathetic system in regulating the heartbeat at rates below 100 beats/minute. For this reason, when a patient is found to have sinus bradycardia, atropine (which inhibits the effect of acetylcholine on muscarinic receptors) is the drug of choice, rather than epinephrine.

The cell bodies of vagal nerves are closely associated with the vasodepressor area of the medulla, so that stimulation of the vagus nerve tends to decrease blood pressure. We do not know the precise interconnections between the cell bodies of vagal nerves and the medullary vasomotor center, but such details are not important in understanding the overall purpose for this reflex. For practical purposes it is useful to remember that whenever the parasympathetic nervous system (i.e., glossopharyngeal and vagus nerves) is active, the sympathetic system is inactive and vice versa. (The Cushing reaction to be discussed later is an exception to this rule.) Thus, when blood pressure suddenly falls, reflex tachycardia results (primarily because of vagal reflexes) and simultaneously there is an increase in the general sympathetic outflow to the cardiovascular system, includ-
ing the whole cascade of reactions considered earlier. And, of course, the exact opposite sequence of events occurs when blood pressure rises acutely (e.g., following injection of an alpha adrenergic receptor agonist, such as phenylephrine). It is important to remember that the baroreceptor reflex does not prevent hypertension and that hypertension does not result from an abnormal baroreceptor reflex. This reflex is designed for rapid adjustments in blood pressure. The reflex mechanism adapts to a higher set point if high pressure is maintained for long periods of time, as in hypertension. On the other hand, absence of the baroreceptor reflex does not cause persistent hypotension, but only intermittent hypotension on sudden standing (orthostatic hypotension). This has been nicely demonstrated by Guyton and his co-workers in dog experiments. When the baroreceptor reflex in dogs was blocked, the mean blood pressure over a day’s time did not change. However, blood pressure fluctuated markedly between very high and very low values over short time periods whenever the animal changed its position. Thus, the primary function of the baroreceptor reflex is to adjust the blood pressure rapidly to compensate for positional changes.

When a person stands suddenly, 500 ml of blood or more may pool in the extremities (Fig. 7-7). This would decrease venous return to the heart and decrease cardiac output, which would diminish blood flow to the brain and cause fainting. Within seconds, however, the baroreceptor reflex increases heart rate and the increase in sympathetic outflow from the vasomotor center constricts capacitance vessels, which slows pooling of blood in the limbs so that venous return to the heart (and cardiac output) is maintained. At the same time, constriction of arterioles in skin, kidneys, gut, and muscles increases total peripheral resistance, which, together with the increase in cardiac output, raises arterial blood pressure (and perfusion of the brain) back to normal.

(2) Orthostatic Hypotension

The baroreceptor reflex is quite sensitive to relatively minor disturbances. For example, the baroreceptor reflex may not operate effectively in otherwise healthy individuals who have a cold or have not had sufficient sleep. People who have been sick in bed may faint on taking their first steps, partly because the reflex has been dormant for too long, and partly because bed rest decreases the circulating blood volume (due to diminished vasopressin and
aldosterone secretion in the recumbent position). An ineffective baroreceptor reflex also poses particular difficulties for older individuals and especially for patients with diabetes mellitus, who often have dysfunction of the autonomic nervous system. Orthostatic hypotension is also an expected side effect in patients taking drugs for hypertension or schizophrenia that block neurotransmission at autonomic ganglia or at adrenergic receptor sites. Not all patients with orthostatic hypotension have a defective baroreceptor reflex. An acute hemorrhage will also cause a drop in blood pressure and fainting on sudden standing. The problem in this situation is that the venous capacitance vessels are relatively empty and already maximally constricted, so that a further increase in sympathetic tone on standing does little to enhance venous return.

(3) Stimulation of the Carotid Sinuses

In some individuals the carotid sinus may be unusually sensitive to external pressure (some may have atheromatous plaques in the sinus) and they may faint from reflex bradycardia and prolongation (or block) of atrio-ventricular conduction.

Because carotid sinus massage in normal individuals will increase the parasympathetic tone to the AV node and thereby delay conduction of impulses through the node, this procedure may be used to convert paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm. Of course, this should only be done with careful monitoring of the heart beat by ECG and only after the other carotid artery has been checked for patency (i.e., no bruit is found on auscultation). Another method that has been used to elicit the baroreceptor reflex to revert PSVT to sinus rhythm is to raise blood pressure suddenly by injecting phentylephrine (an alpha1-adrenergic agonist).

B. Carotid and Aortic Chemoreceptors

The carotid and aortic bodies are chemoreceptors that are sensitive primarily to low partial pressures of oxygen (PaO$_2$ $<$ 55 mmHg) and a low pH (pH $<$ 7.3) of arterial blood. The carotid and aortic bodies send impulses via the glossopharyngeal and vagus nerves, respectively, to the medulla where the vasomotor center is stimulated to increase the heart rate and blood pressure. The main function of these receptors, however, is their effect on respiration, which we will discussed in the respiratory section. By increasing the rate and depth of ventilation the peripheral chemoreceptors lower intrathoracic pressure, causing
more blood to move back to the heart and thereby increasing end-diastolic ventricular filling and cardiac output. Tachycardia or a rise in blood pressure are often the only signs on physical examination that the patient may be hypoxemic. Thus, whenever you cannot find a good explanation for a fast heart beat in an elderly patient, draw an arterial blood sample and check the gases.

C. Central Nervous System Ischemia and the Cushing Reaction

When blood pressure falls below a critical value needed to adequately perfuse the vasomotor center, carbon dioxide accumulates and stimulates the center to increase sympathetic outflow until blood flow to the brain is reestablished. In the process blood flow to the kidneys, skin, gut, and muscle may be completely shut down in a desperate attempt to save the vital medullary centers. If this fails, the neurons in the vasomotor center are damaged, all sympathetic outflow stops, blood pressure falls to around 50 mmHg, and the person lapses into a state of neurogenic shock.

A variant of the above ischemic response of the central nervous system is the Cushing reaction. An intracranial tumor or an increase in cerebrospinal fluid pressure will obstruct blood flow to the brain because there is no space in the cranial vault for one structure to expand without compressing another. Accumulation of carbon dioxide (and lack of oxygen) in areas of the brain where blood flow is poor triggers an intense sympathetic outflow (via the vasomotor center), causing peripheral vasoconstriction and an increase in blood pressure, which stabilizes at exactly the pressure required to overcome the obstruction, i.e., the pressure at which carbon dioxide will be washed away by blood flow. Baroreceptors sense the blood pressure to be too high, and, in response, the heart rate is slowed via the vagus. Note that, in this instance, the increased parasympathetic inflow to the medulla from the baroreceptors does not (as usual) result in a decreased sympathetic outflow and in peripheral vasodilation. Instead, the carbon dioxide and other metabolites accumulating in the brain under pressure dictate the continued need for peripheral vasoconstriction. Therefore, beware of the patient with a high blood pressure and a slow pulse, especially if he has a headache. He may have a brain tumor or another reason for an increase in cerebrospinal fluid pressure. Take out your ophthalmoscope and check his retina for papilledema (swelling of the optic disc), and perform a careful neuro-
logical examination, looking for local signs of weakness or paralysis.

**D. Effects of Pain and Emotion on Vasomotor Activity**

There are other stimuli that influence the sympathetic outflow from the vasomotor center. For instance, pain induces an increase in blood pressure by stimulating the vasomotor center. However, when the pain is severe and prolonged, the vasomotor center becomes desensitized and blood pressure then drops to a very low level as the patient lapses into neurogenic shock. For this reason - in addition to humane concern - the medic on the battlefield is always liberal in dispensing morphine to the severely wounded who are in pain.

The effects of emotions on blood pressure are well known: Anger and rage usually increase blood pressure. Fear may cause sympathetic vasoconstriction of the skin and sweating (sympathetic cholinergic reaction) so that a person who is terrified may look pale and have cold sweats. A person who is embarrassed may blush by selective vasodilation of vessels in the skin of the face, neck, and chest. More severe embarrassment may cause emotional fainting, or vasovagal syncope. **Vasovagal syncope** occurs when there is an increase in vagal impulse traffic to the heart, causing cardiac slowing, and activation of sympathetic vasodilator fibers to muscle (presumably in preparation for exercise that does not happen). The sudden decrease in total peripheral resistance (TPR) in the absence of muscle contraction to move blood back to the heart and the decrease in cardiac output (CO) causes a sudden fall in mean systemic arterial pressure (MSAP) (i.e., MSAP = TPR x CO), which results in diminished cerebral perfusion and loss of consciousness.

**E. Blood Volume Receptors**

Venous return determines cardiac output (as long as the heart is normal) and cardiac output is a major determinant of arterial blood pressure (*vide supra*). Venous return, which is important to ensure adequate blood pressure and adequate perfusion of the brain, is monitored by **volume receptors** (or low pressure baroreceptors). These volume receptors stretch in response to small changes in pressure or blood volume. They are situated in the subendocardium of the right and left atria. The volume of blood in the atria is proportional to venous return, so that these receptors monitor the amount of blood returning to the heart and the degree to which the ventricles fill during diastole. The end-
diastolic filling volume of the ventricles is, in turn, proportional to the stroke volume, and stroke volume (SV) times heart rate (HR) equals cardiac output (CO), \((SV \times HR = CO)\).

These volume receptors in the atria fire during atrial systole or atrial filling, sending impulses along the vagus nerve to the medulla. When venous return is decreased, the atria fill less than usual so that fewer impulses are sent along these nerve fibers to the medulla. This results in reflex tachycardia and increased sympathetic outflow from the vasomotor center, which initially tenses only the large veins and taps the venous reservoirs in the liver, spleen, skin, and muscle. The increase in pressure in the large veins, in turn, moves more blood toward the heart. Such adjustments are often all that is required to restore cardiac output and prevent arterial blood pressure from falling, without a need for extensive constriction of arterioles to the gut or kidneys.
In this 44 minute video-lecture Dr. Eggema discusses hormonal regulation of blood pressure, vasopressin, aldosterone, and epinephrine secretion and action, hypertension, and physiological approaches in the treatment of hypertension.
Hormonal Regulation
The actions of the autonomic nervous system in regulating arterial blood pressure are supported by the actions of different hormones; namely, antidiuretic hormone (ADH), aldosterone, atrial natriuretic hormone, and epinephrine.

**Antidiuretic Hormone.** When blood pressure (and volume) in the atria declines, low pressure baroreceptors in the subendocardium relay this information not only to the medullary vasomotor center but also to the **supraoptic nucleus** in the hypothalamus (via a series of neurons between medulla and hypothalamus). Nerve cells in the supraoptic nucleus depolarize, causing release of ADH from axon terminals in the posterior pituitary into the bloodstream. ADH is carried by blood to principal cells in the renal collecting duct, where it interacts with **V2-receptors** to increase membrane permeability to water by a mechanism mediated by intracellular cyclic AMP (see Fig. 3-9). As more water is reabsorbed back to blood from the forming urine, plasma volume (as well as all other body fluid volumes) increases, leading to increased venous return and cardiac output. This antidiuretic action of ADH is usually sufficient to prevent blood pressure from falling. If arterial blood pressure does start to decline, despite maximal water retrieval from urine, much greater amounts of ADH (about 100 times the antidiuretic dose) are secreted from the posterior pituitary into the blood-stream. At these relatively high blood concentrations, ADH becomes a powerful vasopressor agent, i.e., it constricts veins and arterioles. Indeed, this is how ADH got its name, vasopressin. The vasoconstrictor effects of vasopressin are mediated by **V1-receptors** that trigger smooth muscle contraction by raising the intracellular concentration of calcium ions.

**Renin-Angiotensin-Aldosterone.** Like ADH, aldosterone is also released into the circulation with a fall in atrial pressure. However, secretion of aldosterone does not occur by direct nervous stimulation of the adrenal cortex, where aldosterone is synthesized in cells of the **zona glomerulosa**, but by a circuitous route involving the renin-angiotensin system.

Volume receptors in the atria relay information of decreased filling to the medullary vasomotor center, which, in turn, increases impulse traffic over sympathetic nerves to the kidneys where renin is released from the **juxta-glomerular apparatus** (JG apparatus) into the bloodstream. The JG apparatus is situated close to the glomerulus where the afferent arteriole touches the ascending limb of Henle's loop (Fig. 7-8). Specialized smooth muscle cells here in
the wall of the afferent arteriole contain granules filled with renin. These granules are released by impulses arriving along sympathetic nerves or by circulating epi-
nephrine acting on beta-adrenergic recep-
tors. The renin-secreting smooth muscle cells are closely associated with special-
ized epithelial cells in the late thick ascend-
ing limb of Henle, that form the macula densa (or Polkissen). These epithelial cells are specialized in sensing changes in tubular fluid composition, so that when osmolarity or the concentration of chloride or calcium ions falls (e.g., when renal blood flow and glomerular filtration rate decrease), more renin is secreted into blood.

In the circulation, renin interacts with renin substrate (also called angiotensinogen, an alpha2-globulin synthesized by the liver), to form angiotensin I (a decapep-
tide). Angiotensin I, in turn, is converted to angiotensin II (an octapeptide) in the lung (and other tissues), where an enzyme (angio-
tensin converting enzyme or ACE) cleaves off two terminal amino acids. Angio-
tensin II finally reaches the adrenal cortex where it stimulates the release of aldosterone from cells in the zona glomerulosa. Aldosterone, in turn, interacts with principal cells in the renal collecting duct where it increases the reabsorption of sodium and chloride from the forming urine.

The extra salt reabsorbed by aldosterone and the extra water reabsorbed by vaso-
pressin restore plasma volume toward normal, which increases venous return and cardiac output. In addition, both vaso-
pressin and angiotensin II are potent vaso-
constrictors that raise blood pressure more directly by increasing total peripheral resis-
tance.

**Atrial Natriuretic Peptide.** Atrial muscle cells contain granules loaded with a 28 amino acid peptide that is a potent vasodi-
lator and, because it induces loss of so-
dium (natrium) in urine, has been named atrial natriuretic peptide (or factor) (ANF). The compound is released by atrial stretch that occurs when the plasma volume is ab-
normally expanded, as, for example, after drinking excess fluid following ingestion of salty food. ANF interacts with receptors in vascular smooth muscle, causing an in-
crease in intracellular cyclic GMP (and a decrease in cyclic AMP) that stimulates the activity of Ca++-ATPase. This lowers intra-
cellular free calcium ion concentration and causes muscle relaxation. Dilation of affer-
ent arterioles in the kidney increases the glomerular filtration rate, which increases the amount of sodium presented to the re-
nal tubules for reabsorption. This increased sodium load together with inhibition of sodium reabsorption by the renal collecting ducts causes excess sodium to be lost in urine (natriuresis). Thus ANF is a counter-hormone that limits the actions of ADH and aldosterone by (1) promoting the loss of salt and water in the urine, (2) moving fluid from plasma to interstitium, (3) decreasing venous return, (4) decreasing preload of the heart, (5) decreasing cardiac output, and (6) diminishing blood pressure.

**Epinephrine.** We pointed out earlier that a preganglionic sympathetic fiber goes directly to the adrenal medulla where the release of acetylcholine from nerve endings triggers the release of epinephrine (and a little norepinephrine) into the circulation (see Fig.1-4). Usually about two-thirds epinephrine and one-third norepinephrine are found in the circulation, but these ratios are not fixed. For example, relatively more norepinephrine is present in hemorrhage. Most of the norepinephrine in the blood stream is not from the adrenal medulla, but rather from sympathetic nerve endings in vascular beds. In vascular smooth muscle, norepinephrine behaves as a pure alpha1-adrenergic agonist and has no effect on beta-2-adrenergic receptors. Epinephrine, by contrast, acts both on alpha1- and beta-2-adrenergic receptors in the circulation. When alpha-1-receptors are activated by either norepinephrine or by epinephrine, arteriolar smooth muscle contracts. When epinephrine acts on beta-2-receptors, smooth muscle relaxes. Epinephrine has a higher affinity for beta-2 than for alpha1-receptors. This means that epinephrine will interact with beta-2-receptors at a lower dose, causing vasodilation. At higher concentrations the vasodilation will be overruled by an effect on alpha-1-receptors, causing vasoconstriction. To make matters even more complex, the question of whether epinephrine will cause vasodilation or vasoconstriction depends on the relative concentration of alpha1 and beta-2-receptors in the circulations of different organs. In vessels of skeletal muscle, for example, there is a high density of beta-2-receptors, so that epinephrine causes vasodilation, which is an important factor in enhancing blood flow to skeletal muscle in exercise. By contrast, skin has a higher density of alpha-1-receptors so that the primary action of epinephrine in skin is vasoconstriction, which shunts blood away from the body surfaces. (Recall that norepinephrine and epinephrine are equally potent in the heart where both compounds bind with beta-1-adrenergic receptors to increase heart rate and cardiac contractility.)
Vasoactive Agents Produced by Endothelial Cells.

Very little attention was given to the possible interaction between endothelial cells and the underlying smooth muscle cells of vessels until recently when researchers were stunned to find that classical vasodilator stimuli, such as acetylcholine, failed to work when the endothelial layer was removed from vessels. It was soon revealed that endothelial cells produce a vascular relaxing factor, which was named endothelium-derived relaxing factor (EDRF). EDRF later turned out to be a very simple compound, nitric oxide (NO), which is highly diffusible and difficult to detect because it is an unstable compound. Nitric oxide (not nitrous oxide [NO₂]!), like ANF, stimulates cyclic GMP formation in smooth muscle cells, which makes them relax. Nitric oxide is formed in response to shear stress on endothelial cells as blood flows at high velocity through arterioles. Such high velocities of blood flow in arterioles are a sign that precapillary vessels downstream have been dilated by autoregulatory mechanisms and that subsequent relaxation of arterioles by nitric oxide has supplied the capillary beds with the extra blood they can now accept. The vasodilator action of nitric oxide is closely associated with (and synergistic with) the vasodilator effects of prostacyclin (PGI₂), which is also released by endothelial cells. PGI₂ relaxes vascular smooth muscle by increasing intracellular cyclic AMP.

The action of EDRF to relax vascular smooth muscle is opposed by a vasoconstrictor substance called endothelin, which is also produced by endothelial cells. Stimuli that enhance EDRF release, such as shear stress, inhibit endothelin synthesis. Some evidence suggests that this balance may be upset in patients with hypertension, which may contribute to the inappropriate vasoconstriction that increases their total peripheral vascular resistance. More localized constrictions in areas where endothelial cells have been damaged (by an atheromatous plaque, for example) could be responsible for the vascular spasms of coronary vessels seen in patients with attacks of angina. It is no coincidence that nitroglycerine - the traditional remedy for angina pectoris - contains nitric oxide that is liberated during metabolism of nitroglycerin and causes relaxation of coronary smooth muscle.
Hypertension
It is clear that we do not have one, but many, overlapping mechanisms for regulation of blood pressure, suggesting that precise and rapid adjustments of blood pressure had a high adaptive value during the course of evolution. Because of this complexity, when something goes wrong with these control systems - as it does in patients with hypertension - it is difficult to pinpoint which part of the overall system is at fault. For this reason, the underlying cause of hypertension for the great majority of patients (about 93%) with this condition is still not known; they are said to have idiopathic, or essential, or primary hypertension. For the remaining 7% of patients with hypertension the cause is known to be secondary to a certain abnormality and they are, therefore, said to have secondary hypertension.

A person is said to have hypertension if he or she has been found to have a blood pressure in excess of 140/90 mmHg on at least three separate occasions in a quiet and relaxing environment. The physician then searches for possible causes for the hypertension that can be treated. Secondary hypertension should be ruled out before a person is committed to a lifetime of symptomatic treatment for high blood pressure.

1. Secondary Hypertension

A. Renovascular Hypertension

When blood flow to one kidney is obstructed, less fluid is filtered at the glomeruli. This decrease in glomerular filtration is sensed by the macula densa as decreased chloride, calcium, or osmolarity. Increased amounts of renin are secreted in order to raise blood pressure to overcome the obstruction. This mechanism for hypertension was originally described by Goldblatt in animal experiments in which he restricted blood flow to one kidney with a clamp (the Goldblatt kidney preparation). In humans, the obstruction could be a calcified plaque in the renal artery or a malformation of the artery resulting in narrowing of its lumen. This cause for hypertension is important to rule out, because it can be cured by surgery. Therefore, look for this possibility - especially in a young person with hypertension. Listen carefully for a bruit (from turbulence) over the renal artery on physical examination. Definitive diagnosis (before surgery) requires demonstration of a stenotic artery by angiography and evidence of significantly higher plasma renin activity in a blood sample from the renal vein of the affected kidney than a control sample from the healthy kidney.
B. Primary Hyperaldosteronism

Patients with renovascular hypertension (and many patients with essential hypertension) have high circulating concentrations of renin (i.e., high plasma renin activity) which, in turn, leads to secondary hyperaldosteronism. However, occasionally (< 1% of hypertensives) a patient is found to have high aldosterone levels either from a tumor of the adrenal cortex or from hyperplasia of the adrenal gland. This primary hyperaldosteronism is typically associated with low plasma renin activity. The inappropriate secretion of aldosterone causes potassium loss and sodium chloride retention by the kidney. The hypokalemia (serum potassium < 3.0 mEq/l) causes muscle weakness and cardiac arrhythmias. Sodium chloride retention briefly raises plasma osmolarity which, in turn, triggers ADH secretion and water retention by the kidneys. The extra salt water increases plasma volume, venous return, left ventricular preload, cardiac output, and blood pressure. The hypertension, low plasma renin activity, and hypokalemia suggest the correct diagnosis, especially if plasma aldosterone levels are found to be elevated.

Surgery is recommended for patients with an adrenal tumor but not when aldosteronism is due to hyperplasia of the adrenal cortex. To distinguish between these, plasma aldosterone levels are measured before and after an infusion of 2 liters of isotonic saline over a period of 2-4 hours. Plasma aldosterone levels will decrease in hyperplasia (or in a normal subject), but will not change significantly in a patient with an adrenal tumor. Furthermore, sudden standing will increase plasma renin and aldosterone in normal subjects and in patients with adrenal hyperplasia, but will not increase aldosterone levels in patients with an adrenal tumor.

C. Pheochromocytoma

Pheochromocytoma is a chromaffin cell tumor of the adrenal medulla (or Zuckerkandl bodies along the abdominal aorta) that causes hypertension by releasing large amounts of norepinephrine and epinephrine. The hypertension tends to be quite sporadic as catecholamines are released in bursts into the circulation, for instance, following abdominal palpation (on physical examination) or, at times, simply on urination. This condition is suspected in a patient with paroxysmal hypertension associated with headaches, profuse sweating, and tachycardia. A diagnosis is made by finding elevated levels of metanephrine, a metabolite of catecholamines, in a 24-hour urine sample and by localizing the
tumor(s) using radiological techniques (e.g., computed tomography). During surgery to remove the tumor(s), blood pressure and heart rate fluctuate widely, and alpha-1-adrenergic receptor blockers are administered to reduce blood pressure and beta-1-blockers to treat tachycardia and cardiac arrhythmias.

2. Primary (Essential) Hypertension

Although we do not know the cause of primary hypertension, the high blood pressure must be treated because we do know that it leads to arteriosclerosis and progressive damage to vessels, which, in turn, causes more hypertension, particularly as blood flow to kidneys is compromised. In some patients blood pressure rapidly spirals out of control (with diastolic blood pressure exceeding 120 mmHg) as hypertension triggers more hypertension (presumably by causing the kidneys to secrete large amounts of renin). This phenomenon is referred to as malignant hypertension.

High blood pressure places an extra strain on the heart and leads to hypertrophy, coronary artery disease, and myocardial infarction. The high pressure in the cerebral circulation predisposes to strokes, and in the renal circulation to renal failure. Hypertension, therefore, must be treated. There is a large arsenal of drugs that can be used for this purpose.

Regardless of the underlying mechanism for the hypertension, the increased pressure means that there is too much blood in the aorta and large arteries (pressure is related to volume via the aortic compliance curve, see Figure 6-12). This could be due to an increased plasma volume with more blood being pumped into the large vessels (an increased cardiac output [CO]) or it
could be due to an increased total peripheral resistance (TPR) with less blood being allowed to leave the large arteries (MSAP = CO x TPR). Measurements of cardiac output in patients with hypertension have shown that cardiac output is normal or even less than normal, so that an increased total peripheral resistance must be responsible for the increased blood pressure in patients with well established hypertension. Nevertheless, it has been suggested that an increase in cardiac output could have been initially responsible - at least in some patients - for the increase in peripheral vascular resistance. Thus, if cardiac output were increased out of proportion to the tissues' needs for blood flow (e.g., in a person on a high salt intake), autoregulatory mechanisms would constrict peripheral vessels to adjust flow to the metabolic needs of the tissues. This, in turn, would cause an increase in blood pressure (MSAP = CO x TPR). If this situation prevailed for some time, the high pressure would induce irreversible changes in the vasculature so that peripheral resistance would now remain higher than normal, even after cardiac output had returned to normal or even fallen below normal. The treatment for hypertension is aimed at decreasing the plasma volume (and thus the cardiac output) and/or decreasing the total peripheral resistance. Figure 7-8 summarizes physiologic approaches in the treatment of hypertension.
In this 46 minute video-lecture Dr. Eggens discusses the regulation of cardiac output and venous return and the use of Guyton’s curves in the graphic analysis of altered states.
Regulation of Cardiac Output
This section examines how left and right ventricular output are regulated by end-diastolic filling volume, myocardial contractility, and heart rate.

1. Effect of CVP and PAWP on Right and Left Ventricular Output

Cardiac output by the right or left ventricles is equal to ventricular stroke volume times heart rate (CO = SV x HR). Because stroke volume increases as a function of end-diastolic volume (Frank-Starling phenomenon), and end-diastolic volume is proportional to CVP (right ventricle) or PAWP (left ventricle), cardiac output also increases as a function of CVP or PAWP (Fig. 8-4, normal function curve at rest). Because cardiac output also changes as a function of heart rate and myocardial contractility at any end-diastolic filling volume, the normal (resting) cardiac function curve is shifted upward when the heart is contracting more powerfully and/or more rapidly. The normal function curve is shifted downward when myocardial contractility is depressed and/or heart rate is abnormally slow. Conditions that raise the normal (resting) cardiac function curve include: sympathetic stimulation, beta-1-adrenergic agonists, or cardiac glycosides. Conditions that decrease the normal (resting) cardiac function curve include: parasympathetic stimulation (causing sino-atrial and atrio-nodal conduction blocks), beta-1-adrenergic antagonists, calcium channel blockers, myocardial infarction, valvular heart disease, atrial fibrillation, or acidosis. It is important to bear in mind
that an increase in heart rate will only increase cardiac output up to a point, which depends (among other factors) upon the level of conditioning and the duration of the tachycardia. Indeed, in patients with atrial fibrillation and hypertension, as in Mr. M, decreasing heart rate below 100 beats/min and decreasing the afterload by reducing blood pressure will shift the cardiac function curve upward.

We will return to these various function curves a little later. For now let's focus on the normal (resting) curve. At rest, cardiac output is about 5 liters/min and the CVP is about 5 mmHg and the PAWP about 10 mm Hg. According to the normal cardiac function curve in Figure 8-4, when CVP and PAWP double cardiac output increases almost two and one-half times.

So why does the heart actually pump about 5 liters/min instead of 12 liters/min? Only 5 liters of blood are returned to the heart each minute, and the heart cannot pump more blood than is being delivered to it. If venous return were 12 liters/min, then the heart would pump 12 liters/min and do so without any additional stimulation (the heart would not have to shift to a higher function curve). In other words, venous return regulates cardiac output for a normally functioning heart. When the heart is diseased or its normal function (contractility or heart rate) is otherwise depressed, cardiac output is limited not by venous return but by the pumping capability of the right and left ventricles.
Regulation of Venous Return
The amount of blood that flows into the central veins and generates the filling pressure of the right ventricle (and subsequently [via the PAWP] of the left ventricle) will depend upon the amount of blood that flows from the capillary beds of the various organs and tissues of the body. Blood flow through these capillary beds depends, in turn, upon the various autoregulatory mechanisms that allow blood to enter organs and tissues. Thus, when tissues need more blood to meet their metabolic needs, vasodilator substances accumulate and cause pre-capillary sphincters and metarterioles to relax. As more blood flows to tissues and organs, more is returned to the heart and cardiac output increases, accordingly. Therefore, cardiac output is regulated by the sum of the individual metabolic needs of the tissues. When more blood is needed, for instance, with exercise, skeletal muscle will take a larger fraction of the cardiac output, which it will rapidly return via low resistance channels to the veins. The CVP will increase and fill the right ventricle more, so the right ventricle will pump more blood into the pulmonary artery. The PAWP, in turn, will increase and fill the left ventricle more, so that the left ventricle will pump more blood into the aorta, from where the increased cardiac output is delivered to exercising muscles.

Thus, in the normal heart, venous return determines cardiac output.

1. Increased Venous Return (and Cardiac Output) with Shunts and Altered Metabolic States

Venous return and cardiac output are normally regulated by the metabolic needs and functions of the various organs and tissues that make up the body. There are times, however, when blood flow through tissues is excessive, for example when tissue metabolism is abnormally increased (e.g., hyperthyroidism) or when blood is bypassing capillary beds altogether by flowing via low resistance shunts between arteries and veins (e.g., Paget’s disease). In both instances, the total peripheral resistance is decreased without changing the compliance of the capacitance vessels responsible for conducting blood back to the heart. This increase in venous return results in increased cardiac output.

Let us illustrate this with a simulation (Fig. 8-5) of experiments carried out by Guyton and colleagues on anesthetized dogs. Catheters are inserted into a femoral artery and vein, and the ends are connected by a three-way stopcock. When the stopcock is closed, only 5 L/min of blood flows
through capillary beds of various organs and tissues and is returned to the heart. When the stopcock is first opened, 5 L/min of blood flows through the shunt and none through the tissues. The sudden drop in total peripheral resistance causes a fall in blood pressure, which activates the baroreceptor reflex, resulting in movement of fluids from the interstitium to blood and retention of salt and water by the kidneys. By this regulatory mechanism, blood flow to tissues is soon reestablished. With the additional 5 L/min of blood flowing directly from the femoral artery into the femoral vein, venous return will increase to 10 L/min. The cardiac output will now increase to 10 L/min, not from sympathetic stimulation, but simply from the increase in the end-diastolic ventricular volume that increases the stroke volume by the Frank-Starling mechanism. This experiment illustrates that cardiac output is regulated by venous return.

There are a number of conditions that are characterized by an increase in cardiac output where the **high cardiac output state** can be ascribed to a primary decrease in the total peripheral resistance (without a change in venous compliance). This is seen, for example, in patients with **Paget's disease**, where extensive arterio-venous fistulae are formed in bone. Also, during the third trimester of **pregnancy** venous return and cardiac output increase markedly as blood is shunted through low resistance pathways in the placenta. For this reason, young women with rheumatic valvular heart disease may not be aware of their cardiac disability until they develop...
signs and symptoms of congestive heart failure in the late stages of pregnancy. Hyperthyroidism also is often associated with an increased cardiac output, partly because the heart is stimulated to contract more and tissues and is returned to the heart. When the forcefully, partly because an increase in tissue metabolism leads to enhanced blood flow through capillary beds. Marked peripheral vasodilation is seen in beriberi (thiamine deficiency), when glucose metabolism cannot proceed normally. This condition causes high cardiac output states and high output cardiac failure when the heart cannot keep up with the high venous return. (The heart also contracts less forcefully than normal in beriberi.) We have already seen that severe anemia in the man in case 6 can lead to an increase in cardiac output. In this situation cardiac output increases as tissues deprived of oxygen vasodilate and return more blood to the heart.

It must be emphasized that a decrease in total peripheral resistance (e.g., by relaxation of arteriolar smooth muscle) will only lead to an increase in venous return and in cardiac output, provided that venous compliance is not also increased (e.g., by relaxation of venous smooth muscle). When both arterioles and veins relax simultaneously - as occurs in neurogenic shock with a decrease in sympathetic outflow to the vascular system - cardiac output decreases because blood pools in the veins and is not returned to the heart.

2. Effect of Gravity on Venous Return (and Cardiac Output)

Gravity is an important factor in venous return (Fig. 8-6). Blood in veins below the level of the heart is subjected to gravity, which pulls on the column of blood, distending vessels below the heart. Just look at the veins in your hand, when your arm is relaxed and hanging down by your side. Now raise your arm and watch the veins in your hand collapse as it passes the level of your heart. The veins above the heart, such as those in the neck, are normally collapsed when a person is sitting or standing. As blood flows with gravity from the head to the chest, it creates a partial vacuum in the venous sinuses of the cranium that tends to siphon blood from arteries into brain capillaries. The neurosurgeon must be aware of this when operating on a patient in the sitting position. If a vein in the head or neck is cut, air may be sucked into the heart, resulting in an air embolus.
3. Importance of Venous-Compliance, Valves, and Skeletal Muscle in Facilitating Venous Return (and Cardiac Output)

The tendency for gravity to cause pooling of blood in the legs is counteracted in three major ways:

(1) Pooling of blood in the extremities upon sudden standing minimized by the baroreceptor reflex, which increases sympathetic outflow to the smooth muscle of veins, decreasing their compliance.

(2) The major veins have one-way valves pointing toward the heart. These valves, when competent, break up the long column of blood between heart and feet into smaller sections, so that the hydrostatic pressure is felt only over the distance between any two valves. This is not true, however, when valves become incompetent. Then the full effect of gravity is transmitted to the walls and the veins bulge and become tortuous. This is particularly true for superficial veins, such as the saphenous veins in the legs, which lack support from surrounding musculature. Such incompetent veins are called varicose veins.

(3) Most deep veins are surrounded by skeletal muscle, and as muscles contract, veins are squeezed and blood is milked from one valve past the next toward the heart. Lack of muscle contraction - as for soldiers standing at attention - may lead to peripheral venous pooling and fainting, especially in hot weather.

Fig. 8-6. Effect of Gravity on Venous Pressure
(A) The hydrostatic pressure of blood due to gravity for a person standing quietly is shown to be a positive value in veins below the heart and a negative value in veins above the heart. Accordingly, in a foot vein 80 cm below the heart pressure will equal +80 cm of water, whereas in a hand held 40 cm above the heart, venous pressure will equal -40 cm of water. (B) Venous pressures at the ankle are compared for a person lying, standing quietly, or running. Note that during running skeletal muscle contraction squeezes veins, which pumps blood from the ankle against the force of gravity toward the heart.
4. Importance of Inspiration on Venous Return (and Cardiac Output)

Another important factor aiding venous return is inspiration (Fig. 8-7). During inspiration the intrapleural (or intrathoracic) pressure drops, becoming more subatmospheric and causing distention of the large vessels in the chest. This tends to suck more blood into the right atrium. Because the downward movement of the diaphragm increases intra-abdominal pressure, vessels in the abdominal cavity are compressed, which simultaneously forces blood toward the heart. It is noteworthy that some patients in hemorrhagic shock, who suffer from a decreased venous return, are found to have intense constriction of the abdominal muscles, which would tend to facilitate venous return.

While a deep inspiration increases venous return to the right ventricle, left ventricular filling and cardiac output actually decrease. Indeed, this is why the second heart sound is split on inspiration (physiological splitting of S2). Only on expiration does the extra blood (returned to the heart during the deep inspiration) increase left ventricular output. The reason is that distention of pulmonary vessels on inspiration allows more blood to pool (temporarily) in the lungs, so less flows into the left ventricle, and, therefore, the left ventricular stroke volume is diminished (Fig. 8-7).

As more blood enters the right atrium on inspiration, the rhythm of the heart becomes irregular (sinus arrhythmia) due to a brief increase in the rate of depolarization of the SA node. This is partly caused by stretching of SA nodal tissues and partly by stimulation of the SA node by the
**Bainbridge reflex.** This reflex is initiated when the atrium is stretched. Afferent impulses are carried over vagal fibers to the medulla and result in decreased parasympathetic and increased sympathetic stimulation of the SA node and atrial muscle. This reflex moves blood out of the atrium and into the ventricle.

While inspiration facilitates venous return to the heart, an increased (positive) intrathoracic pressure during a forced expiration impedes venous return. This is why a trumpet player has a red face and distended neck veins. Blood will not drain from the neck and face into the right atrium as long as these structures are compressed. This is, in part, why patients with prolonged and repeated coughing spells may faint. The continued positive intrathoracic pressure during the coughing episodes prevents venous return and diminishes cardiac output. Patients on positive pressure ventilators, especially when the ventilator is set for **PEEP** (i.e., **positive end-expiratory pressure**), experience a decrease in venous return and in cardiac output. It is, therefore, important to weigh the potential benefits of using PEEP (e.g., increased arterial oxygen tension of blood) against a diminished cardiac output and decreased delivery of oxygenated blood to tissues. We sometimes seem to forget that life is not divided into inspiration and expiration but that there are relatively long periods of time between breathing in or out. It is in these long intervals between breaths that intrathoracic pressure is normally slightly subatmospheric (e.g., -2 mmHg). This is also true for patients on positive pressure ventilators, unless the ventilator has been set for **continuous positive airway pressure (CPAP)**.

Important changes in venous return, cardiac output, and blood pressure are observed in breathholding and straining during the **Valsalva maneuver** (Fig. 8-8). During the Valsalva maneuver, a person takes in a deep breath, then exhales forcefully against a closed glottis. This may increase intrathoracic pressure, for example, from -2 to +40 mmHg. Because the aorta and large arteries in the chest are exposed to this additional 42 mmHg, blood pressure in the brachial artery rises by an extra 42 mmHg and then falls gradually, as venous return to the right and left ventricles declines and cardiac output decreases. The decrease in blood pressure initiates the baroreceptor reflex, which causes heart rate and peripheral vascular resistance to increase. This results in a small increase in blood pressure toward the end of the period of straining, which is an inadequate compensatory response. As the glottis sud-
suddenly opens and the diaphragm relaxes, intrathoracic pressure returns to normal (i.e., -2 mm Hg), and brachial artery blood pressure falls precipitously. Within seconds, however, blood pressure and pulse rate shoot up to levels well beyond normal (i.e., the overshoot of the Valsalva maneuver) as blood, waiting to enter the heart during the straining phase, suddenly floods the ventricles and markedly increases cardiac output at a time when the total peripheral resistance is still high from the vasoconstrictor response initiated toward the end of the straining phase. The high blood pressure decreases heart rate (via the baroreceptor reflex) and decreases peripheral resistance with the result that blood pressure slowly returns to its pre-straining level.

The Valsalva maneuver (with adequate blood pressure monitoring as in Figure 8-8) is useful in testing the responsiveness of the baroreceptor reflex (and the autonomic nervous system). However, for certain patients, such as those with a recent myocardial infarction, the Valsalva maneuver places an inordinate strain on the heart and should be avoided.

5. Effect of Plasma Volume on Venous Return (and Cardiac Output)

Finally, an important factor in regulating venous return is the extent to which the veins are filled with blood. It is not just the blood volume that is important, but the relationship between the amount of blood and the compliance of the veins (e.g., their sympathetic tone), because it is ultimately the ve-
nous pressure that moves blood toward the heart. This force, which is generated by veins as they contract around the volume of blood they hold, is sometimes referred to as *vis a tergo*. Also contributing to this force is the pressure transmitted through the capillaries by blood pumped into arteries. Of course the volume of blood and the pressure in veins changes constantly as blood flows continuously into veins from capillaries on one end and is pumped out by the right ventricle on the other end. Therefore, the resting recoil pressures of veins and arteries can only be measured when no blood is flowing, i.e., when the heart has stopped. We observed such resting recoil pressures upon stopping the heart during a student laboratory exercise on an anesthetized dog (Fig. 8-9). Stimulating the animal's right vagus with an electrical impulse caused sinus arrest (note the absence of P waves on the ECG tracing in the bottom panel), followed by a series of ventricular escape beats (note the large, wide QRS complexes). As the heart stopped beating, the femoral artery blood pressure decreased to a basal value of approximately 10 mmHg (middle panel) and pulmonary artery pressure equilibrated at a similar level, i.e., at about the level of the PAWP (top panel). These observations indicated that, in the absence of the heart's pumping action, blood simply flows down its pressure gradient from arteries into veins until all pressures in the circulation are equal. This equilibrium pressure is called the **mean circulatory filling pressure**. In the experiment in Fig.8-9, the mean circulatory filling pressure is about equal to the pulmonary artery wedge pressure, or about 10 mmHg (A).

When the electrical stimulus was removed from the vagus (B), systemic blood pressure returned over a period of five beats to normal (C). The sequence of events responsible for returning the dog's blood pressure to normal is shown in human terms in Figure 8-10. In this model of the peripheral circulation, we will assume that the peripheral vascular resistance is 20 mmHg/L/min.

During vagal stimulation at point A (Figs. 8-9, 8-10), cardiac output was 0 L/min and systemic arterial and venous pressures had equilibrated to a value of about 10 mmHg, i.e., the mean circulatory filling pressure (MCFP). When vagal stimulation was stopped (B), the heart resumed beating. The first beat moved some blood from central veins into the aorta and large arteries, causing the CVP to drop from 10 mm Hg to 9 mmHg and systemic mean arterial pressure to rise from 10 mmHg to 29.
mmHg. The greater increase in arterial pressure as compared to the fall in CVP for an equivalent blood volume change is explained by the much lower compliance of arteries than veins. Although the left ventricle ejects a certain stroke volume into the aorta during the first beat (B), only part of this stroke volume moves through capillaries and veins and is eventually returned to the heart. The other portion of the stroke volume was used to prime the arterial pump. In other words, the aorta and large arteries had to be first stretched to a point where the recoil pressure was sufficient to move blood through a peripheral resistance of 20 mmHg/L/min. We can calculate the amount of blood flow (the cardiac output) that occurred during the first two beats, where the average systemic mean arterial pressure was 29 mmHg and the CVP 9 mmHg, in the following way:

$$\text{CO} = \frac{\text{MSAP} - \text{CVP}}{\text{TPR}}$$

The cardiac output (CO) is equal to the difference between the mean systemic arterial pressure (MSAP) and central venous pressure (CVP) divided by the total peripheral resistance (TPR, fixed at 20 mmHg/L/min). Accordingly, during the first two heartbeats (B):

$$\text{CO} = \frac{(29 - 9) \text{ mmHg}}{20 \text{ (mmHg/ L/min)}} = 1 \text{ L/min}$$

In other words, when vagal stimulation was stopped, blood started to move around the circulation at a rate of 1 L/min during the first two heartbeats.
Five heart beats later (C), enough blood had accumulated in the aorta and large arteries to increase the systemic mean arterial pressure to 105 mmHg, and the loss of blood from the central veins had reduced CVP to 5 mmHg. Now:

\[
CO = \frac{(105 - 5) \text{ mmHg}}{20 \text{ (mmHg/ L/min)}} = 5 \text{ L/min}
\]

In other words, once the large arteries had been primed with their usual blood volume, blood again moved around the circulation at a rate of 5 L/min, which is the normal resting value for both cardiac output and venous return.

6. The Effects of CVP on Venous Return

Let us focus for a moment on the venous part of the model in Figure 8-10. For blood to flow from peripheral to central veins, pressure must be higher in the periphery than it is centrally. Thus, the greater the CVP, the smaller venous return would tend to be. We could make a graph that shows the relationship between CVP and venous return (Fig. 8-11). For example, when the heart is stopped, venous return falls to 0 L/min, and CVP rises to 10 mmHg (Fig. 8-11,A, point A), which is the MCFP. As the heart starts beating (Figs. 8-9,B and 8-10,B), the right ventricle removes blood from the central veins so that the CVP falls from 10 to 9 mmHg, and venous return increases to 1 L/min (Fig.8-11,A, point B). Once the heart is beating normally (Figs. 8-9,C and 8-10,C), CVP decreases to 5
mmHg, and venous return increases to 5 L/min (8-11,A, point C).

In addition to the normal venous return curve, other curves may be drawn to depict conditions in which the mean circulatory filling pressure is increased or decreased from normal (Fig. 8-11,A). For example, when the plasma volume is increased (hypervolemia) or the walls of the venous capacitance vessels are tensed (venoconstriction), the CVP will increase at any given level of venous return. This will cause the venous return curve to shift to the right. Such rightward shifts in the venous return curve are seen, for instance, in patients with right ventricular failure or in patients who have been overtransfused with isotonic saline (e.g., Fig. 3-17).

On the other hand, when the blood volume is reduced (hypovolemia) or the capacitance vessels are relaxed (venodilation), the CVP will be decreased at any given level of venous return. This will cause the venous return curve to shift to the left. Such leftward parallel shifts in the venous return curve are seen, for instance, in patients who have been hemorrhaging or in patients with severe diarrhea who are volume depleted (e.g., Fig. 3-14).

Venous return curves may not only be shifted (in parallel), but also rotated upward or downward as the total peripheral resistance is decreased or increased, respectively (Fig. 8-11,B). For example, an increase in sympathetic outflow to arterioles will increase total peripheral resistance (arteriolar constriction) and will cause the venous return curve to be rotated downward. On the other hand, a decrease in sympathetic outflow to arterioles
will decrease the total peripheral resistance (arteriolar dilation) and will cause the venous return curve to rotate upward.

Note that sympathetic stimulation of arterioles produces opposite effects on venous return than does sympathetic stimulation of veins (see Fig. 8-11,A). Note also that the MCFP is not influenced by constriction or relaxation of arterioles. The reason for this is as follows. If the arterioles were more constricted when the heart was stopped in the dog experiment in Figure 8-9, systemic arterial blood pressure would have declined more slowly, but would eventually have reached the same MCFP pressure of 10 mmHg. Similarly, if the arterioles had been more dilated when the heart was stopped, arterial pressure would have fallen more rapidly, but the same MCFP would be reached.
Graphic Analysis of Cardiac Output and Venous Return
We can now combine the curves for cardiac output and venous return as a function of CVP (or PAWP) into a single graph (Fig. 8-12). Similar graphs have been employed by Guyton, who used right atrial pressure as the independent variable, to analyze the relationship between cardiac output and venous return in a variety of common physiological as well as clinical situations. Because cardiac output must equal venous return (at least over a short time interval) a person's circulation will stabilize at the point of intersection between venous return and cardiac output. At rest, this point is at a CVP of about 5 mmHg (for the right ventricle) or at a PAWP of 10 mmHg (for the left ventricle) when venous return and cardiac output are 5 L/min.

1. Graphic Analysis of Exercise

Point A on the graph in Figure 8-13 represents a person at rest with a cardiac output of 5 liters/min and a CVP of 5 mmHg. As he anticipates exertion, sympathetic cholinergic nerves cause vasodilation in skeletal muscle and a decrease in the total peripheral resistance. This causes an increase in venous return and results in an upward rotation of the venous return curve. Note that the curve is rotated upward rather than shifted in parallel to the left, so that the MCFP (i.e., the pressure when cardiac output and venous return are 0 liters/min) has not changed. As a consequence of this decrease in total peripheral resistance, and a relatively normal heart cannot handle the excessive load (high output failure). A good example of a pa-
A patient with high cardiac output failure is a man with severe anemia.

Let us assume that he was at point A in figure 8-14 when he was not anemic. As his hemoglobin concentration gradually fell from 15 gm/dL to less than 7 gm/dL, his total peripheral resistance gradually decreased, presumably due to a combination of diminished blood viscosity and release of vasodilator substances from hypoxic tissues. His cardiac output increased progressively.
sively from A to B to C as his venous return curve rotated upward. Unlike a young person with a normal heart (Fig. 8-13), the 95 year old man in our example, whose heart had been driven excessively for months, was incapable of shifting his cardiac output curve to a higher level. As a consequence, his PAWP and CVP were elevated and he had pulmonary and peripheral edema, respectively.

2. Graphic Analysis of Shock

When tissues are inadequately perfused with blood a person is said to be in shock. Shock can result from diminished venous return, i.e., circulatory shock, or from pump failure, i.e., cardiogenic shock (Fig. 8-15). Note that in circulatory shock CVP and PAWP are decreased; whereas, in cardiogenic shock these pressures are increased.

A. Circulatory Shock

Circulatory shock may result from a decrease in blood volume (hypovolemic shock), from loss of sympathetic vasomotor tone (neurogenic shock), allergic reactions (anaphylactic shock), or from toxins released in certain infections (septic shock).

Let us consider the case where a young girl had ruptured her spleen (Fig. 8-16). Internal hemorrhage resulted in a decreased mean circulatory filling pressure and a shift in the venous return curve to a lower level. At this new equilibrium point (B), her cardiac output had decreased to about one-half of normal, resulting in a decrease in
blood pressure. Within seconds the baroreceptor reflex increased heart rate and cardiac contractility, moving the equilibrium point to a higher cardiac output curve, and sympathetic stimulation decreased the compliance of capacitance vessels, which shifted the venous return curve upward and to the right, resulting in a new equilibrium point C. This latter effect, however, was offset by intense vasoconstriction (by sympathetic nerves and high circulating concentrations of epinephrine acting on alpha-1-adrenergic receptors of vascular smooth muscle) that caused the venous return curve now to rotate downward, resulting in a decrease in cardiac output to point D. This was the price that had to be paid to maintain blood pressure as high as possible in order to perfuse the most vital organs - the brain and the heart. In other words, the reduction in cardiac output was more than offset by the increase in total peripheral resistance, so that blood pressure increased (BP = CO x TPR).

The intense vasoconstriction lowered capillary blood pressure, which facilitated reabsorption of fluids from the interstitium. As this fluid was slowly added to plasma, the venous return curve shifted to the right. To continue to increase plasma volume and venous return, isotonic saline (and later whole blood) were infused intravenously in
the hospital, which moved cardiac output to point E. As the plasma volume returned to normal, the intense sympathetic outflow was no longer needed, and her pulse slowed and became fuller and her color returned as the compensatory vasoconstriction of skin vessels subsided.

B. Cardiogenic Shock

When Mr. M first came to the hospital for help, he was in a state of compensated heart failure. His ECG showed evidence of an inferior myocardial infarction, which he had suffered several years earlier. The curves in Figure 8-17 reconstruct the sequence of events that took place immediately following the heart attack.

As his left ventricle was injured as a result of the coronary occlusion, his cardiac output curve decreased and he stabilized at a new equilibrium point B, where cardiac output was reduced and pulmonary artery wedge pressure increased. The fall in blood pressure resulted, perhaps, in a short spell of dizziness or fainting, and certainly in a feeling of weakness. Within seconds, however, the baroreceptor reflex initiated the compensatory responses, which we have already considered in hemorrhagic shock. Briefly, sympathetic outflow tenses capacitance vessels, which shifts the venous return curve to the right (point C). This action, aimed at increasing cardiac output, is reserve, which he lost and which he needed when he had to exert himself. He was not normal in another important respect. His pulmonary artery wedge pressure was significantly higher than normal.

Fig. 8-17. Compensated Heart Failure. Cardiac output and venous return curves for Mr. M. Following a myocardial infarction, cardiac output dropped to a lower function curve and the equilibrium point moved from A to B. Compensation occurred by vasoconstriction and mobilization of fluids from the interstitium, shifting the equilibrium to point C. Increased sympathetic stimulation of the heart, in turn, raised cardiac output to a higher function curve so that complete compensation (normal cardiac output at rest) was obtained at point D. At point D the PAWP is elevated above normal, and the cardiac reserve is diminished.
The difference between this pressure and a pulmonary artery wedge pressure of about 27 mmHg is a safety margin for avoiding pulmonary edema.

Mr. M was in a precarious situation without an adequate cardiac reserve when his atria started to fibrillate and his ventricles contracted irregularly at about 130 beats/min. Because of the reduced stroke volume per beat, his cardiac output curve fell and he arrived at point C in Figure 8-18. Note that this curve spells trouble. It is so flat that even at its highest point it does not reach a minimum cardiac output for sustaining tissue metabolism at rest (about 5 L/min). Although the heart is once again bombarded with sympathetic stimuli, it has been stimulated for too long and norepinephrine receptors have been downregulated. The kidney, however, attempts to compensate for the reduced cardiac output by retaining more salt and water (this is mediated, as usual, by sympathetic stimuli, vasopressin, and aldosterone). Although renal compensation usually works well with a normal or near-normal heart, this strategy becomes counterproductive in a heart with a flat cardiac output curve. As days pass, the retained salt and water shifts the venous return curve progressively to the right from point C to E to F to G. Not only is the increased venous return not increasing cardiac output, but the pulmonary artery wedge pressure is continuously rising and the lungs are being pro-

Fig. 8-18. Decompensated Heart Failure. Cardiac output and venous return curves are shown for Mr. M. after he had compensated for a myocardial infarct (Fig. 8-17,D). He then develops atrial fibrillation and moves to a lower cardiac function curve and a new equilibrium point C. His heart is incapable of compensating by moving to a higher cardiac function curve with sympathetic stimulation, but his kidneys function normally and retain more salt and water, causing the venous return curve to shift progressively to the right from C to F to G. Note that the cardiac output curve is flat, so that these shifts in the venous return curve do not increase cardiac output to the minimum requirement of 5 L/min (at rest). Moreover, as PAWP exceeds a value of about 27 mmHg, pulmonary edema develops.
gressively flooded with more and more edema fluid. In addition, the ventricular chambers are becoming progressively more dilated, causing wall tension to rise according to the Laplace equation \( T = P \times \frac{R}{2} \). This means that the heart must now generate a greater than normal contractile force to overcome wall tension to eject a normal stroke volume.

Decompensated heart failure, as Mr. M had on his second visit to the hospital is a medical emergency requiring immediate intervention. Treatment included measures aimed at moving the venous return curve back to the left. This was accomplished by decreasing the preload on the heart by administering intravenous furosemide. In addition, carvedilol was administered to improve cardiac function and reduce the afterload which moved the cardiac output curve to a higher level.

Activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system are essential in increasing cardiac output acutely following myocardial injury. However, the long term effects of these two systems results in remodeling, hypertrophy, and apoptosis of the myocardium which results in a decrease in cardiac output. Indeed, clinical trials have shown that mortality from congestive heart failure is significantly reduced with the use of angiotensin-converting enzyme inhibitors (e.g., ramipril), aldosterone antagonists (e.g., spironolactone), and beta-adrenergic blockers (e.g., metoprolol, carvedilol).
Coronary and Cerebral Circulation
Coronary Circulation
1. Blood Flow to Heart Muscle During the Cardiac Cycle

About 4% of the cardiac output (or 200 ml/min) is distributed to the heart. The cardiac blood supply is derived almost entirely from the coronary arteries, not from blood in the chambers. This blood flows through the right and left coronary arteries to atrial and ventricular muscle (Fig. 9-4). The left coronary divides into an anterior descending branch and a circumflex branch. Between these three major arteries and their branches are a limited number of collaterals. These collaterals are normally not well developed so that sudden occlusion of a major coronary artery will result in a myocardial infarction. Gradual occlusion over a period of several months, however, may not result in a myocardial infarction because, given adequate time, more (and larger) collateral vessels develop which carry an increasing amount of blood to circumvent obstructed sections of arteries.

Blood flows into the coronaries at the ostia (entrances) at the root of the aorta behind the valve cusps. The rate of flow will depend on two factors: (1) the pressure in the aorta and (2) the resistance to flow in the coronaries. Both aortic pressure and flow to right and left ventricles change during the cardiac cycle, as shown in Figure 9-5.

This figure shows the aortic pressure (A) and blood flow through the coronaries to the right (B) and left (C) ventricles measured simultaneously during the cardiac cycle. Changes in blood flow to the right ventricle over the cardiac cycle are shown to have a pattern similar to changes in blood pressure in the aorta. That is, the tissues of the right ventricle are better perfused during systole, when aortic pressure is high, than during diastole, when aortic pressure is reduced. Right ventricular flow is not reduced during systole, because ventricular
pressure during systole (e.g., 25 mmHg) is much lower than aortic (or coronary artery) pressure (e.g., 120 mmHg), so that vessels in the right ventricle are not compressed. By contrast, left ventricular flow is markedly reduced during systole due to compression of coronaries by the high intraventricular pressure, especially during the isovolumic phase of left ventricular muscle contraction. Therefore, the cells that make up left ventricle receive most of their blood supply during diastole when intraventricular pressure is low and vessels are no longer compressed. Thus, we would expect that when the duration of diastole is shorter (when the heart rate increases, for instance), that coronary perfusion of the left ventricle would be decreased. There is a compensatory mechanism, however. When the heart rate increases, vasodilators, such as adenosine are released by myocardial cells that diminish the resistance to blood flow in the coronary blood vessels and thus help maintain coronary perfusion.

2. Regulation of Blood Flow in Coronary Vessels

Vessels in the subendocardium of the left ventricle are more compressed during systole than vessels in the epicardium. To minimize differences in blood flow during diastole to the inner and outer surfaces of the heart, vessels in the subendocardium are interconnected with a more extensive network of collaterals. Moreover, the vessels in the subendocardium are richer in beta2-adrenergic receptors that cause vasodilation when occupied by epinephrine.
Sympathetic nerves (and the presence of alpha-1-adrenergic receptors on vascular smooth muscle) can cause coronary artery constriction. This tendency for constriction by activation of the sympathetic nervous system (e.g., as with exercise, excitement, or circulatory shock) is overridden by local metabolic regulation, which is very powerful in the heart. Thus, whenever the heart is stimulated to contract more forcefully and more rapidly, the increased metabolism of myocardial cells leads to formation of more adenosine (as well as other vasodilator substances) which, in turn, causes relaxation of arteriolar smooth muscle and increased blood flow to active cells.

Intravenous infusions of adenosine have been shown to be highly effective in terminating paroxysmal supraventricular tachycardia (PSVT). It is, therefore, tempting to speculate that in the normal heart the vasodilator metabolite, adenosine, not only helps ensure adequate blood flow to cardiac tissues but also prevents or corrects arrhythmias that are prevalent when tissues are ischemic.

3. Oxygen Supply and Demand

Skeletal muscle extracts little oxygen from blood at rest, but during exercise it extracts nearly all the oxygen from blood flowing through its capillary beds. In contrast, the heart extracts about 50% of oxygen at rest and extracts no more during exercise. Instead, the heart increases oxygen delivery to its own cells by increasing blood flow. It does this by increasing cardiac output without increasing its share (about 4%) of the cardiac output. Thus, if oxygen demand by heart muscle increases threefold (e.g., from 20 ml/min to 60 ml/min), the extra oxygen is supplied by increasing the cardiac output threefold (e.g., from 5 to 15 liters/min). When the demand for oxygen exceeds its supply, heart muscle shifts to anaerobic metabolism which produces excess lactic acid. Lactic acid and/or other products of metabolism (including perhaps the release of kinin-like substances and adenosine) trigger a sensation of pain. This pain is, of course, angina pectoris.

The common, stable type of angina pectoris that is provoked by exertion and subsides with rest is caused by relatively fixed obstructions of coronaries by atheromatous plaques - usually involving all three major coronary vessels. Because vessels in the subendocardium are compressed most during systole, ischemia starts first in this area, causing ST segment depression.
and T wave inversion on the ECG during anginal attacks.

In some persons, angina occurs at night or during rest. This phenomenon, Prinzmetal's angina, is thought to be caused by vascular spasms. The reasons for such spasms are unclear, even though it is well known that coronary vessels do have alpha-1-adrenergic receptors that are capable of triggering vasoconstriction when occupied by norepinephrine. Normally, however, it is believed that such tendencies for vasoconstriction are overruled by local release of adenosine. Because the spasms leading to Prinzmetal's angina are not limited to subendocardial vessels, ST segment elevations (rather than ST segment depression) are seen with this form of atypical angina.

People with stable angina pectoris are given nitroglycerine tablets. The major action of nitroglycerine is to relax smooth muscle in large veins. This diminishes venous return to the heart and decreases ventricular preload. In addition, nitroglycerine (to a lesser extent) also decreases the afterload by relaxing arteriolar smooth muscle. The decrease in preload and afterload, in turn, diminishes the oxygen requirements of the heart and the balance between oxygen supply and oxygen demand is once again established so that the pain subsides. Nitroglycerine has little or no effect on enhancing blood flow past the point of obstruction in the coronaries. Vessels that are distal to the point of obstruction will already be maximally dilated from the release of adenosine and other vasodilators released from ischemic cells. In Prinzmetal's angina, the vasospasm is usually relieved with a calcium channel blocker, which relaxes vascular smooth muscle.

When chest pain (due to activation of cardiopulmonary afferents) persists even with nitroglycerine and rest, unstable angina or a myocardial infarction is suspected. In either case, patients with such pains must be taken without delay to a cardiac care unit for evaluation and treatment.

A major concern in managing patients with acute heart attacks is to minimize the size of the infarcted area. The final extent of the infarction is not determined immediately after the initial insult. As shown in Figure 9-6, the size of an infarction may increase if the injured heart is not allowed to rest. Right next to the area of infarction is an area of injury, and next to it is an area of ischemia (Fig. 9-6,A). Blood supply is borderline, at best, in the areas of injury and ischemia. If a patient such as Mr. A were to exert himself or become excited and the heart was
stimulated to beat faster and more forcefully, the undamaged areas of the heart would release adenosine (and other substances, such as lactic acid or carbon dioxide) which would cause vessels to dilate (Fig. 9-6,B). This, in turn, would cause blood to be diverted from injured tissues (where resistance to blood flow remains high from the thrombosis) to healthy tissues. This circumstance is appropriately called the **coronary steal phenomenon**. Stealing blood from an area of ischemia will convert it to an area of injury; stealing blood from an area of injury will convert it to an area of infarction. For this reason Mr. A was not permitted to walk down the stairs --as he had requested --but he was instead carried on a stretcher by the firemen.

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**Fig. 9-6. The coronary steal phenomenon.**
A. Sudden occlusion of the anterior descending branch of the left coronary artery is shown to produce an acute anterior septal infarct. B. Exercise (or any maneuver that increases myocardial oxygen consumption, such as an increase in heart rate or myocardial contractility) causes the release of adenosine, which dilates coronary vessels (without decreasing the degree of obstruction by the thrombus) and, thereby, diverts blood flow from the anterior descending to the circumflex branch of the left coronary artery. This causes expansion of the infarct.
Cerebral Circulation
1. Functional Anatomy of the Cerebral Circulation

Although the brain contributes only 2% to body weight, it consumes about 20% of the body's oxygen and receives about 15% of the cardiac output. This blood flows to the brain by two separate systems: the internal carotid arteries (located laterally in the neck) and the vertebral arteries (located posteriorly in the neck), (Fig. 9-7). Blood flows from the carotid and vertebral arteries into a circular conduit (the circle of Willis) from where blood is distributed to the various parts of the brain via the anterior, middle, and posterior cerebral arteries. Blood drains from the brain by veins that empty into the superior sagittal sinus and returns to the heart by the jugular and vertebral veins in the neck. The neck veins are normally collapsed because the flow of blood into the heart creates a partial vacuum. The superior sagittal sinus, however, cannot collapse (despite the vacuum within) because its walls are anchored to the bones of the skull. Thus, if the sagittal sinus is nicked during surgery, air will rush in and form an air-embolus that will travel to the heart and lungs where it will block blood flow (pulmonary embolus).

2. The Blood-Brain Barrier

Between the arteries and veins of the brain are capillary networks, as are found elsewhere in the body. Capillaries of the brain, however, are different in one important regard: brain capillaries are considerably less permeable to solutes. Brain capillaries have unusually tight junctions between endothelial cells and have a thick basement membrane that is supported by foot processes of astrocytes (non-neural brain cells with a connective tissue function). This diffusion barrier between blood and brain interstitial fluid is called the blood-brain barrier.

The blood-brain barrier cannot be readily penetrated by ions (e.g., $\text{Na}^+$, $\text{K}^+$, $\text{H}^+$, or $\text{HCO}_3^-$) or other polar solutes (e.g., glucose or amino acids), unless the endothelial cell has specific transport proteins for such substances; even then, transport is relatively slow. In contrast, nonpolar solutes such as alcohol or other substances that influence behavior, such as diazepam, heroin, or nicotine, have high oil/water partition coefficients and readily penetrate the blood-brain barrier by diffusing through the lipid portion of cell membranes. For this reason, nonpolar antibiotics are much more effective in treating bacterial meningi-
tis (inflammation of the dura mater, arachnoid, and pia mater) than are polar antibiotics like penicillin.

While a blood-brain barrier is essential for protecting the brain by keeping certain solutes out, absence of a blood-brain barrier in some areas of the brain is essential for selectively allowing certain solutes out. In the hypothalamus, for example, the absence of a blood-brain barrier allows hormones (e.g., thyrotropin-releasing hormone, corticotropin-releasing hormone, gonadotropin-releasing hormone, etc.) to be released from nerve endings into capillaries from where they are carried by portal vessels to the anterior pituitary to trigger secretion of other hormones (e.g., thyroid stimulating hormone, adrenocortical stimulating hormone, and luteinizing hormone, respectively). Absence of a blood-brain barrier in this area also allows certain large polar molecules, such as angiotensin II, to enter the hypothalamus, which is essential for feedback regulation of drinking behavior. Angiotensin II is primarily synthesized in blood (in response to plasma volume depletion) and must reach thirst centers in the lateral hypothalamus to initiate drinking.

3. Cerebrospinal fluid

A. Secretion and Absorption of Cerebrospinal Fluid (CSF)

The brain floats in about 150 ml of CSF that fills the four ventricles and covers the surface of the brain in the subarachnoid space where it serves as a protective cushion, preventing the brain from hitting the hard cranium during sudden movements. CSF is not stagnant, but is continuously secreted by the choroid plexus into the cerebral ventricles from where it flows through the aqueduct of Sylvius down the spinal cord and back up over the brain in the subarachnoid space where the arachnoid villi absorb CSF back into the superior sagittal sinus (Fig. 9-7). In the process, CSF is replaced about four times daily, i.e., about 600 ml of CSF is secreted and absorbed each day. Roughly 400 ml/day of CSF is formed by the choroid plexus. This secretory organ consists of a plexus of capillaries, supported by connective tissue and covered with a layer of secretory epithelial cells. These vascular structures are found in the walls of the ventricles, especially in the lateral ventricles of the cerebrum. The rest of the CSF (200 ml/day) comes from interstitial fluid that percolates through brain tissue and seeps across the pia mater (a single layer of cells covering
the brain and ventricular surfaces) into the ventricles or subarachnoid space. In other organs, excess interstitial fluid is returned to the circulation by lymphatics. The brain, however, does not have lymphatics; CSF serves this function.

B. Composition of CSF

The secretory epithelial cells of the choroid plexus as well as the endothelial cells of brain capillaries generate and maintain differences in the solute composition between CSF and blood (Fig. 9-7). Significantly, the pH and potassium concentration of CSF are lower than values found in blood. Small changes in hydrogen, potassium, calcium, or magnesium ion concentration have marked effects on signal transduction in neuronal circuits, so that the concentrations of these ions in CSF are carefully maintained despite fluctuations in their plasma concentrations. (Recall from the Nernst equation that the resting membrane potential of nerve cells is primarily a potassium diffusion potential.) When CSF potassium concentration increases, more potassium ions are pumped out of the CSF by sodium/potassium ATPases in membranes of choroid plexus cells (see Fig. 9-7). When CSF hydrogen ion concentration increases in respiratory failure from accumulation of carbon dioxide (respiratory acidosis), the choroid plexus cells pump more hydrogen ions into blood on hydrogen/sodium antiporters and deliver more bicarbonate ions to CSF on bicarbonate/chloride antiporters, which raises CSF pH toward normal (pH 7.33 in CSF, not 7.40 as in arterial blood!).
The concentration of glucose is normally about 20 mg/dl lower in CSF than it is in blood. In bacterial meningitis, however, when glucose in CSF is consumed by bacteria and white blood cells, glucose is reduced by more than 20 mg/dl. Although diffusion of glucose from blood into CSF requires special sodium-dependent transport proteins, the rate of transport into brain (unlike glucose transport into muscle) does not depend upon insulin, so that brain cells of patients with diabetes mellitus are not deprived of glucose.

The concentration of proteins is much lower in CSF than it is in blood (35 mg/dL versus 7,000 mg/dL). This is partly due to the very tight junctions between endothelial cells in brain capillaries and partly due to a lack of protein transport through endothelial cells by pinocytosis, which occurs in systemic capillaries. Diseases that disrupt the blood-brain barrier (e.g., meningitis) are typically associated with high CSF protein concentrations, because plasma proteins simply leak across the defective barrier into CSF.

C. Sampling CSF

CSF fluid is analyzed for its protein, electrolyte, and glucose concentration and examined for bacteria and the presence of blood cells when diseases of the central nervous system (e.g., meningitis, cerebral hemorrhage, Guillain-Barre syndrome, poliomyelitis or tumors) are suspected on physical examination. To obtain a CSF fluid sample, a lumbar puncture is performed. The patient lies on his or her side with back and neck flexed (chin almost touching knees). A long spinal needle is inserted into the spinal cord at a level where it is least likely to cause nerve damage (usually between lumbar segments 3 and 4). When a manometer is attached to the needle a pressure of 10-20 cm H₂O is normally observed. This CSF pressure is similar to venous pressure. To ensure that CSF is flowing freely between the ventricles and the spinal cord, the jugular veins in the neck are compressed. This causes blood to accumulate in the head, where the increased blood volume compresses CSF in the cerebral ventricles. This pressure, in turn, is transmitted to the spinal cord where the increased pressure causes CSF to rise in the manometer (Queckenstedt test). When the aqueduct of Sylvius is blocked, so that CSF cannot flow freely from the ventricles to the spinal cord, the manometric pressure does not rise when the neck veins are compressed.
Before performing a lumbar puncture (especially if a fluid sample is to be taken for analysis), it is important to check for signs of raised intracranial pressure. This is done by looking at the patient’s retina with an ophthalmoscope. When CSF pressure increases, edema fluid forces itself along retinal vessels, bulging the optic disc and blurring its margins (papilledema). If a spinal fluid sample is removed in the presence of an elevated intracranial pressure, the sudden drop in fluid pressure in the spinal cord may cause the brain to be forced downward and damage vital centers in the brain stem, which is usually fatal.

4. Increased Intracranial Pressure

A. The Kellie-Monro Doctrine

Brain cells, blood, interstitial fluid, and CSF occupy the space in the cranium. If any of these four volumes increases, intracranial pressure must rise (Kellie-Monro doctrine), resulting in mental obtundation that usually progresses to coma and death if not treated. (1) Brain cells require more intracranial space when they swell from hypoxemia (e.g., cardiac arrest) or from hyponatremia (e.g., syndrome of inappropriate ADH secretion), or when they differentiate into tumor cells and multiply. (2) Blood requires more space when outflow via the jugular veins is obstructed (Queckenstedt test) or when a blood vessel ruptures following head trauma and blood clots in the subdural space (subdural hematoma). (3) Head trauma may increase capillary permeability, allowing proteins to leak into the interstitium, which leads to accumulation of fluids in this space. Because there is no extra room, this (initially) localized edema compresses veins, raising venous pressure proximal to the point of obstruction and causing more fluid to leak into the interstitium, which compresses more veins. The cycle repeats itself, resulting in generalized brain edema and often in coma. (4) The volume of fluid in the cerebral ventricles increases when the choroid plexus continues to secrete CSF but the arachnoid villi fail to absorb it because of an obstruction or disease. When a congenital malformation blocks the aqueduct of Sylvius in infants, in whom the cranial bones have not yet fused into the rigid structure of the adult cranium, the head expands to accommodate the increased volume of CSF. This condition is called hydrocephalus. A similar obstruction after the cranial bones have fused, causes expansion of the cerebral ventricles at the expense of the surrounding brain tissue. This is one of the few curable causes of dementia, be-
cause compression of brain tissue can be prevented by relieving the high intraventricular pressure with a tube that shunts CSF around the point of obstruction into the atrium or peritoneum.

**B. Circulatory Adaptation to Increased Intracranial Pressure**

The circulatory system adapts to an increase in intracranial pressure. For example, when a tumor diminishes blood flow to part of the brain by compressing blood vessels, carbon dioxide and other metabolites accumulate in the underperfused tissues, triggering an increase in sympathetic outflow from the vasomotor center in the medulla. Activation of sympathetic nerves and release of epinephrine increase cardiac contractility and divert blood from the kidneys, gut, skin, and muscle to the brain. Systemic blood pressure rises rapidly to a level where flow through the obstructed vessels is reestablished, and the excess carbon dioxide is washed away (Cushing response). Blood pressure then stabilizes at this higher set point. If the obstruction cannot be overcome, despite an increase in systolic blood pressure by roughly 50 mmHg, the patient usually lapses into a coma.

The sudden increase in blood pressure (due to increased intracranial pressure) stretches baroreceptors in the carotid sinuses, resulting in reflex bradycardia. In this situation, sympathetic stimulation of the SA node, which tends to increase heart rate, is overridden by more powerful parasympathetic stimulation of the SA node, which tends to decrease heart rate.

**5. Regulation of Cerebral Blood Flow**

**A. Autoregulation**

Besides stimulating the vasomotor center, carbon dioxide has another important function in enhancing blood flow to selected areas of the brain. An increase in metabolism in one area of the cortex causes local release of carbon dioxide, which dilates vessels and increases blood flow to that region. Reading, for example, will increase oxygen consumption and carbon dioxide production by neurons in Wernicke's area of the cerebrum (see Fig. 9-8), resulting in more blood flow to that part of the brain involved in language comprehension. The increased local concentration of carbon dioxide relaxes vascular smooth muscle by forming hydrogen ions in brain interstitial fluid, i.e.,

\[
\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{HCO}_3^-
\]
A decrease in carbon dioxide constricts vascular smooth muscle by reducing the concentration of hydrogen ions in brain interstitial fluid. This explains why a person feels dizzy when he or she hyperventilates. During hyperventilation (e.g., during an anxiety attack), excessive amounts of carbon dioxide are exhaled, so that the concentration (or gas tension) of carbon dioxide in blood decreases. Because carbon dioxide has a high oil/water partition coefficient, carbon dioxide equilibrates rapidly across the blood-brain barrier, decreasing carbon dioxide tension and hydrogen ion concentration in brain interstitial fluid. The low hydrogen ion concentration (high pH) constricts blood vessels and decreases delivery of oxygen and nutrients, such as glucose, to brain cells, causing the person to become light headed or even faint.

B. Neural Regulation

While circulatory adjustments between different regions of the brain are achieved primarily by autoregulatory mechanisms involving carbon dioxide, blood flow to the whole brain is regulated by the pumping action of the heart and by changes in the peripheral vascular resistance. Thus, brain perfusion increases or decreases to match the metabolic needs of all of its component neurons. Although sympathetic fibers (from the Stellate ganglia) do innervate brain vessels, their function is not clear. Presumably, they do not constrict cerebral vessels at the same time as sympathetic fibers constrict peripheral blood vessels, e.g., during hemorrhage, because that would be counterproductive. Experimental evidence has suggested that sympathetic fibers to brain vessels may serve a buffering function by constricting on those few occasions when a sudden surge in blood pressure (e.g., during exercise or an emotional outburst) might otherwise rupture a brain vessel. Moreover, sympathetic fibers may protect the brain from edema when blood pressure is high.


The classical method for measuring blood flow to the brain uses the Fick principle, which we have discussed previously in the context of measuring blood flow to the lungs. To measure cerebral blood flow, we measure nitrous oxide uptake by the brain. The subject breathes a gas mixture containing 15% nitrous oxide, which dissolves in blood and readily penetrates the blood-brain barrier and is taken up by brain cells. The amount of nitrous oxide extracted by brain tissue as a function of time ($Q$), divided by the difference in ni-
tros oxide concentration in arterial ($A_N^2O$-any artery) and venous (jugular) blood ($V_N^2O$), equals the cerebral blood flow (CBF).

$$CBF = Q_{N^2O}/[A_N^2O] - [V_N^2O]$$

At rest, the cerebral blood flow is about 15% of the cardiac output. When cardiac output is increased (e.g., during exercise), a smaller fraction of the cardiac output is delivered to the brain to keep blood flow constant. However, when cardiac output is reduced (e.g., in hemorrhage) a higher fraction of the cardiac output is delivered to the brain at the expense of blood flow to the kidneys, gut, skin, and muscle. About 75% of the cerebral blood flow perfuses the cortical gray matter (containing the bodies of nerve cells) and the remaining 25% the white matter (deep cerebral tissue containing the axons of nerves and astrocytes). Even though there is considerably more white than gray matter in the brain, differences in blood flow reflect the fact that oxygen consumption is much greater in gray than in white matter.

Even though blood flow to the brain as a whole is quite stable, blood flow to different regions of the brain changes with behavior. Such regional changes in cerebral blood flow can be measured with positron emission tomography (PET) brain scans. A non-metabolizable sugar, deoxyglucose, is labeled with a positron emitter, e.g., carbon$^{11}$, and injected. The $^{11}$C-deoxyglucose moves across the blood-brain barrier and accumulates in areas of the brain that are metabolically most active. When carbon$^{11}$ decays, gamma rays are emitted that are quantified by scanners placed around the head. This information is combined with computerized tomography to give the precise anatomic location where $^{11}$C-deoxyglucose is accumulating. As the subject engages in different tasks, e.g., reading, thinking about the meaning of a word, or playing the piano, the PET scan (displayed on a video screen) shows different areas of the brain “lighting up”. In this way it is becoming possible to correlate behavior with anatomical structures of the brain and to construct functional maps of the brain. Interestingly, the distribution of positron emitters is altered in patients with Alzheimer's disease and in some with schizophrenia. The carbon$^{11}$-label (or other positron emitters, such as nitrogen$^{13}$, oxygen$^{15}$, or fluorine$^{18}$) can be placed on neuroleptic drugs, such as haloperidol. This makes possible a correlation of the site of drug action with its amelioration of psychotic symptoms.
7. Cerebro-vascular Accidents

Cerebro-vascular accidents (strokes) result from occlusion of a cerebral blood vessel (usually due to atherosclerosis or thrombosis) or from hemorrhage (usually due to rupture of a congenital aneurysm or due to hypertension). The affected brain cells become ischemic and die (cerebral infarct) if blood flow is not rapidly reestablished. When the ischemia is transient and symptoms such as weakness, slurred speech, or dizziness last only a few minutes (less than one hour), the episode is referred to as a transient ischemic attack (TIA). TIAs serve as a warning that a stroke may soon follow.

Strokes most often affect the middle cerebral artery. This reduces or stops blood flow to much of the cerebrum, including parts of the frontal, parietal, temporal, and occipital lobes (see Fig. 9-8). Damage done to neurons of the motor cortex in the frontal lobe results in weakness or paralysis of limbs (arms more than legs) on the contralateral side of the infarct, because nerve fibers from motor cortex to muscle cross to the other side of the body between the brain and the spinal cord. Injury to neurons of the parietal lobe results in impaired sensation of pressure, pain, and temperature. Moreover, the normal sense of joint position i.e., the position of a limb in space, is lost (ataxia), which contributes to the characteristic unsteady gait. Fine discrimination by touching or feeling an object is also lost (astereognosis). Thus, if you ask the patient to close his or her eyes and place a dime in his or her hand, he or she will not be able to distinguish it from a nickel or a quarter. If Broca’s area in the left cerebral hemisphere is affected (and the person is right-handed), the patient will have difficulty in the mechanics of speaking and writing (Broca’s aphasia), although he or she will comprehend language and will be able to read. If Wernicke’s area, however, is affected, the patient will not be able to comprehend the
written or spoken word (Wernicke's aphasia).

The left hemisphere is dominant for language in over 95% of right-handed individuals and in more than half of those who are left-handed. If the right hemisphere is affected in such individuals, ability to communicate is largely preserved, but spatial perception is impaired. This may cause difficulties in performing simple tasks, such as getting dressed (dressing apraxia) or finding one's way. Some patients seem unaware of the left half of their bodies and will tend to neglect that half (hemineglect). Brain functions and the loss of these functions are obviously much more complex than the few examples given here to illustrate the effects of obstructing blood flow in the middle cerebral artery. Hearing, sight, memory, affect, emotions, reasoning, balance, consciousness, and automatic processes such as breathing may all be affected when blood flow to specific areas of the brain is diminished by obstruction or hemorrhage of a cerebral blood vessel.
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