CHAPTER

20

Cardiovascular Physiology & Anesthesia

KEY CONCEPTS

1. In contrast to action potentials in axons, the spike in cardiac action potentials is followed by a plateau phase that lasts 0.2–0.3 sec. Whereas the action potential for skeletal muscle and nerves is due to the abrupt opening of voltage-gated sodium channels in the cell membrane, in cardiac muscle it is initiated by voltage-gated sodium channels (the spike) and maintained by voltage-gated calcium channels (the plateau).
2. Potent inhalational agents depress sinoatrial (SA) node automaticity. These agents seem to have only modest direct effects on the atrioventricular (AV) node, prolonging conduction time and increasing refractoriness. This combination of effects likely explains the frequent occurrence of junctional tachycardia when an anticholinergic agent is administered for sinus bradycardia during inhalation anesthesia; junctional pacemakers are accelerated more than those in the SA node.
3. Studies suggest that volatile anesthetics depress cardiac contractility by decreasing the entry of Ca^{2+} into cells during depolarization (affecting T- and L-type calcium channels), altering the kinetics of its release and uptake into the sarcoplasmic reticulum, and decreasing the sensitivity of contractile proteins to calcium.
4. Because the normal cardiac index (CI) has a wide range, it is a relatively insensitive measurement of ventricular performance. Abnormalities in CI therefore usually reflect gross ventricular impairment.
5. In the absence of hypoxia or severe anemia, measurement of mixed venous oxygen tension (or saturation) is an excellent estimate of the adequacy of cardiac output.
6. Patients with reduced ventricular compliance are most affected by loss of a normally timed atrial systole.
7. Cardiac output in patients with marked right or left ventricular impairment is very sensitive to acute increases in afterload.
8. The ventricular ejection fraction, the fraction of the end-diastolic ventricular volume ejected, is the most commonly used clinical measurement of systolic function.
9. Left ventricular diastolic function can be assessed clinically by Doppler echocardiography in a transthoracic or transesophageal examination.

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10 Because the endocardium is subjected to the greatest intramural pressures during systole, it tends to be most vulnerable to ischemia during decreases in coronary perfusion pressure.

11 The failing heart becomes increasingly dependent on circulating catecholamines. Abrupt withdrawal in sympathetic outflow or decreases in circulating catecholamine levels, such as can occur following induction of anesthesia, may lead to acute cardiac decompensation.

Anesthesiologists must have a thorough understanding of cardiovascular physiology both for its scientific significance in anesthesia and for its practical applications to patient management. Anesthetic successes and failures are often directly related to the skill of the practitioner in manipulating cardiovascular physiology. This chapter reviews the physiology of the heart and the systemic circulation and the pathophysiology of heart failure.

The circulatory system consists of the heart, blood vessels, and blood. Its function is to provide oxygen and nutrients to the tissues and to carry away the products of metabolism. The heart propels blood through two vascular systems arranged in series. In the normally low-pressure pulmonary circulation, venous blood flows past the alveolar–capillary membrane, takes up oxygen, and eliminates CO_2. In the high pressure systemic circulation, oxygenated arterial blood is pumped to metabolizing tissues, and the by-products of metabolism are taken up for elimination by the lungs, kidneys, or liver.

The Heart

Although anatomically one organ, the heart can be functionally divided into right and left pumps, each consisting of an atrium and a ventricle. The atria serve as both conduits and priming pumps, whereas the ventricles act as the major pumping chambers. The right ventricle receives systemic venous (deoxygenated) blood and pumps it into the pulmonary circulation, whereas the left ventricle receives pulmonary venous (oxygenated) blood and pumps it into the systemic circulation. Four valves normally ensure unidirectional flow through each chamber. The normal pumping action of the heart is the result of a complex series of electrically driven and mechanical events. Electrical events precede mechanical ones.

The heart consists of specialized striated muscle in a connective tissue skeleton. Cardiac muscle can be divided into atrial, ventricular, and specialized pacemaker and conducting cells. The self-excitatory nature of cardiac muscle cells and their unique organization allow the heart to function as a highly efficient pump. Serial low-resistance connections (intercalated disks) between individual myocardial cells allow the rapid and orderly spread of depolarization in each pumping chamber. Electrical activity readily spreads from one atrium to another and from one ventricle to another via specialized conduction pathways. The normal absence of direct connections between the atria and ventricles except through the atrioventricular (AV) node delays conduction and enables atrial contraction to prime the ventricle.

CARDIAC ACTION POTENTIALS

At rest, the myocardial cell membrane is nominally permeable to K^+, but is relatively impermeable to Na^+. A membrane-bound Na^+–K^+-adenosine triphosphatase (ATPase) concentrates K^+ intracellularly in exchange for extrusion of Na^+ out of the cell. Intracellular Na^+ concentration is kept low, whereas intracellular K^+ concentration is kept high relative to the extracellular space. The relative impermeability

of the membrane to calcium also maintains a high extracellular to cytoplasmic calcium gradient. Movement of K^+ out of the cell and down its concentration gradient results in a net loss of positive charges from inside the cell. An electrical potential is established across the cell membrane, with the inside of the cell negative with respect to the extracellular environment, because anions do not accompany K^+. Thus, the resting membrane potential represents the balance between two opposing forces: the movement of K^+ down its concentration gradient and the electrical attraction of the negatively charged intracellular space for the positively charged potassium ions.

The normal ventricular cell resting membrane potential is –80 to –90 mV. As with other excitable tissues (nerve and skeletal muscle), when the cell membrane potential becomes less negative and reaches a threshold value, a characteristic action potential (depolarization) develops (**Figure 20–1** and **Table 20–1**). The action potential transiently raises the membrane potential of the myocardial cell to +20 mV. In contrast to action potentials in axons, the spike in cardiac action potentials is followed by a plateau phase that lasts 0.2–0.3 sec. Whereas the action potential for skeletal muscle and nerves is due to the abrupt opening of voltage-gated sodium channels in the cell membrane, in cardiac muscle, it is initiated by voltage-gated sodium channels (the spike) and maintained by voltage-gated calcium channels (the plateau). Depolarization is also accompanied by a transient decrease in potassium permeability. Subsequent restoration of normal potassium permeability and termination of sodium and calcium channel permeability eventually restores the membrane potential to its resting value.

Following depolarization, the cells are typically refractory to subsequent normal depolarizing stimuli until "phase 4." The effective refractory period is the minimum interval between two depolarizing impulses that will propagate. In fast-conducting myocardial cells, this period is generally closely correlated with the duration of the action potential. In contrast, the effective refractory period in more slowly conducting myocardial cells can outlast the duration of the action potential.

Table 20–2 lists some of the multiple types of ion channels in cardiac muscle membrane. Some are activated by a change in cell membrane voltage, whereas others open only when bound by ligands. T-type (transient) voltage-gated calcium channels play a role in phase 0 of depolarization. During the plateau phase (phase 2), Ca^{2+} inflow occurs through slow L-type (long-lasting), voltage-gated calcium channels. Three major types of potassium channels are responsible for repolarization. The first results in a transient outward K^+ current (I_{To}), the second is responsible for a short rectifying current (I_{Kr}), and the third produces a slowly acting rectifying current (I_{Ks}) that helps to restore the cell membrane potential to its resting value.

INITIATION & CONDUCTION OF THE CARDIAC IMPULSE

The cardiac impulse normally originates in the sinoatrial (SA) node, a group of specialized pacemaker cells in the sulcus terminalis, located posteriorly at the junction of the right atrium and the superior vena cava. These cells seem to have an outer membrane that leaks Na^+ (and possibly Ca^{2+}). The slow influx of Na^+, which results in a less negative resting membrane potential (–50 to –60 mV), has three important consequences: near constant inactivation of voltage-gated sodium channels, an action potential with a threshold of –40 mV that is primarily due to ion movement across the slow calcium channels, and regular spontaneous depolarizations. During each cycle, intracellular leakage of Na^+ causes the cell membrane to become progressively less negative; when the threshold potential is reached, calcium channels open, K^+ permeability decreases, and an action potential develops. Restoration of normal K^+ permeability returns the cells in the SA node to their normal resting membrane potential.

The impulse generated at the SA node is normally rapidly conducted across the atria and to the AV node. Specialized atrial fibers may speed up conduction to both the left atrium and the AV node. The AV node, which is located in the septal wall of the right atrium, just anterior to the opening of the coronary sinus and above the insertion of the septal leaflet of the tricuspid valve, is actually made up of three distinct areas: an upper junctional (AN) region, a middle nodal (N) region, and a lower junctional (NH) region. Although the N region does not

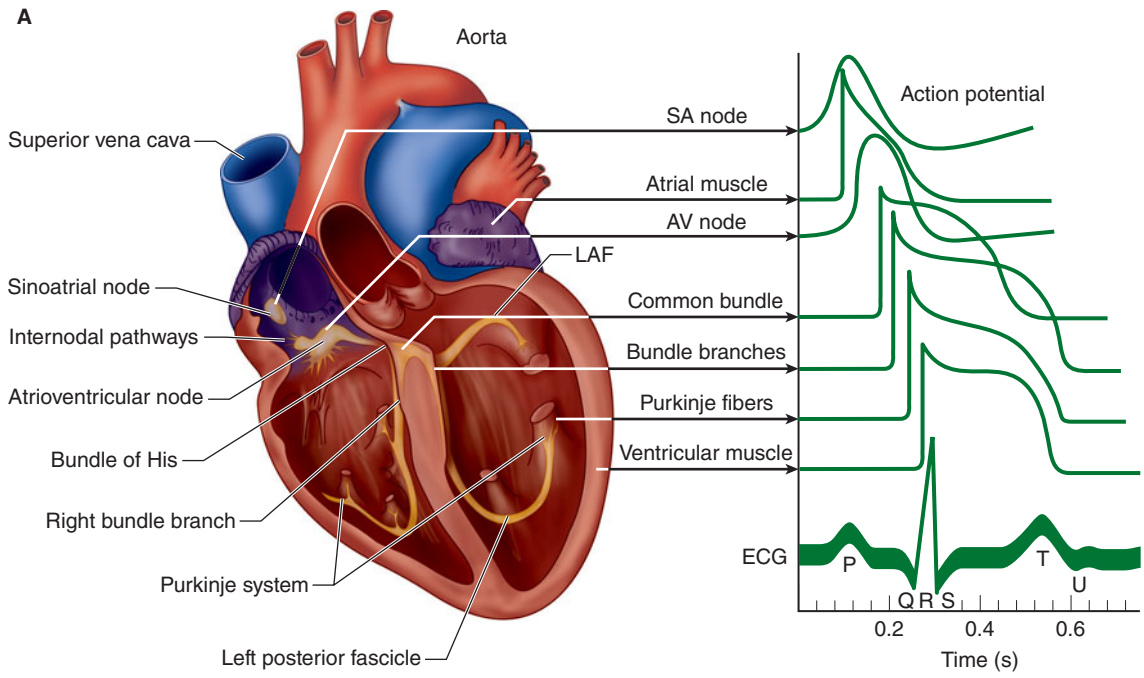


FIGURE 20–1 Cardiac action potentials. **A**: Note the characteristic contours of action potentials recorded from different parts of the heart. **B**: Pacemaker cells in the sinoatrial (SA) node lack the same distinct phases as atrial and ventricular muscle cells and display prominent spontaneous diastolic depolarization. See Table 20–1 for an explanation of the different phases of the action potential. (Modified and reproduced, with permission, from Barrett KE: Ganong's *Review of Medical Physiology*, 24th ed., McGraw-Hill, 2012.)

TABLE 20–1 Cardiac action potential.

Phase	Name	Event	Cellular Ion Movement
0	Upstroke	Activation (opening) of voltage-gated Na^+ channels	Na^+ entry and decreased permeability to K^+
1	Early rapid repolarization	Inactivation of Na^+ channel and transient increase in K^+ permeability	K^+ out (I_{To})
2	Plateau	Activation of slow calcium channels	Ca^{2+} entry
3	Final repolarization	Inactivation of calcium channels and increased permeability to K^+	K^+ out
4	Resting potential	Normal permeability restored (atrial and ventricular cells)	Na^+–K^+-ATPase pumps K^+ in and Na^+ out
	Diastolic repolarization	Intrinsic slow leakage of Ca^{2+} into cells that spontaneously depolarize	Ca^{2+} in

TABLE 20–2 Cardiac ion channels.[1]

Voltage-gated channels
Na^+
T Ca^{2+}
L Ca^{2+}
K^+
Transient outward
Inward rectifying
Slow (delayed) rectifying
Ligand-gated K^+ channels
Ca^{2+} activated
Na^+ activated
ATP sensitive[2]
Acetylcholine activated
Arachadonic acid activated

[1]From Ganong WF: *Review of Medical Physiology*, 21st ed. McGraw-Hill, 2003.

[2]ATP, adenosine triphosphate.

possess intrinsic spontaneous activity (automaticity), both junctional areas do. The normally slower rate of spontaneous depolarization in AV junctional areas (40–60 times/min) allows the faster SA node to control heart rate. Any factor that decreases the rate of SA node depolarization or increases the automaticity of AV junctional areas allows the junctional areas to function as the pacemaker for the heart.

Impulses from the SA node normally reach the AV node after about 0.04 sec, but leave after another 0.11 sec. This delay is the result of the slowly conducting small myocardial fibers within the AV node, which depend on slow calcium channels for propagation of the action potential. In contrast, conduction of the impulse between adjoining cells in the atria and in the ventricles is due primarily to activation of sodium channels. The lower fibers of the AV node combine to form the common bundle of His. This specialized group of fibers passes into the interventricular septum before dividing into left and right branches to form the complex network of Purkinje fibers that depolarizes both ventricles. In sharp contrast to AV nodal tissue, His–Purkinje fibers have the fastest conduction velocities in the heart, resulting in nearly simultaneous depolarization of the entire endocardium of both ventricles (normally within 0.03 s). Synchronized depolarization of the lateral and septal walls of the left ventricle promotes effective ventricular contraction. The spread of the impulse from the endocardium to the epicardium through ventricular muscle requires an additional 0.03 sec. Thus, an impulse arising from the SA node normally requires less than 0.2 sec to depolarize the entire heart.

2 Potent inhaled anesthetics depress SA node automaticity. These agents seem to have only modest direct effects on the AV node, prolonging conduction time and increasing refractoriness. This combination of effects likely explains the occurrence of junctional tachycardia when an anticholinergic is administered for sinus bradycardia during inhalation anesthesia; junctional pacemakers are accelerated more than those in the SA node. The electrophysiological effects of volatile agents on Purkinje fibers and ventricular muscle are complex due to autonomic interactions. Both antiarrhythmic and arrhythmogenic properties are described. The former may be due to direct depression of Ca^{2+} influxes,

whereas the latter generally involves potentiation of catecholamines, especially with halothane. The arrhythmogenic effect requires activation of both α_1- and β-adrenergic receptors. Intravenous induction agents have limited electrophysiological effects in usual clinical doses. Opioids, particularly fentanyl and sufentanil, can depress cardiac conduction, increasing AV node conduction and the refractory period and prolonging the duration of the Purkinje fiber action potential.

Local anesthetics have important electrophysiological effects on the heart at blood concentrations that are generally associated with systemic toxicity. In the case of lidocaine, electrophysiological effects at low blood concentrations can be therapeutic. At high blood concentrations, local anesthetics depress conduction by binding to sodium channels; at extremely high concentrations, they also depress the SA node. The most potent local anesthetics—bupivacaine, etidocaine, and to a lesser degree, ropivacaine—seem to have the most potent effects on the heart, particularly on Purkinje fibers and ventricular muscle. Bupivacaine binds open or inactivated sodium channels and dissociates from them slowly. It can cause profound sinus bradycardia and sinus node arrest and malignant ventricular arrhythmias; furthermore, it can depress left ventricular contractility. Twenty percent lipid emulsions have been used to treat local anesthetic cardiac toxicity. The mechanisms of action of this therapy are unclear, although possibilities include serving as a lipid reservoir and decreasing lipophilic toxic local anesthetics in the myocardium.

Calcium channel blockers are organic compounds that block Ca^{2+} influx through L-type but not T-type channels. Dihydropyridine blockers, such as nifedipine, simply plug the channel, whereas other agents, such as verapamil, and to a lesser extent, diltiazem, preferentially bind the channel in its depolarized inactivated state (use-dependent blockade).

MECHANISM OF CONTRACTION

Myocardial cells contract as a result of the interaction of two overlapping, rigid contractile proteins, actin and myosin. These proteins are fixed in position within each cell during both contraction and relaxation. Dystrophin, a large intracellular protein, connects actin to the cell membrane (sarcolemma). Cell shortening occurs when the actin and myosin are allowed to fully interact and slide over one another. This interaction is normally prevented by two regulatory proteins, troponin and tropomyosin; troponin is composed of three subunits (troponin I, troponin C, and troponin T). Troponin is attached to actin at regular intervals, whereas tropomyosin lies within the center of the actin structure. An increase in intracellular Ca^{2+} concentration (from about 10^{-7} to 10^{-5} mol/L) promotes contraction as Ca^{2+} ions bind troponin C. The resulting conformational change in these regulatory proteins exposes the active sites on actin that allow interaction with myosin bridges (points of overlapping). The active site on myosin functions as a magnesium-dependent ATPase whose activity is enhanced by the increase in intracellular Ca^{2+} concentration. A series of attachments and disengagements occur as each myosin bridge advances over successive active sites on actin. Adenosine triphosphate (ATP) is consumed during each attachment. Relaxation occurs as Ca^{2+} is actively pumped back into the sarcoplasmic reticulum by a Ca^{2+}–Mg^{2+}-ATPase; the resulting drop in intracellular Ca^{2+} concentration allows the troponin–tropomyosin complex to again prevent the interaction between actin and myosin.

Excitation–Contraction Coupling

The quantity of Ca^{2+} ions required to initiate contraction exceeds that entering the cell through slow calcium channels during phase 2. The small amount that does enter through slow calcium channels triggers the release of much larger amounts of Ca^{2+} stored intracellularly (calcium-dependent calcium release) within cisterns in the sarcoplasmic reticulum.

The action potential of muscle cells depolarizes their T systems, tubular extensions of the cell membrane that transverse the cell in close approximation to the muscle fibrils, via dihydropyridine receptors (voltage-gated calcium channels). This initial increase in intracellular Ca^{2+} triggers an even greater Ca^{2+} inflow across ryanodine receptors, a nonvoltage-dependent calcium channel in the sarcoplasmic reticulum. The force of contraction is directly dependent on the magnitude of the initial Ca^{2+} influx. During relaxation, when the slow channels close, a

membrane-bound ATPase actively transports Ca^{2+} back into the sarcoplasmic reticulum. Ca^{2+} is also extruded extracellularly by an exchange of intracellular Ca^{2+} for extracellular sodium by an ATPase in the cell membrane. Thus, relaxation of the heart also requires ATP.

The quantity of intracellular Ca^{2+} available, its rate of delivery, and its rate of removal determine, respectively, the maximum tension developed, the rate of contraction, and the rate of relaxation. Sympathetic stimulation increases the force of contraction by raising intracellular Ca^{2+} concentration via a β_1-adrenergic receptor-mediated increase in intracellular cyclic adenosine monophosphate (cAMP) through the action of a stimulatory G protein. The increase in cAMP recruits additional open calcium channels. Moreover, adrenergic agonists enhance the rate of relaxation by enhancing Ca^{2+} reuptake by the sarcoplasmic reticulum. Phosphodiesterase inhibitors, such as inamrinone, enoximone, and milrinone, produce similar effects by preventing the breakdown of intracellular cAMP. Digitalis glycosides increase intracellular Ca^{2+} concentration through inhibition of the membrane-bound Na^+–K^+-ATPase; the resulting small increase in intracellular Na^+ allows for a greater influx of Ca^{2+} via the Na^+–Ca^{2+} exchange mechanism. Glucagon enhances contractility by increasing intracellular cAMP levels via activation of a specific nonadrenergic receptor. The new agent levosimendan is a calcium sensitizer that enhances contractility by binding to troponin C. In contrast, release of acetylcholine following vagal stimulation depresses contractility through increased cyclic guanosine monophosphate (cGMP) levels and inhibition of adenylyl cyclase; these effects are mediated by an inhibitory G protein. Acidosis blocks slow calcium channels and therefore also depresses cardiac contractility by unfavorably altering intracellular Ca^{2+} kinetics.

3 Studies suggest that volatile anesthetics depress cardiac contractility by decreasing the entry of Ca^{2+} into cells during depolarization (affecting T- and L-type calcium channels), altering the kinetics of its release and uptake into the sarcoplasmic reticulum, and decreasing the sensitivity of contractile proteins to Ca^{2+}. Halothane and enflurane seem to depress contractility more than isoflurane, sevoflurane, and desflurane. Anesthetic-induced cardiac depression is potentiated by hypocalcemia, β-adrenergic blockade, and calcium channel blockers. Nitrous oxide also produces concentration-dependent decreases in contractility by reducing the availability of intracellular Ca^{2+} during contraction. The mechanisms of direct cardiac depression from intravenous anesthetics are not well established, but presumably involve similar actions. Of all the major intravenous induction agents, ketamine seems to have the least direct depressant effect on contractility. Local anesthetic agents also depress cardiac contractility by reducing Ca^{2+} influx and release in a dose-dependent fashion. The more potent (at nerve block) agents, such as bupivacaine, tetracaine, and ropivacaine, more significantly depress left ventricular contractility than less potent (at nerve block) agents, such as lidocaine or chloroprocaine.

INNERVATION OF THE HEART

Parasympathetic fibers primarily innervate the atria and conducting tissues. Acetylcholine acts on specific cardiac muscarinic receptors (M_2) to produce negative chronotropic, dromotropic, and inotropic effects. In contrast, sympathetic fibers are more widely distributed throughout the heart. Cardiac sympathetic fibers originate in the thoracic spinal cord (T1–T4) and travel to the heart initially through the cervical (stellate) ganglia and from the ganglia as the cardiac nerves. Norepinephrine release causes positive chronotropic, dromotropic, and inotropic effects primarily through activation of β_1-adrenergic receptors. β_2-Adrenergic receptors are normally fewer in number and are found primarily in the atria; activation increases heart rate and, to a lesser extent, contractility.

Cardiac autonomic innervation has an apparent *sidedness*, because the right sympathetic and right vagus nerves primarily affect the SA node, whereas the left sympathetic and vagus nerves principally affect the AV node. Vagal effects frequently have a very rapid onset and resolution, whereas sympathetic influences generally have a more gradual onset and dissipation. Sinus arrhythmia is a cyclic variation in heart rate that corresponds to respiration (increasing with inspiration and decreasing during expiration); it is due to cyclic changes in vagal tone.

THE CARDIAC CYCLE

The cardiac cycle can be defined by both electrical and mechanical events (Figure 20–2). *Systole* refers to contraction and *diastole* refers to relaxation. Most diastolic ventricular filling occurs passively before atrial contraction. Contraction of the atria normally contributes 20% to 30% of ventricular filling. **Three waves can generally be identified on atrial pressure tracings** (Figure 20–2). The *a* wave is due to

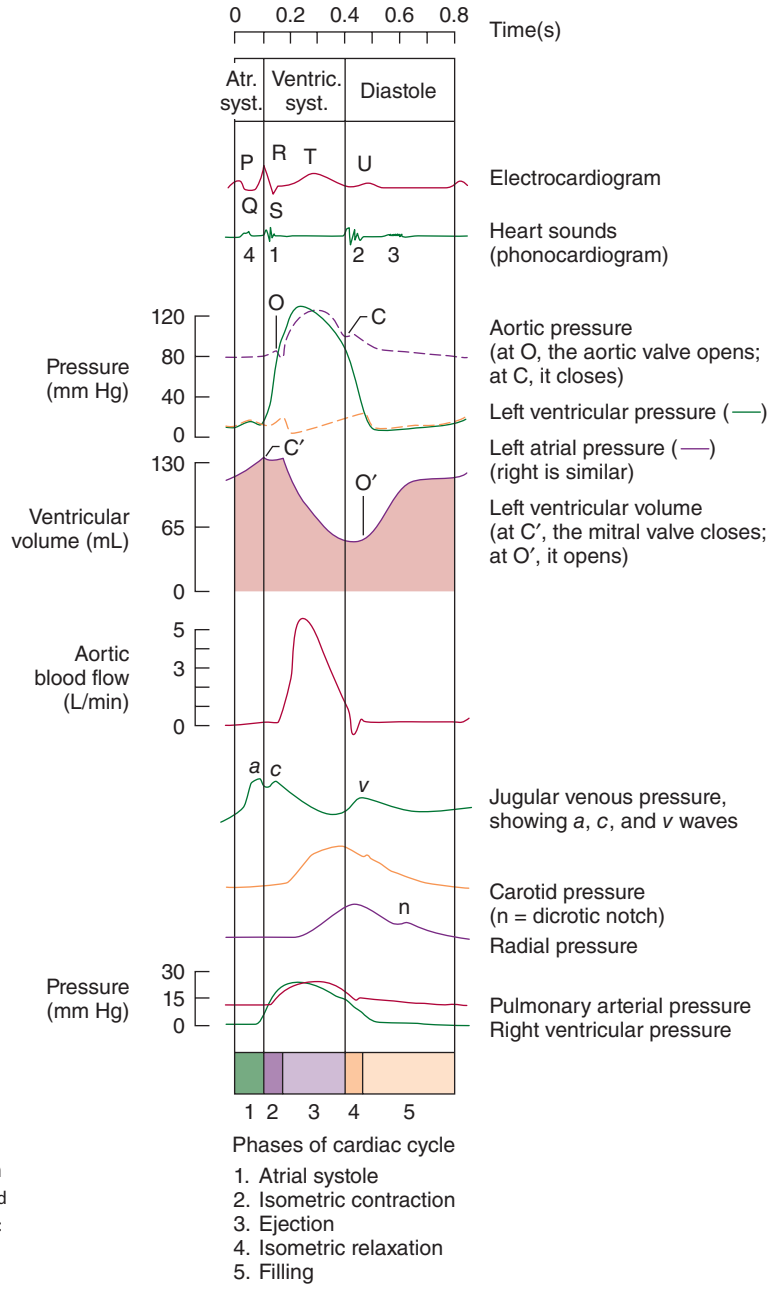


FIGURE 20–2 The normal cardiac cycle. Note the correspondence between electrical and mechanical events. (Modified and reproduced, with permission, from Barrett KE: Ganong's *Review of Medical Physiology*, 24th ed. McGraw-Hill, 2012.)

atrial systole. The *c* wave coincides with ventricular contraction and is said to be caused by bulging of the AV valve into the atrium. The *v* wave is the result of pressure buildup from venous return before the AV valve opens again. The *x* descent is the decline in pressure between the *c* and *v* waves and is thought to be due to a pulling down of the atrium by ventricular contraction. Incompetence of the AV valve on either side of the heart abolishes the *x* descent on that side, resulting in a prominent *cv* wave. The *y* descent follows the *v* wave and represents the decline in atrial pressure as the AV valve opens. The notch in the aortic pressure tracing is referred to as the *incisura* and is said to represent the brief pressure change from transient backflow of blood into the left ventricle just before aortic valve closure.

DETERMINANTS OF VENTRICULAR PERFORMANCE

Discussions of ventricular function usually refer to the left ventricle, but the same concepts apply to the right ventricle. Although the ventricles are often thought of as functioning separately, their interdependence has clearly been demonstrated. Moreover, factors affecting systolic and diastolic functions can be differentiated: Systolic function involves ventricular ejection, whereas diastolic function is related to ventricular filling.

Ventricular systolic function is often (erroneously) equated with cardiac output, which can be defined as the volume of blood pumped by the heart per minute. Because the two ventricles function in series, their outputs are normally equal. Cardiac output (CO) is expressed by the following equation:

$$CO = SV \times HR$$

where SV is the stroke volume (the volume pumped per contraction) and HR is heart rate. To compensate for variations in body size, CO is often expressed in terms of total body surface area:

$$CI = \frac{CO}{BSA}$$

where CI is the cardiac index and BSA is body surface area. BSA is usually obtained from nomograms based on height and weight (**Figure 20–3**). Normal CI is 2.5–4.2 L/min/m^2. Because the normal CI has a wide range, it is a relatively insensitive measurement of ventricular performance. Abnormalities in CI therefore usually reflect gross ventricular impairment. A more accurate assessment can be obtained if the response of the cardiac output to exercise is evaluated. Under these conditions, failure of the cardiac output to increase and keep up with oxygen consumption is reflected by a decreasing mixed venous oxygen saturation. A decrease in mixed venous oxygen saturation in response to increased demand usually reflects inadequate tissue perfusion. Thus, in the absence of hypoxia or severe anemia, measurement of mixed venous oxygen tension (or saturation) is an excellent estimate of the adequacy of cardiac output.

1. Heart Rate

When stroke volume remains constant, cardiac output is directly proportional to heart rate. Heart rate is an intrinsic function of the SA node (spontaneous depolarization), but is modified by autonomic, humoral, and local factors. The normal intrinsic rate of the SA node in young adults is about 90–100 beats/min, but it decreases with age based on the following formula:

$$\text{Normal intrinsic heart rate} = 118 \text{ beats/min} - (0.57 \times \text{age})$$

Enhanced vagal activity slows the heart rate via stimulation of M_2 cholinergic receptors, whereas enhanced sympathetic activity increases the heart rate mainly through activation of β_1-adrenergic receptors and, to lesser extent, β_2-adrenergic receptors (see above).

2. Stroke Volume

Stroke volume is normally determined by three major factors: preload, afterload, and contractility. This analysis is analogous to laboratory observations on skeletal muscle preparations. Preload is muscle length prior to contraction, whereas afterload is the tension against which the muscle must

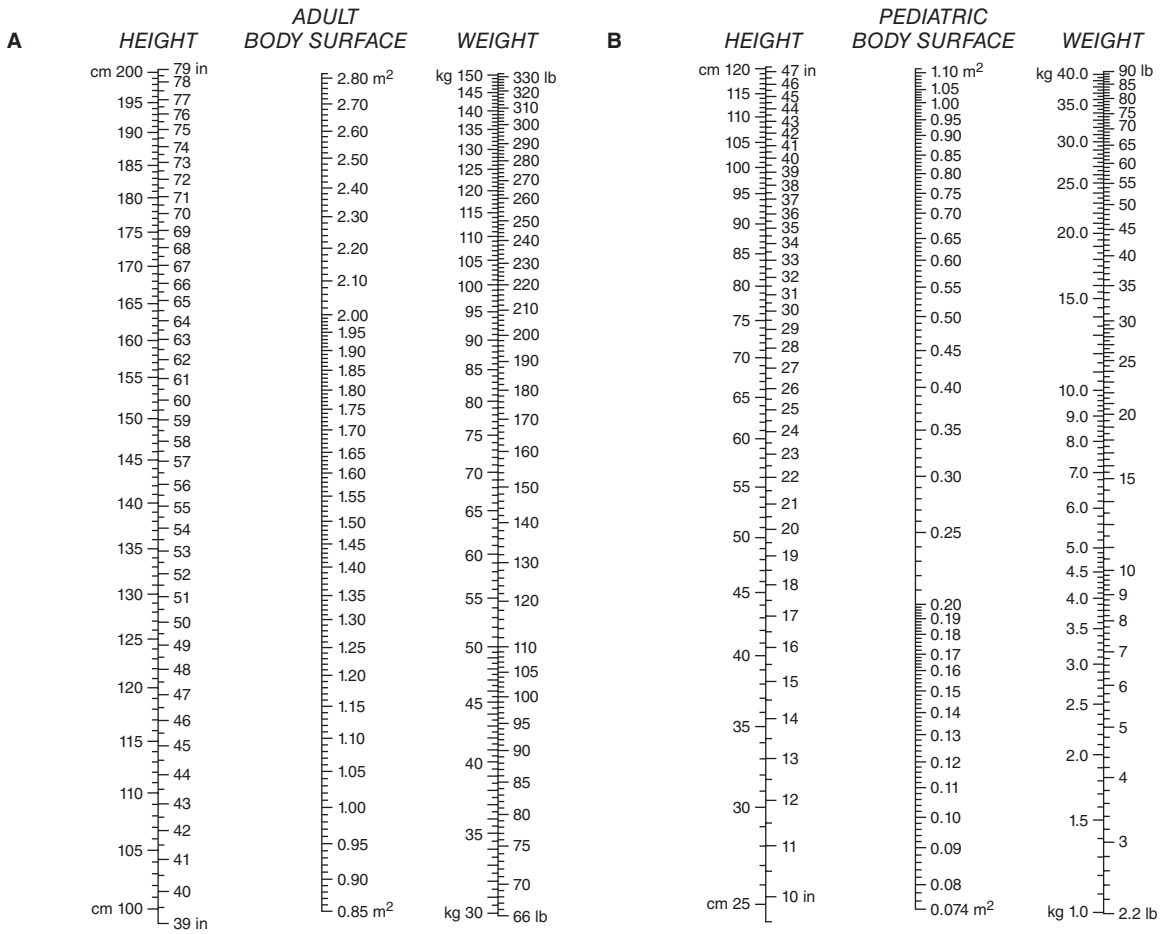


FIGURE 20–3 Nomograms for calculating body surface area (BSA) in adult (**A**) and pediatric (**B**) patients. (Data from the formula of Du Bois and Du Bois: Arch Intern Med 1916;17:863. Copyright 1916, American Medical Association.)

contract. Contractility is an intrinsic property of the muscle that is related to the force of contraction but is independent of both preload and afterload. Because the heart is a three-dimensional multichambered pump, both ventricular geometric form and valvular dysfunction can also affect stroke volume (Table 20–3).

Preload

Ventricular preload is end-diastolic volume, which is generally dependent on ventricular filling. The relationship between cardiac output and left ventricular end-diastolic volume is known as Starling's law of the heart (Figure 20–4). Note that when the heart rate and contractility remain constant, cardiac output is directly proportional to preload until excessive end-diastolic volumes are reached. At that

TABLE 20–3 Major factors affecting cardiac stroke volume.

Preload
Afterload
Contractility
Wall motion abnormalities
Valvular dysfunction

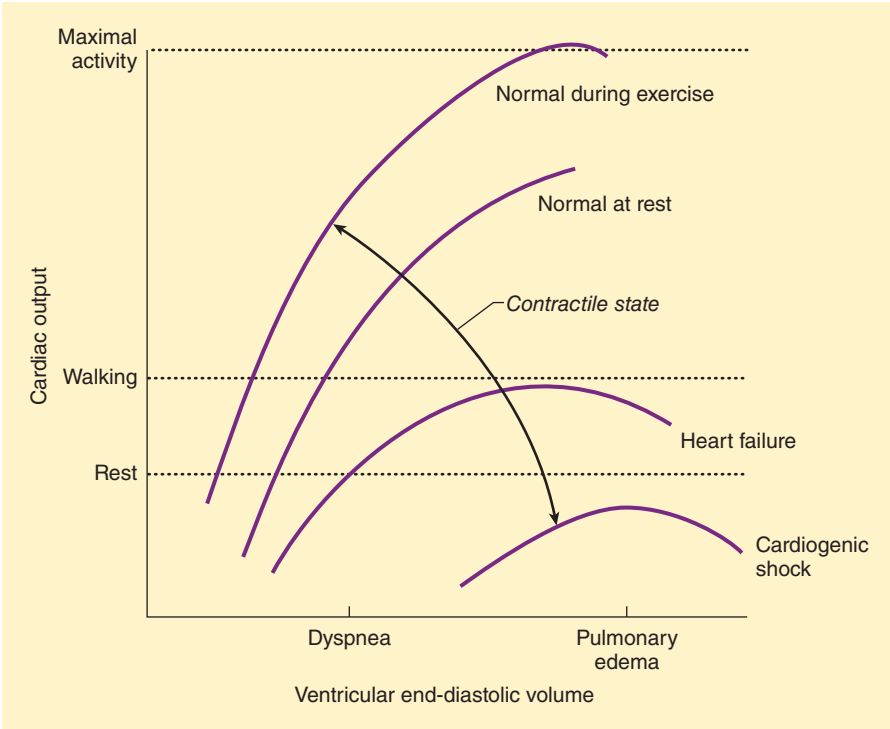


FIGURE 20–4 Starling's law of the heart.

point, cardiac output does not appreciably change—or may even decrease. Excessive distention of either ventricle can lead to excessive dilatation and incompetence of the AV valves.

A. Determinants of Ventricular Filling

Ventricular filling can be influenced by a variety of factors (Table 20–4), of which the most important is venous return. Because most of the other factors affecting venous return are usually fixed, vascular capacity is normally its major determinant. Increases in metabolic activity reduce vascular capacity, so that venous return to the heart increases as the volume of venous capacitance vessels decreases. Changes in blood volume and venous tone are important causes of intraoperative and postoperative changes in ventricular filling and cardiac output. Any factor that alters the normally small venous pressure gradient favoring blood return to the heart also affects cardiac filling. Such factors include changes in intrathoracic pressure (positive-pressure ventilation or thoracotomy), posture (positioning during surgery), and pericardial pressure (pericardial disease).

TABLE 20–4 Factors affecting ventricular preload.

Blood volume
Distribution of blood volume
Posture
Intrathoracic pressure
Pericardial pressure
Venous tone
Rhythm (atrial contraction)
Heart rate

The most important determinant of right ventricular preload is venous return. **In the absence of significant pulmonary or right ventricular dysfunction, venous return is also the major determinant of left ventricular preload**. Normally, the end-diastolic volumes of both ventricles are similar,

and, normally, the venous return is numerically equivalent to the cardiac output.

Both heart rate and rhythm can also affect ventricular preload. Increases in heart rate are associated with proportionately greater reductions in diastole than systole. Ventricular filling therefore progressively becomes impaired at increased heart rates (>120 beats/min in adults). Absent (atrial fibrillation), ineffective (atrial flutter), or altered timing of atrial contraction (low atrial or junctional rhythms) can also reduce ventricular filling by 20% to 30%. Patients with reduced ventricular compliance are more affected by the loss of a normally timed atrial systole than are those with normal ventricular compliance.

B. Diastolic Function and Ventricular Compliance

Left ventricular end-diastolic pressure (LVEDP) can be used as a measure of preload only if the relationship between ventricular volume and pressure (ventricular compliance) is constant. However, ventricular compliance is normally nonlinear (Figure 20–5). Impaired diastolic function reduces ventricular compliance. Therefore, the same LVEDP that corresponds to a normal preload in a normal patient may correspond to a decreased preload in a patient with impaired diastolic function.

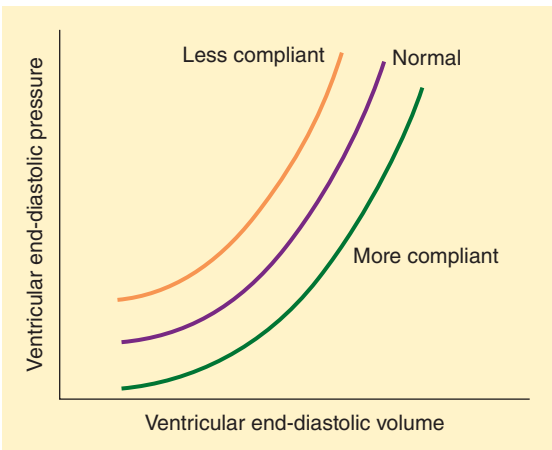


FIGURE 20–5 Normal and abnormal ventricular compliance.

Many factors are known to influence ventricular diastolic function and compliance. Nonetheless, measurement of LVEDP or other pressures approximating LVEDP (such as pulmonary artery occlusion pressure) are potential means of estimating left ventricular preload. Changes in central venous pressure can be used as a rough index for changes in right and left ventricular preload in most normal individuals.

Factors affecting ventricular compliance can be separated into those related to the rate of relaxation (early diastolic compliance) and passive stiffness of the ventricles (late diastolic compliance). Hypertrophy (from hypertension or aortic valve stenosis), ischemia, and asynchrony reduce early compliance; hypertrophy and fibrosis reduce late compliance. Extrinsic factors (such as pericardial disease, excessive distention of the contralateral ventricle, increased airway or pleural pressure, tumors, and surgical compression) can also reduce ventricular compliance. Because of its normally thinner wall, the right ventricle is more compliant than the left.

Afterload

Afterload for the intact heart is commonly equated with either ventricular wall tension during systole or arterial impedance to ejection. Wall tension may be thought of as the pressure the ventricle must overcome to reduce its cavity volume. If the ventricle is assumed to be spherical, ventricular wall tension can be expressed by Laplace's law:

$$\text{Circumferential stress} = \frac{P \times R}{2 \times H}$$

where P is intraventricular pressure, R is the ventricular radius, and H is wall thickness. Although the normal ventricle is usually ellipsoidal, this relationship is still useful. The larger the ventricular radius, the greater the wall tension required to develop the same ventricular pressure. Conversely, an increase in wall thickness reduces ventricular wall tension.

Systolic intraventricular pressure is dependent on the force of ventricular contraction; the viscoelastic properties of the aorta, its proximal branches,

and blood (viscosity and density); and **systemic vascular resistance (SVR)**. Arteriolar tone is the primary determinant of SVR. Because viscoelastic properties are generally fixed in any given patient, left ventricular afterload is usually equated clinically with SVR, which is calculated by the following equation:

$$SVR = 80 \times \frac{MAP - CVP}{CO}$$

where MAP is mean arterial pressure in millimeters of mercury, CVP is central venous pressure in millimeters of mercury, and CO is cardiac output in liters per minute. Normal SVR is 900–1500 dyn · s cm^{-5}. Systolic blood pressure may also be used as an approximation of left ventricular afterload in the absence of chronic changes in the size, shape, or thickness of the ventricular wall or acute changes in systemic vascular resistance. Some clinicians prefer to use CI instead of CO in calculating a systemic vascular resistance index (SVRI), so that SVRI = SVR × BSA.

Right ventricular afterload is mainly dependent on pulmonary vascular resistance (PVR) and is expressed by the following equation:

$$PVR = 80 \times \frac{PAP - LAP}{CO}$$

where PAP is mean pulmonary artery pressure and LAP is left atrial pressure. In practice, pulmonary capillary wedge pressure (PCWP) is usually substituted as an approximation for LAP. Normal PVR is 50–150 dyn · s cm^{-5}.

Cardiac output is inversely related to large changes in afterload on the left ventricle; however, small increases or decreases in afterload may have no effect at all on cardiac output. Because of its thinner wall, the right ventricle is more sensitive to changes in afterload than is the left ventricle. **7** Cardiac output in patients with marked right or left ventricular impairment is very sensitive to acute increases in afterload. The latter is particularly true in the presence of drug- or ischemia-induced myocardial depression or chronic heart failure.

Contractility

Cardiac contractility (inotropy) is the intrinsic ability of the myocardium to pump in the absence of changes in preload or afterload. Contractility is related to the rate of myocardial muscle shortening, which is, in turn, dependent on the intracellular Ca^{2+} concentration during systole. Increases in heart rate can also enhance contractility under some conditions, perhaps because of the increased availability of intracellular Ca^{2+}.

Contractility can be altered by neural, humoral, or pharmacological influences. Sympathetic nervous system activity normally has the most important effect on contractility. Sympathetic fibers innervate atrial and ventricular muscle, as well as nodal tissues. In addition to its positive chronotropic effect, norepinephrine release also enhances contractility primarily via β_1-receptor activation. α-Adrenergic receptors are also present in the myocardium, but seem to have only minor positive inotropic and chronotropic effects. Sympathomimetic drugs and secretion of epinephrine from the adrenal glands similarly increase contractility via β_1-receptor activation.

Myocardial contractility is depressed by hypoxia, acidosis, depletion of catecholamine stores within the heart, and loss of functioning muscle mass as a result of ischemia or infarction. At large enough doses, most anesthetics and antiarrhythmic agents are negative inotropes (ie, they decrease contractility).

Wall Motion Abnormalities

Regional wall motion abnormalities cause a breakdown of the analogy between the intact heart and skeletal muscle preparations. Such abnormalities may be due to ischemia, scarring, hypertrophy, or altered conduction. When the ventricular cavity does not collapse symmetrically or fully, emptying becomes impaired. Hypokinesis (decreased contraction), akinesis (failure to contract), and dyskinesis (paradoxic bulging) during systole reflect increasing degrees of contraction abnormalities. Although contractility may be normal or even enhanced in some areas, abnormalities in other areas of the ventricle can impair emptying and reduce stroke volume. The severity of the impairment depends on the size and number of abnormally contracting areas.

Valvular Dysfunction

Valvular dysfunction can involve any one of the four valves in the heart and can include stenosis, regurgitation (incompetence), or both. Stenosis of an AV valve (tricuspid or mitral) reduces stroke volume primarily by decreasing ventricular preload, whereas stenosis of a semilunar valve (pulmonary or aortic) reduces stroke volume primarily by increasing ventricular afterload. In contrast, valvular regurgitation can reduce stroke volume without changes in preload, afterload, or contractility and without wall motion abnormalities. The effective stroke volume is reduced by the regurgitant volume with every contraction. When an AV valve is incompetent, a significant part of the ventricular end-diastolic volume can flow backward into the atrium during systole; the stroke volume is reduced by the regurgitant volume. Similarly, when a semilunar valve is incompetent, a fraction of end-diastolic volume arises from backward flow into the ventricle during diastole.

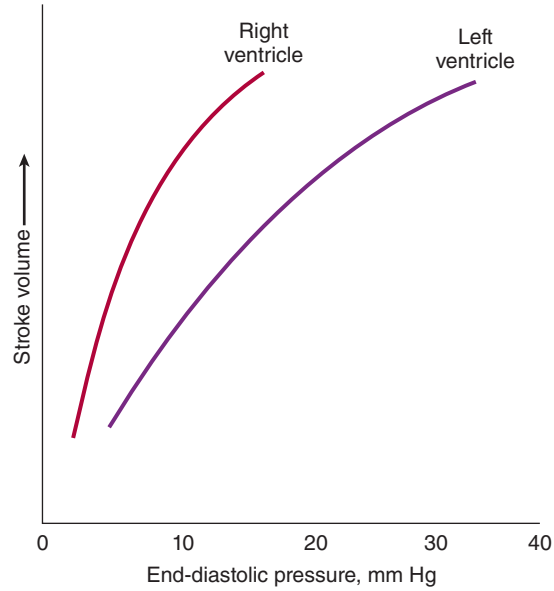


FIGURE 20–6 Function curves for the left and right ventricles.

ASSESSMENT OF VENTRICULAR FUNCTION

1. Ventricular Function Curves

Plotting cardiac output or stroke volume against preload is useful in evaluating pathological states and understanding drug therapy. Normal right and left ventricular function curves are shown in Figure 20–6.

Ventricular pressure–volume diagrams are useful because they dissociate contractility from both preload and afterload. Two points are identified on such diagrams: the end-systolic point (ESP) and the end-diastolic point (EDP) (Figure 20–7). ESP is reflective of systolic function, whereas EDP is more reflective of diastolic function. For any given contractile state, all ESPs are on the same line (ie, the relationship between end-systolic volume and end-systolic pressure is fixed).

2. Assessment of Systolic Function

The change in ventricular pressure over time during systole (*dP/dt*) is defined by the first derivative of the ventricular pressure curve and is often used as a measure of contractility. Contractility is directly proportional to *dP/dt*, but accurate measurement of this value requires a high-fidelity ("Millar") ventricular catheter; however, it can be estimated with echocardiography. Although arterial pressure tracings are distorted due to properties of the vascular tree, the initial rate of rise in pressure (the slope) can serve as a rough approximation; the more proximally the arterial line catheter is located in the arterial tree, the more accurate the extrapolation will be. The usefulness of *dP/dt* is also limited in that it may be affected by preload, afterload, and heart rate.

Ejection Fraction

8 The ventricular ejection fraction (EF), the fraction of the end-diastolic ventricular volume ejected, is the most commonly used clinical measurement of systolic function. EF can be calculated by the following equation:

$$EF = \frac{EDV - ESV}{EDV}$$

where EDV is left ventricular diastolic volume and ESV is end-systolic volume. Normal EF is

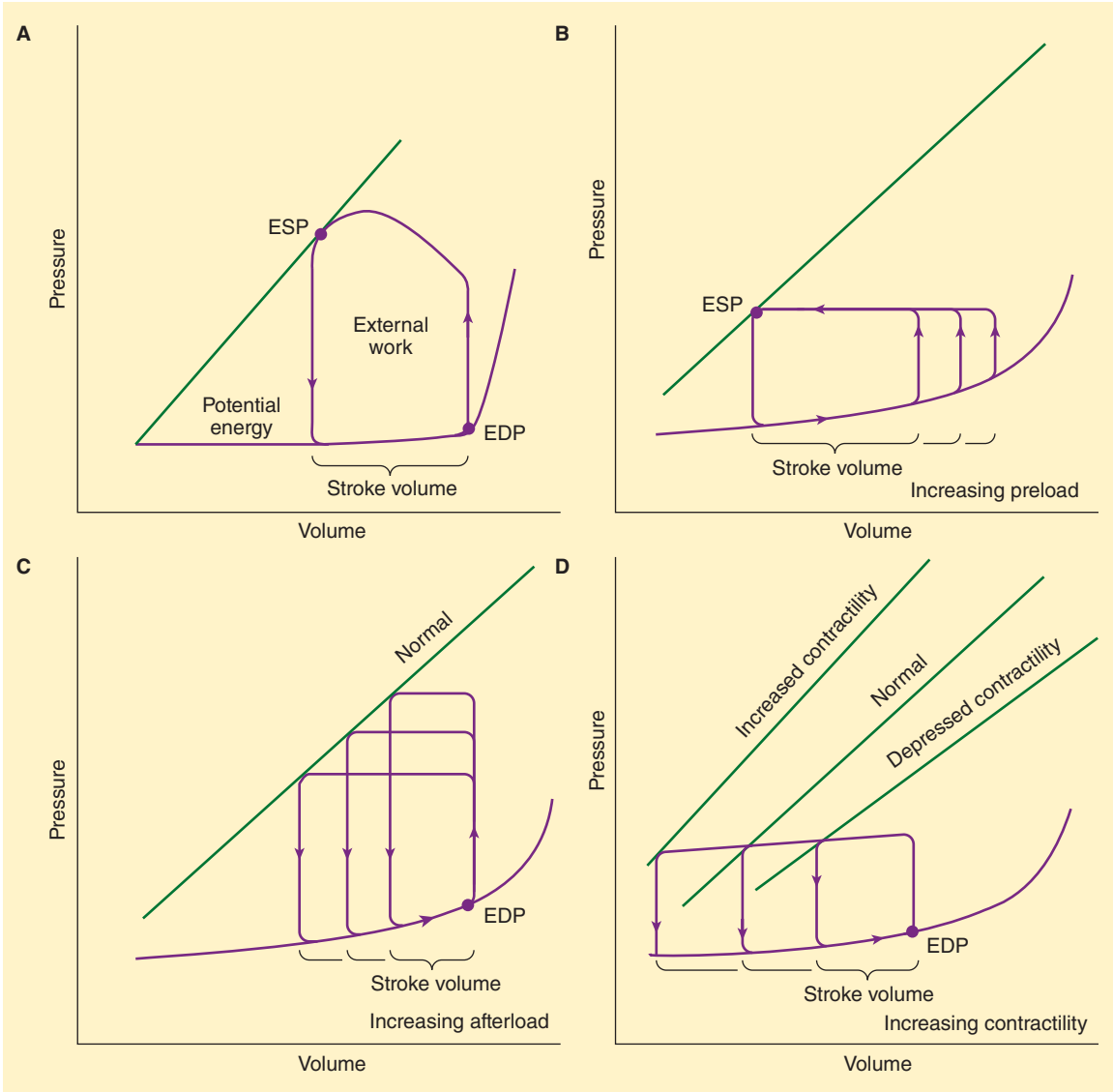
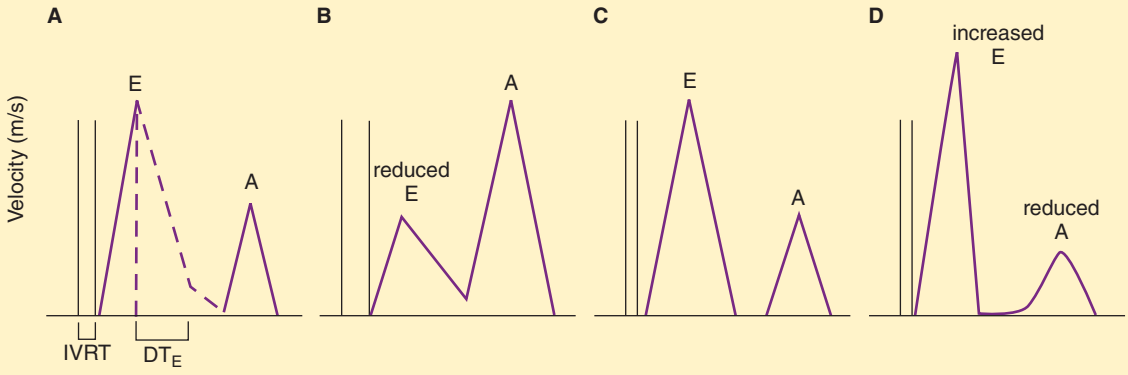


FIGURE 20–7 Ventricular pressure-volume diagrams. **A**: A single ventricular contraction. Note that stroke volume represents change in volume on the x-axis (difference between end-systolic volume and end-diastolic volume). Note also that the circumscribed area represents external work performed by the ventricle. **B**: Increasing preload with constant contractility and afterload. **C**: Increasing afterload with constant preload and contractility. **D**: Increasing contractility with constant preload and afterload. ESP, end-systolic point; EDP, end-diastolic point.

approximately 0.67 ± 0.08. Measurements can be made preoperatively from cardiac catheterization, radionucleotide studies, or transthoracic (TTE) or transesophageal echocardiography (TEE). Pulmonary artery catheters with fast-response thermistors allow measurement of the right ventricular EF. Unfortunately, when pulmonary vascular resistance increases, decreases in right ventricular



	Normal	*Impaired relaxation*	*Pseudonormalization*	*Restricted*
IVRT	70 – 90 ms	>100 ms	70 – 90 ms	<90 ms
E/A ratio	0.8 – 1.2	<0.8	0.8 – 1.2	>1.2
DT$_E$	150 – 300 ms	>250 ms	150 – 300 ms	<150 ms

FIGURE 20–8 Doppler echocardiography of diastolic flow across the mitral valve. **A–D** (from left to right) represents increasing severity of diastolic dysfunction. E, early diastolic flow; A, peak atrial systolic flow; IVRT, isovolumic relaxation time; DT$_E$, deceleration time of E.

EF may reflect afterload rather than contractility. Left ventricular EF is not an accurate measure of ventricular contractility in the presence of mitral insufficiency.

3. Assessment of Diastolic Function

9 Left ventricular diastolic function can be assessed clinically by Doppler echocardiography on a transthoracic or transesophageal examination. Flow velocities are measured across the mitral valve during diastole. Three patterns of diastolic dysfunction are generally recognized based on isovolumetric relaxation time, the ratio of peak early diastolic flow (E) to peak atrial systolic flow (A), and the deceleration time (DT) of E (DT$_E$) (Figure 20–8). Tissue Doppler is frequently used to distinguish "pseudonormal" from normal diastolic function. Tissue Doppler is also an excellent way to detect "conventional" diastolic dysfunction. An e' wave peak velocity of less than 8 cm/sec is associated with impaired diastolic function. An E/e' wave ratio that is greater than 15 is consistent with elevated left ventricular end-diastolic pressure (Figure 20–9).

Systemic Circulation

The systemic vasculature can be divided functionally into arteries, arterioles, capillaries, and veins. Arteries are the high-pressure conduits that supply the various organs. Arterioles are the small vessels that directly feed and control blood flow through each capillary bed. Capillaries are thin-walled vessels that allow the exchange of nutrients between blood and tissues. Veins return blood from capillary beds to the heart.

The distribution of blood between the various components of the circulatory system is shown in Table 20–5. Note that most of the blood volume is in the systemic circulation—specifically, within systemic veins. Changes in systemic venous tone allow these vessels to function as a reservoir for blood. Following significant blood or fluid losses, a sympathetically mediated increase in venous tone reduces the caliber of these vessels and shifts blood into other parts of the vascular system. Conversely, venodilation allows these vessels to accommodate increases in blood volume. Sympathetic control of venous tone is an important determinant of venous

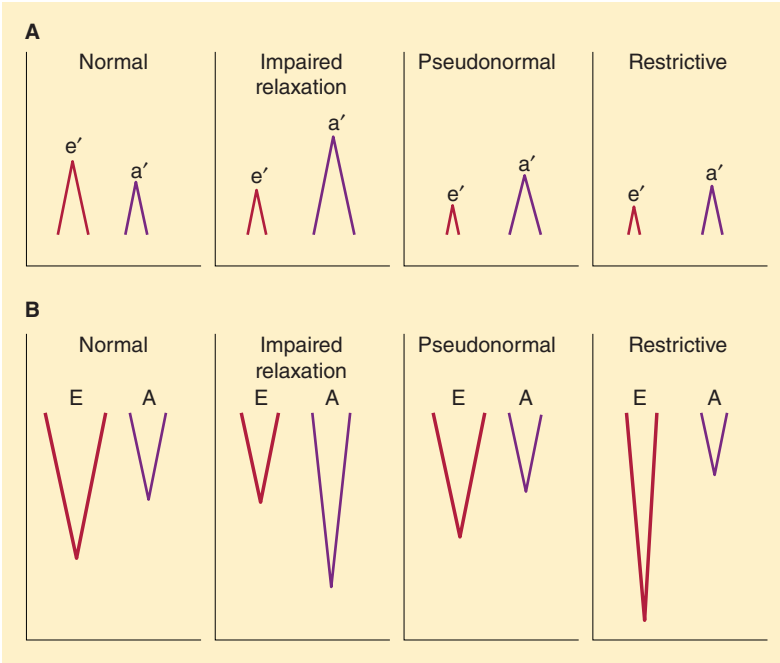


FIGURE 20–9 Tissue Doppler. **A**: Tissue Doppler at the lateral mitral annulus. During diastole the annulus moves toward the transesophageal examination transducer in the esophagus. Thus the e′ and a′ waves of diastolic filling are positive deflections above the baseline. **B**: When transesophageal examination is used to measure transmitral diastolic inflow, the E and A waves of early and late filling are below the baseline because flow is moving away from the Doppler probe in the esophagus. Tissue Doppler can be used to distinguish normal from pseudonormal diastolic inflow pattern because the e′ wave remains depressed as diastolic dysfunction progresses. (Reproduced with permission from Wasnick JD, et al: *Cardiac Anesthesia and Transesophageal Echocardiography*, McGraw-Hill, 2011.)

return to the heart. Reduced venous tone following induction of anesthesia frequently results in venous pooling of blood and contributes to hypotension.

A multiplicity of factors influences blood flow in the vascular tree. These include mechanisms of local and metabolic control, endothelium-derived factors, the autonomic nervous system, and circulating hormones.

TABLE 20–5 Distribution of blood volume.

Heart	7%
Pulmonary circulation	9%
Systemic circulation	
Arterial	15%
Capillary	5%
Venous	64%

AUTOREGULATION

Most tissue beds regulate their own blood flow (autoregulation). Arterioles generally dilate in response to reduced perfusion pressure or increased tissue demand. Conversely, arterioles constrict in response to increased pressure or reduced tissue demand. These phenomena are likely due to both an intrinsic response of vascular smooth muscle to stretch and the accumulation of vasodilatory metabolic by-products. The latter may include K^+, H^+, CO_2, adenosine, and lactate.

ENDOTHELIUM-DERIVED FACTORS

The vascular endothelium is metabolically active in elaborating or modifying substances that directly or indirectly play a major role in controlling blood

pressure and flow. These include vasodilators (eg, nitric oxide, prostacyclin [PGI_2]), vasoconstrictors (eg, endothelins, thromboxane A_2), anticoagulants (eg, thrombomodulin, protein C), fibrinolytics (eg, tissue plasminogen activator), and factors that inhibit platelet aggregation (eg, nitric oxide and PGI_2). Nitric oxide is synthesized from arginine by nitric oxide synthetase. This substance has a number of functions In the circulation, it is a potent vasodilator. It binds guanylate cyclase, increasing cGMP levels and producing vasodilation. Endothelially derived vasoconstrictors (endothelins) are released in response to thrombin and epinephrine.

AUTONOMIC CONTROL OF THE SYSTEMIC VASCULATURE

Although the parasympathetic system can exert important influences on the circulation, autonomic control of the vasculature is primarily sympathetic. Sympathetic outflow to the circulation passes out of the spinal cord at all thoracic segments and the first two lumbar segments. These fibers reach blood vessels via specific autonomic nerves or by traveling along spinal nerves. Sympathetic fibers innervate all parts of the vasculature except for capillaries. Their principal function is to regulate vascular tone. Variations of arterial vascular tone serve to regulate blood pressure and the distribution of blood flow to the various organs, whereas variations in venous tone alter vascular capacity, venous pooling, and venous return to the heart.

The vasculature has sympathetic vasoconstrictor and vasodilator fibers, but the former are more important physiologically in most tissue beds. Sympathetic-induced vasoconstriction (via α_1-adrenergic receptors) can be potent in skeletal muscle, kidneys, gut, and skin; it is least active in the brain and heart. The most important vasodilatory fibers are those feeding skeletal muscle, mediating increased blood flow (via β_2-adrenergic receptors) in response to exercise. Vasodepressor (vasovagal) syncope, which can occur following intense emotional strain associated with high sympathetic tone, results from reflex activation of both vagal and sympathetic vasodilator fibers.

Vascular tone and autonomic influences on the heart are controlled by vasomotor centers in the reticular formation of the medulla and lower pons. Distinct vasoconstrictor and vasodilator areas have been identified. Vasoconstriction is mediated by the anterolateral areas of the lower pons and upper medulla. They are also responsible for adrenal secretion of catecholamines, as well as the enhancement of cardiac automaticity and contractility. Vasodilatory areas, which are located in the lower medulla, are also adrenergic, but function by projecting inhibitory fibers upward to the vasoconstrictor areas. Vasomotor output is modified by inputs from throughout the central nervous system, including the hypothalamus, cerebral cortex, and the other areas in the brainstem. Areas in the posterolateral medulla receive input from both the vagal and the glossopharyngeal nerves and play an important role in mediating a variety of circulatory reflexes. The sympathetic system normally maintains some tonic vasoconstriction on the vascular tree. Loss of this tone following induction of anesthesia or sympathectomy frequently contributes to perioperative hypotension.

ARTERIAL BLOOD PRESSURE

Systemic blood flow is pulsatile in large arteries because of the heart's cyclic activity; by the time blood reaches the systemic capillaries, flow is continuous (laminar). The mean pressure falls to less than 20 mm Hg in the large systemic veins that return blood to the heart. The largest pressure drop, nearly 50%, is across the arterioles, and the arterioles account for the majority of SVR.

MAP is proportionate to the product of SVR × CO. This relationship is based on an analogy to Ohm's law, as applied to the circulation:

$$MAP - CVP \approx SVR \times CO$$

Because CVP is normally very small compared with MAP, the former can usually be ignored. From this relationship, it is readily apparent that hypotension is the result of a decrease in SVR, CO, or both: To maintain arterial blood pressure, a decrease in either SVR or CO must be compensated by an increase in the other. MAP can be measured as the integrated mean of the arterial pressure waveform.

Alternatively, MAP may be estimated by the following formula:

$$\text{MAP} = \text{Diastolic pressure} + \frac{\text{Pulse pressure}}{3}$$

where pulse pressure is the difference between systolic and diastolic blood pressure. Arterial pulse pressure is directly related to stroke volume, but is inversely proportional to the compliance of the arterial tree. Thus, decreases in pulse pressure may be due to a decrease in stroke volume, an increase in SVR, or both. Increased pulse pressure increases shear stress on vessel walls, potentially leading to atherosclerotic plaque rupture and thrombosis or rupture of aneurysms. Increased pulse pressure in patients undergoing cardiac surgery has been associated with adverse renal and neurological outcomes.

Transmission of the arterial pressure wave from large arteries to smaller vessels in the periphery is faster than the actual movement of blood; the pressure wave velocity is 15 times the velocity of blood in the aorta. Moreover, reflections of the propagating waves off arterial walls widen pulse pressure before the pulse wave is completely dampened in very small arteries.

Control of Arterial Blood Pressure

Arterial blood pressure is regulated by a series of immediate, intermediate, and long-term adjustments that involve complex neural, humoral, and renal mechanisms.

A. Immediate Control

Minute-to-minute control of blood pressure is primarily the function of autonomic nervous system reflexes. Changes in blood pressure are sensed both centrally (in hypothalamic and brainstem areas) and peripherally by specialized sensors (baroreceptors). Decreases in arterial blood pressure result in increased sympathetic tone, increased adrenal secretion of epinephrine, and reduced vagal activity. **The resulting systemic vasoconstriction, increased heart rate, and enhanced cardiac contractility serve to increase blood pressure**.

Peripheral baroreceptors are located at the bifurcation of the common carotid arteries and the aortic arch. Elevations in blood pressure increase baroreceptor discharge, inhibiting systemic vasoconstriction and enhancing vagal tone **(baroreceptor reflex)**. Reductions in blood pressure decrease baroreceptor discharge, allowing vasoconstriction and reduction of vagal tone. Carotid baroreceptors send afferent signals to circulatory brainstem centers via Hering's nerve (a branch of the glossopharyngeal nerve), whereas aortic baroreceptor afferent signals travel along the vagus nerve. Of the two peripheral sensors, the carotid baroreceptor is physiologically more important and is primarily responsible for minimizing changes in blood pressure that are caused by acute events, such as a change in posture. Carotid baroreceptors sense MAP most effectively between pressures of 80 and 160 mm Hg. Adaptation to acute changes in blood pressure occurs over the course of 1–2 days, rendering this reflex ineffective for longer term blood pressure control. All volatile anesthetics depress the normal baroreceptor response, but isoflurane and desflurane seem to have less effect. Cardiopulmonary stretch receptors located in the atria, left ventricle, and pulmonary circulation can cause a similar effect.

B. Intermediate Control

In the course of a few minutes, sustained decreases in arterial pressure, together with enhanced sympathetic outflow, activate the renin–angiotensin–aldosterone system, increase secretion of arginine vasopressin (AVP), and alter normal capillary fluid exchange. Both angiotensin II and AVP are potent arteriolar vasoconstrictors. Their immediate action is to increase SVR. In contrast to formation of angiotensin II, which responds to relatively smaller changes, sufficient AVP secretion to produce vasoconstriction will only occur in response to more marked degrees of hypotension. Angiotensin constricts arterioles via AT_1 receptors. AVP mediates vasoconstriction via V_1 receptors and exerts its antidiuretic effect via V_2 receptors.

Sustained changes in arterial blood pressure can also alter fluid exchange in tissues by their secondary effects on capillary pressures. Hypertension increases interstitial movement of intravascular fluid, whereas hypotension increases reabsorption of interstitial fluid. Such compensatory changes in intravascular volume can reduce fluctuations in

blood pressure, particularly in the absence of adequate renal function (see below).

C. Long-Term Control

The effects of slower renal mechanisms become apparent within hours of sustained changes in arterial pressure. As a result, the kidneys alter total body sodium and water balance to restore blood pressure to normal. Hypotension results in sodium (and water) retention, whereas hypertension generally increases sodium excretion in normal individuals.

ANATOMY & PHYSIOLOGY OF THE CORONARY CIRCULATION

1. Anatomy

Myocardial blood supply is derived entirely from the right and left coronary arteries (**Figure 20–10**). Blood flows from epicardial to endocardial vessels. After perfusing the myocardium, blood returns to the right atrium via the coronary sinus and the anterior cardiac veins. A small amount of blood returns directly into the chambers of the heart by way of the thebesian veins.

The right coronary artery (RCA) normally supplies the right atrium, most of the right ventricle, and a variable portion of the left ventricle (inferior wall). In 85% of persons, the RCA gives rise to the posterior descending artery (PDA), which supplies the superior–posterior interventricular septum and inferior wall—a right dominant circulation; in the remaining 15% of persons, the PDA is a branch of the left coronary artery—a left dominant circulation.

The left coronary artery normally supplies the left atrium and most of the interventricular septum and left ventricle (septal, anterior, and lateral walls). After a short course, the left main coronary artery bifurcates into the left anterior descending artery (LAD) and the circumflex artery (CX); the LAD supplies the septum and anterior wall and the CX supplies the lateral wall. In a left dominant circulation, the CX wraps around the AV groove and continues down as the PDA to also supply most of the posterior septum and inferior wall.

The arterial supply to the SA node may be derived from either the RCA (60% of individuals) or the LAD (the remaining 40%). The AV node is usually supplied by the RCA (85% to 90%) or, less frequently, by the CX (10% to 15%); the bundle of His has a dual blood supply derived from the PDA and LAD. The anterior papillary muscle of the mitral valve also has a dual blood supply that is fed by diagonal branches of the LAD and marginal branches of the CX. In contrast, the posterior papillary of the mitral valve is usually supplied only by the PDA and is therefore much more vulnerable to ischemic dysfunction.

2. Determinants of Coronary Perfusion

Coronary perfusion is unique in that it is intermittent rather than continuous, as it is in other organs. During contraction, intramyocardial pressures in the left ventricle approach systemic arterial pressure. The force of left ventricular contraction almost completely occludes the intramyocardial part of the coronary arteries; in fact, blood flow may transiently reverse in epicardial vessels. Even during the latter part of diastole, left ventricular pressure eventually exceeds venous (right atrial) pressure. **Thus, coronary perfusion pressure is usually determined by the difference between aortic pressure and ventricular pressure**, and the left ventricle is perfused almost entirely during diastole. In contrast, the right ventricle is perfused during both systole and diastole (**Figure 20–11**). Moreover, as a determinant of myocardial blood flow, arterial diastolic pressure is more important than MAP:

$$\text{Coronary perfusion pressure} = \text{Arterial diastolic pressure} - \text{LVEDP}$$

Decreases in aortic pressure or increases in ventricular end-diastolic pressure can reduce coronary perfusion pressure. Increases in heart rate also decrease coronary perfusion because of the disproportionately greater reduction in diastolic time as heart rate increases (**Figure 20–12**). Because it is subjected to the greatest intramural pressures during systole, the endocardium tends to be most vulnerable to ischemia during decreases in coronary perfusion pressure.

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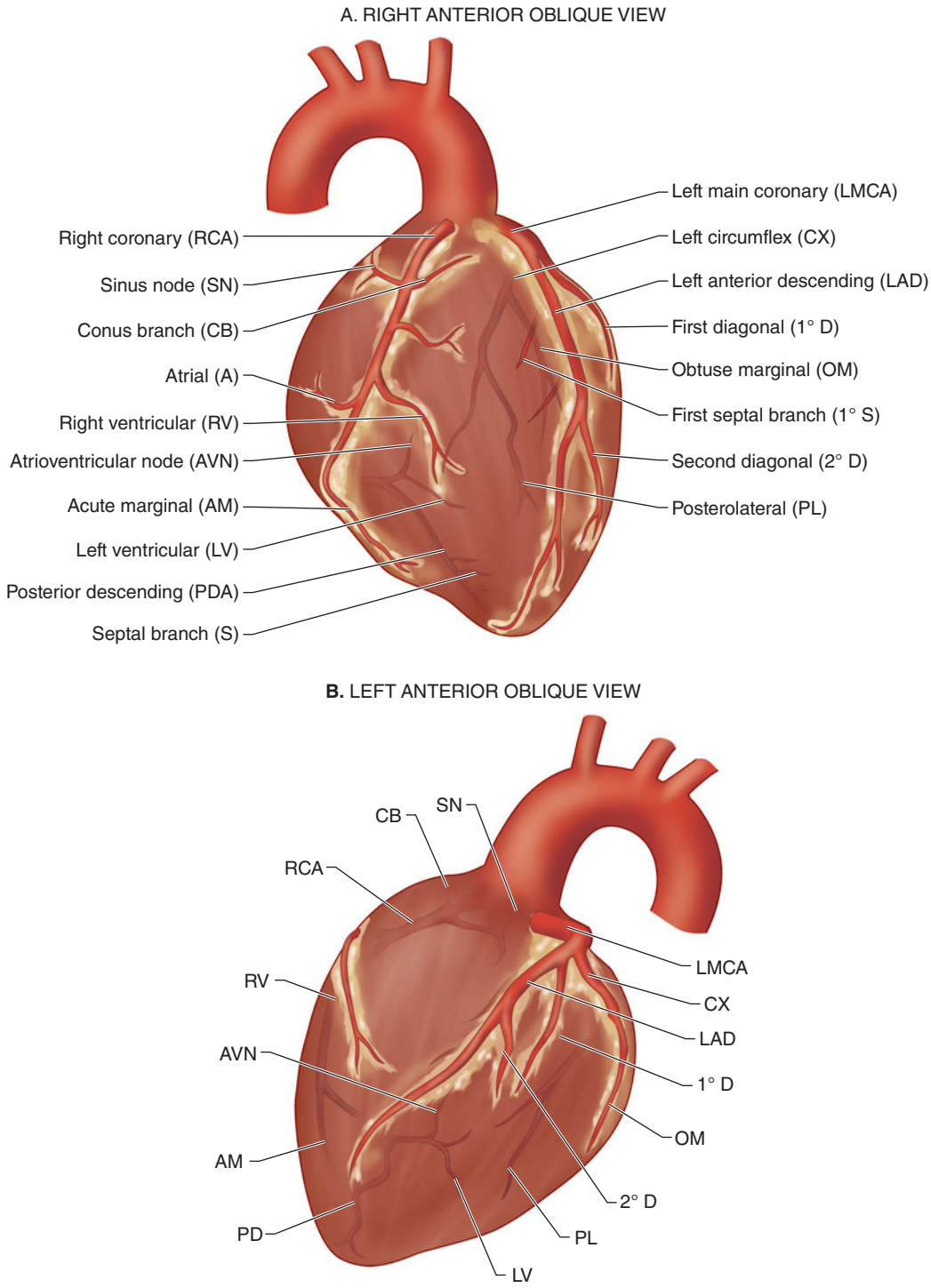

FIGURE 20–10 Anatomy of the coronary arteries in a patient with a right dominant circulation. **A**: Right anterior oblique view. **B**: Left anterior oblique view.

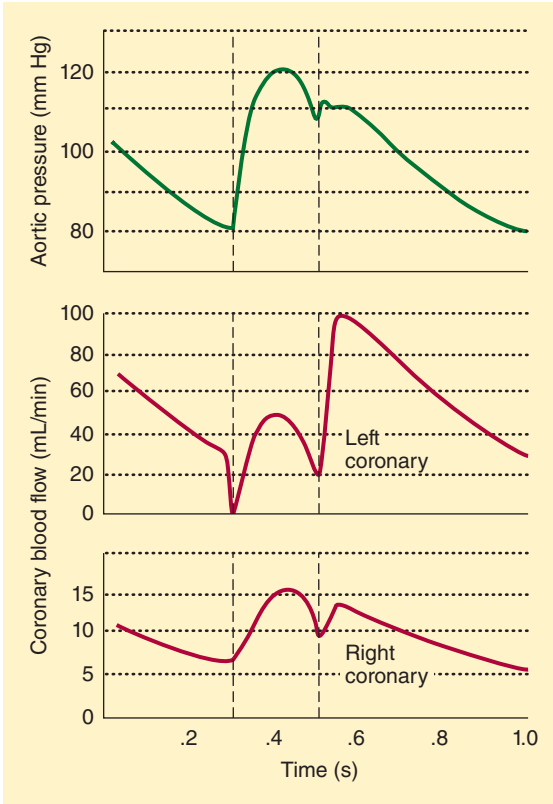

FIGURE 20–11 Coronary blood flow during the cardiac cycle. (Modified and reproduced, with permission, from Pappano A, Wier W: *Cardiovascular Physiology*, 10th ed. Mosby, 2013.)

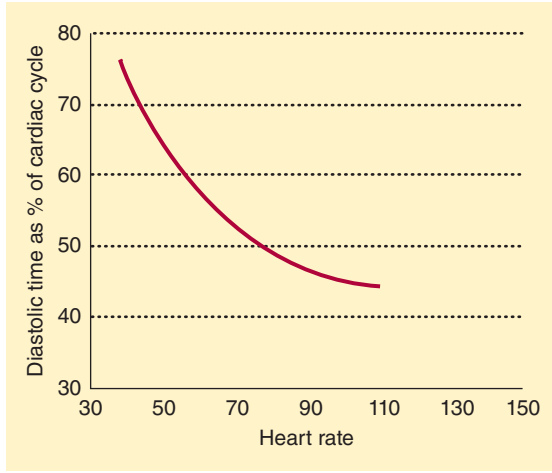

FIGURE 20–12 The relationship between diastolic time and heart rate.

Control of Coronary Blood Flow

Coronary blood flow normally parallels myocardial metabolic demand. In the average adult man, coronary blood flow is approximately 250 mL/min at rest. The myocardium regulates its own blood flow closely between perfusion pressures of 50 and 120 mm Hg. Beyond this range, blood flow becomes increasingly pressure dependent.

Under normal conditions, changes in blood flow are entirely due to variations in coronary arterial tone (resistance) in response to metabolic demand. Hypoxia—either directly, or indirectly through the release of adenosine—causes coronary vasodilation. Autonomic influences are generally weak. Both α_1- and β_2-adrenergic receptors are present in the coronary arteries. The α_1-receptors are primarily located on larger epicardial vessels, whereas the β_2-receptors are mainly found on the smaller intramuscular and subendocardial vessels. Sympathetic stimulation generally increases myocardial blood flow because of an increase in metabolic demand and a predominance of β_2-receptor activation. Parasympathetic effects on the coronary vasculature are generally minor and weakly vasodilatory.

3. Myocardial Oxygen Balance

Myocardial oxygen demand is usually the most important determinant of myocardial blood flow. Relative contributions to oxygen requirements include basal requirements (20%), electrical activity (1%), volume work (15%), and pressure work (64%). The myocardium usually extracts 65% of the oxygen in arterial blood, compared with 25% in most other tissues. Coronary sinus oxygen saturation is usually 30%. Therefore, the myocardium (unlike other tissues) cannot compensate for reductions in blood flow by extracting more oxygen from hemoglobin. Any increases in myocardial metabolic demand must be met by an increase in coronary blood flow. Table 20–6 lists the most important factors in myocardial oxygen demand and supply. Note that the heart rate and, to a lesser extent, ventricular

TABLE 20–6 Factors affecting myocardial oxygen supply–demand balance.

Supply
Heart rate (diastolic filling time)
Coronary perfusion pressure
Aortic diastolic blood pressure
Ventricular end-diastolic pressure
Arterial oxygen content
Arterial oxygen tension
Hemoglobin concentration
Coronary vessel diameter
Demand
Basal metabolic requirements
Heart rate
Wall tension
Preload (ventricular radius)
Afterload
Contractility

end-diastolic pressure are important determinants of both supply and demand.

EFFECTS OF ANESTHETIC AGENTS

Most volatile anesthetic agents are coronary vasodilators. Their effect on coronary blood flow is variable because of their direct vasodilating properties, reduction of myocardial metabolic requirements (and secondary decrease due to autoregulation), and effects on arterial blood pressure. The mechanism is not clear, and these effects are unlikely to have any clinical importance. Halothane and isoflurane seem to have the greatest effect; the former primarily affects large coronary vessels, whereas the latter affects mostly smaller vessels. Vasodilation due to desflurane seems to be primarily autonomically mediated, whereas sevoflurane seems to lack coronary vasodilating properties. Dose-dependent abolition of autoregulation may be greatest with isoflurane.

Volatile agents exert beneficial effects in experimental myocardial ischemia and infarction. They reduce myocardial oxygen requirements and protect against reperfusion injury; these effects are mediated by activation of ATP-sensitive K^+ (K_{ATP}) channels. Some evidence also suggests that volatile anesthetics enhance recovery of the "stunned" myocardium (hypocontractile, but recoverable, myocardium after ischemia). Moreover, although volatile anesthetics decrease myocardial contractility, they can be potentially beneficial in patients with heart failure because most of them decrease preload and afterload.

The Pathophysiology of Heart Failure

Systolic heart failure occurs when the heart is unable to pump a sufficient amount of blood to meet the body's metabolic requirements. Clinical manifestations usually reflect the effects of the low cardiac output on tissues (eg, fatigue, dyspnea, oxygen debt, acidosis), the damming-up of blood behind the failing ventricle (dependent edema or pulmonary venous congestion), or both. The left ventricle is most commonly the primary cause, often with secondary involvement of the right ventricle. Isolated right ventricular failure can occur in the setting of advanced disease of the lung parenchyma or pulmonary vasculature. Left ventricular failure is most commonly the result of myocardial dysfunction, usually from coronary artery disease, but may also be the result of viral disease, toxins, untreated hypertension, valvular dysfunction, arrhythmias, or pericardial disease.

Diastolic dysfunction can be present in the absence of signs or symptoms of heart failure. Symptoms arising from diastolic dysfunction are the result of atrial hypertension (**Figure 20–13**). Failure of the heart to relax during diastole leads to elevated left ventricular end-diastolic pressure, which is transmitted to the left atrium and pulmonary vasculature. Common causes of diastolic dysfunction include hypertension, coronary artery disease, hypertrophic cardiomyopathy, valvular heart disease, and pericardial disease. Although diastolic dysfunction can occasionally cause symptoms of heart failure, even in the presence of normal systolic function (normal left ventricular ejection fraction), it nearly always occurs in association with systolic dysfunction in patients with heart failure.

Diastolic dysfunction is diagnosed echocardiographically. Placing the pulse wave Doppler sample gate at the tips of the mitral valve during

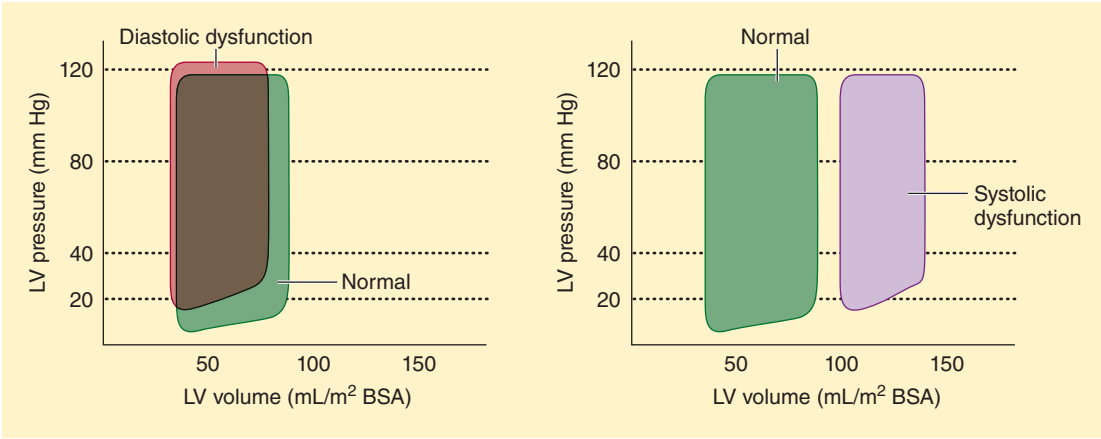

FIGURE 20–13 Ventricular pressure–volume relationships in isolated systolic and diastolic dysfunction.

left ventricular filling will produce the characteristic diastolic flow pattern (Figure 20–9). In patients with normal diastolic function, the ratio between the peak velocities of the early (E) and the atrial (A) waves is from 0.8 to 2. In the early stages of diastolic dysfunction, the primary abnormality is impaired relaxation. When left ventricular relaxation is delayed, the initial pressure gradient between the left atrium and the left ventricle is reduced, resulting in a decline in early filling, and, consequently, a reduced peak E wave velocity. The A wave velocity is increased relative to the E wave, and the E/A ratio is reduced. As diastolic dysfunction advances, the left atrial pressure increases, restoring the gradient between the left atrium and left ventricle with an apparent restoration of the normal E/A ratio. This pattern is characterized as "pseudonormalized." Using the E/A ratio alone cannot distinguish between a normal and pseudonormalized pattern of diastolic inflow. As diastolic dysfunction worsens further, a restrictive pattern is obtained. In this scenario, the left ventricle is so stiff that pressure builds in the left atrium, resulting in a dramatic peak of early filling and a prominent, tall, narrow E wave. Because the ventricle is so poorly compliant, the atrial contraction contributes little to filling, resulting in a diminished A wave and an E/A ratio greater than 2:1.

Doppler patterns of pulmonary venous flow have been used to distinguish between a pseudonormalized and normal E/A ratio. Currently, most echocardiographers use tissue Doppler to examine the movement of the lateral annulus of the mitral valve during ventricular filling (Figure 20–9). Tissue Doppler allows the echocardiographer to determine both the velocity and the direction of the movement of the heart. During systole, the heart contracts toward the apex, away from a TEE transducer in the esophagus. This motion produces the s' wave of systole. During early and late diastolic filling, the heart moves toward the transducer producing the e' and a' waves. Like the inflow patterns achieved with pulse wave Doppler, characteristic patterns of diastolic dysfunction are reflected in the tissue Doppler trace. An e' wave less than 8 cm/sec is consistent with diastolic dysfunction. Of note, the tissue Doppler trace does not produce a pseudonormalized pattern permitting the echocardiographer to readily distinguish between normal and abnormal diastolic function.

Cardiac output *may* be reduced at rest with heart failure, but the key point is that the heart is incapable of appropriately *increasing* cardiac output and oxygen delivery in response to demand. Inadequate oxygen delivery to tissues is reflected by a low mixed venous oxygen tension and an increase in the arteriovenous oxygen content difference. In compensated heart failure, the arteriovenous difference may be normal at rest, but it rapidly widens during stress or exercise.

Heart failure is less commonly associated with an elevated cardiac output. This form of heart failure is most often seen with sepsis, thyrotoxicosis, and other hypermetabolic states, which are typically associated with a low SVR.

COMPENSATORY MECHANISMS

Compensatory mechanisms generally present in patients with heart failure include increased preload, activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, and increased release of AVP. Although these mechanisms can initially compensate for mild to moderate cardiac dysfunction, with increasing severity of dysfunction, they may actually contribute to the cardiac impairment. Many of the drug treatments of chronic heart failure serve to counteract these mechanisms.

Increased Preload

An increase in ventricular size not only reflects an inability to keep up with an increased circulating blood volume, but also serves to increase stroke volume by moving the heart up the Starling curve (see Figure 20–4). Even when EF is reduced, an increase in ventricular end-diastolic volume can maintain a normal stroke volume. Worsening venous congestion caused by the pooling of blood behind the failing ventricle and excessive ventricular dilatation can rapidly lead to clinical deterioration. Left ventricular failure results in pulmonary vascular congestion and progressive transudation of fluid, first into the pulmonary interstitium and then into alveoli (pulmonary edema). Right ventricular failure leads to systemic venous hypertension, which results in peripheral edema, hepatic congestion and dysfunction, and ascites. Dilatation of the annulus of either AV valve leads to valvular regurgitation, further impairing ventricular output.

Increased Sympathetic Tone

Sympathetic activation increases release of norepinephrine from nerve endings in the heart and the adrenal secretion of epinephrine into the circulation. Plasma catecholamine levels are generally directly proportional to the degree of left ventricular dysfunction. Although enhanced sympathetic outflow can initially maintain cardiac output by increasing heart rate and contractility, worsening ventricular function elicits increasing degrees of vasoconstriction in an effort to maintain arterial blood pressure. The associated increase in afterload, however, reduces cardiac output and exacerbates the ventricular failure.

Chronic sympathetic activation in patients with heart failure eventually decreases the response of adrenergic receptors to catecholamines (receptor uncoupling), the number of receptors (down-regulation), and cardiac catecholamine stores. 11 Nonetheless, the failing heart becomes increasingly dependent on circulating catecholamines. Abrupt withdrawal in sympathetic outflow or decreases in circulating catecholamine levels, such as can occur following induction of anesthesia, may lead to acute cardiac decompensation. A reduced density of M_2 receptors also decreases parasympathetic influences on the heart.

Sympathetic activation tends to redistribute systemic blood flow output away from the skin, gut, kidneys, and skeletal muscle to the heart and brain. Decreased renal perfusion, together with β_1-adrenergic activity at the juxtaglomerular apparatus, activates the renin–angiotensin–aldosterone axis, which leads to sodium retention and interstitial edema. Moreover, vasoconstriction secondary to elevated angiotensin II levels increases left ventricular afterload and causes further deterioration of systolic function. The latter partially accounts for the efficacy of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers in heart failure. Symptoms may also improve in some patients with careful, low-dose β-adrenergic blockade. Outcomes in heart failure are improved by administration of ACE inhibitors (and/or angiotensin receptor blockers), certain long-acting β-blockers (carvedilol or extended release metoprolol), and aldosterone inhibitors (spironolactone or eplerenone).

Circulating AVP levels, often markedly increased in patients with severe heart failure, will

increase ventricular afterload and are responsible for a defect in free water clearance that is commonly associated with hyponatremia.

Brain natriuretic peptide (BNP) is produced in the heart in response to myocyte distention. Elevated BNP concentration (>500 pg/mL) usually indicates heart failure, and measurement of BNP concentration can be used to distinguish between heart failure and lung disease as a cause of dyspnea. Recombinant BNP was developed as a vasodilator and inhibitor of the renin–angiotensin–aldosterone system for use in patients with severe decompensated heart failure, but outcomes were not improved with its use.

Ventricular Hypertrophy

Ventricular hypertrophy can occur with or without dilatation, depending on the type of stress imposed on the ventricle. When the heart is subjected to either pressure or volume overload, the initial response is to increase sarcomere length and optimally overlap actin and myosin. With time, ventricular muscle mass begins to increase in response to the abnormal stress.

In the volume-overloaded ventricle, the problem is an increase in diastolic wall stress. The increase in ventricular muscle mass is sufficient only to compensate for the increase in diameter: The ratio of the ventricular radius to wall thickness is unchanged. Sarcomeres replicate mainly in series, resulting in eccentric hypertrophy. Although ventricular EF remains depressed, the increase in end-diastolic volume can maintain normal at-rest stroke volume (and cardiac output).

The problem in a pressure-overloaded ventricle is an increase in systolic wall stress. In this case, sarcomeres mainly replicate in parallel, resulting in concentric hypertrophy: The hypertrophy is such that the ratio of myocardial wall thickness to ventricular radius increases. As can be seen from Laplace's law, systolic wall stress can then be normalized. Ventricular hypertrophy, particularly that caused by pressure overload, usually results in progressive diastolic dysfunction. The most common reasons for isolated left ventricular hypertrophy are hypertension and aortic stenosis.

CASE DISCUSSION

A Patient With a Short P–R Interval

A 38-year-old man is scheduled for endoscopic sinus surgery following a recent onset of headaches. He gives a history of having passed out at least once during one of these headaches. A preoperative electrocardiogram (ECG) is normal, except for a P–R interval of 0.116 sec with normal P-wave morphology.

What is the significance of the short P–R interval?

The P–R interval, which is measured from the beginning of atrial depolarization (P wave) to the beginning of ventricular depolarization (QRS complex), usually represents the time required for depolarization of both atria, the AV node, and the His–Purkinje system. Although the P–R interval can vary with heart rate, it is normally 0.12–0.2 sec in duration. Abnormally short P–R intervals can be seen with either low atrial (or upper AV junctional) rhythms or preexcitation phenomena. The two can usually be differentiated by P-wave morphology: With a low atrial rhythm, atrial depolarization is retrograde, resulting in an inverted P wave in leads II, III, and aVF; with preexcitation, the P wave is normal during sinus rhythm. If the pacemaker rhythm originates from a lower AV junctional focus, the P wave may be lost in the QRS complex or may follow the QRS.

What is preexcitation?

Preexcitation usually refers to early depolarization of the ventricles by an abnormal conduction pathway from the atria. Rarely, more than one such pathway is present. The most common form of preexcitation is due to the presence of an accessory pathway (bundle of Kent) that connects one of the atria with one of the ventricles. This abnormal connection between the atria and ventricles allows electrical impulses to bypass the AV node (hence the term bypass tract). The ability to conduct impulses along the bypass tract can be quite variable and may be only intermittent or rate dependent. Bypass tracts can conduct in both directions, retrograde only (ventricle to atrium), or,

rarely, anterograde only (atrium to ventricle). The name Wolff–Parkinson–White (WPW) syndrome is often applied to ventricular preexcitation associated with tachyarrhythmias.

How does preexcitation shorten the P–R interval?

In patients with preexcitation, the normal cardiac impulse originating from the SA node is conducted simultaneously through the normal (AV nodal) and anomalous (bypass tract) pathways. Because conduction is more rapid in the anomalous pathway than in the AV nodal pathway, the cardiac impulse rapidly reaches and depolarizes the area of the ventricles where the bypass tract ends. This early depolarization of the ventricle is reflected by a short P–R interval and a slurred initial deflection (δ wave) in the QRS complex. The spread of the anomalous impulse to the rest of the ventricle is delayed because it must be conducted by ordinary ventricular muscle, not by the much faster Purkinje system. The remainder of the ventricle is then depolarized by the normal impulse from the AV node as it catches up with the preexcitation front. Although the P–R interval is shortened, the resulting QRS is slightly prolonged and represents a fusion complex of normal and abnormal ventricular depolarizations.

The P–R interval in patients with preexcitation depends on relative conduction times between the AV nodal pathway and the bypass pathway. If conduction through the former is fast, preexcitation (and the δ wave) is less prominent, and QRS will be relatively normal. If conduction is delayed in the AV nodal pathway, preexcitation is more prominent, and more of the ventricle will be depolarized by the abnormally conducted impulse. When the AV nodal pathway is completely blocked, the entire ventricle is depolarized by the bypass pathway, resulting in a very short P–R interval, a very prominent δ wave, and a wide, bizarre QRS complex. Other factors that can affect the degree of preexcitation include interatrial conduction time, the distance of the atrial end of the bypass tract from the SA node, and autonomic tone. The P–R interval is often normal or only slightly shortened with a left lateral bypass tract (the most common location). Preexcitation may be more apparent at fast heart rates because conduction slows through the AV node with increasing heart rates. Secondary ST-segment and T-wave changes are also common because of abnormal ventricular repolarization.

What is the clinical significance of preexcitation?

Preexcitation occurs in approximately 0.3% of the general population. An estimated 20% to 50% of affected persons develop paroxysmal tachyarrhythmias, typically paroxysmal supraventricular tachycardia (PSVT). Although most patients are otherwise normal, preexcitation can be associated with other cardiac anomalies, including Ebstein's anomaly, mitral valve prolapse, and cardiomyopathies. Depending on its conductive properties, the bypass tract in some patients may predispose them to tachyarrhythmias and even sudden death. Tachyarrhythmias include PSVT, atrial fibrillation, and, less commonly, atrial flutter. Ventricular fibrillation can be precipitated by a critically timed premature atrial beat that travels down the bypass tract and catches the ventricle at a vulnerable period. Alternatively, very rapid conduction of impulses into the ventricles by the bypass tract during atrial fibrillation can rapidly lead to myocardial ischemia, hypoperfusion, and hypoxia and culminate in ventricular fibrillation.

Recognition of the preexcitation phenomenon is also important because its QRS morphology on the surface ECG can mimic bundle branch block, right ventricular hypertrophy, ischemia, myocardial infarction, and ventricular tachycardia (during atrial fibrillation).

What is the significance of the history of syncope in this patient?

This patient should be evaluated preoperatively by a cardiologist for possible electrophysiological studies, curative radiofrequency ablation of the bypass tract, and the need for perioperative drug therapy. Such studies can identify the location of the bypass tracts, reasonably predict the potential for malignant arrhythmias by programmed

pacing, and assess the efficacy of antiarrhythmic therapy if curative ablation is not possible. Ablation is reported to be curative in over 90% of patients. A history of syncope may be ominous because it may indicate the ability to conduct impulses very rapidly through the bypass tract, leading to systemic hypoperfusion and perhaps predisposing the patient to sudden death.

Patients with only occasional asymptomatic tachyarrhythmias generally do not require investigation or prophylactic drug therapy. Those with frequent episodes of tachyarrhythmias or arrhythmias associated with significant symptoms require drug therapy and close evaluation.

How do tachyarrhythmias generally develop?

Tachyarrhythmias develop as a result of either abnormal impulse formation or abnormal impulse propagation (reentry). Abnormal impulses result from enhanced automaticity, abnormal automaticity, or triggered activity. Usually, only cells of the SA node, specialized atrial conduction pathways, AV nodal junctional areas, and the His–Purkinje system depolarize spontaneously. Because diastolic repolarization (phase 4) is fastest in the SA node, other areas of automaticity are suppressed. Enhanced or abnormal automaticity in other areas, however, can usurp pacemaker function from the SA node and lead to tachyarrhythmias. Triggered activity is the result of either early after-depolarizations (phase 2 or 3) or delayed after-depolarizations (after phase 3). It consists of small-amplitude depolarizations that can follow action potentials under some conditions in atrial, ventricular, and His–Purkinje tissue. If these after-depolarizations reach threshold potential, they can result in an extrasystole or repetitive sustained tachyarrhythmias. Factors that can promote the formation of abnormal impulses include increased catecholamine levels, electrolyte disorders (hyperkalemia, hypokalemia, and hypercalcemia), ischemia, hypoxia, mechanical stretch, and drug toxicity (particularly digoxin).

The most common mechanism for tachyarrhythmias is reentry. Four conditions are necessary to initiate and sustain reentry (**Figure 20–14**): (1) two areas in the myocardium that differ in conductivity or refractoriness and that can form a closed electrical loop; (2) unidirectional block in one pathway (Figure 20–14A and B); (3) slow conduction or sufficient length in the circuit to allow recovery of the conduction block in the first pathway (Figure 20–14C); and (4) excitation of the initially blocked pathway to complete the loop (Figure 20–14D). Reentry is usually precipitated by a premature cardiac impulse.

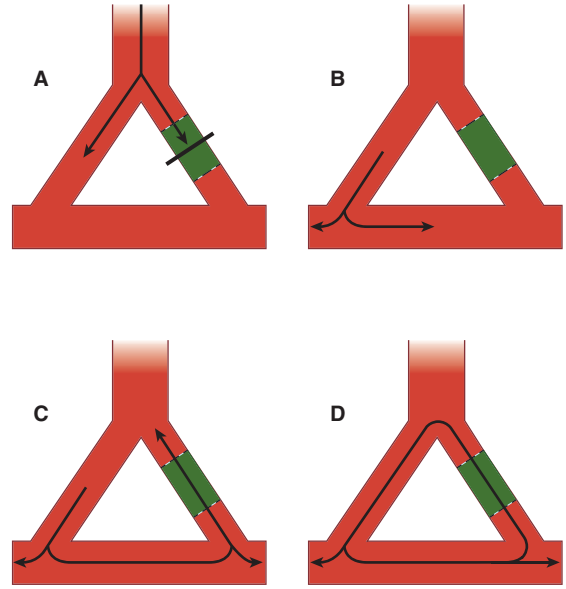

FIGURE 20–14 **A–D**: The mechanism of reentry. See text for description.

What is the mechanism of PSVT in patients with WPW syndrome?

If the bypass tract is refractory during anterograde conduction of a cardiac impulse, as during a critically timed atrial premature contraction (APC), and the impulse is conducted by the AV node, the same impulse can be conducted retrograde from the ventricle back into the atria via the bypass tract. The retrograde impulse can then depolarize the atrium and travel down the AV nodal pathway again, establishing a continuous repetitive circuit (circus movement). The impulse reciprocates between the atria and ventricles and conduction

alternates between the AV nodal pathway and the bypass tract. The term "concealed conduction" is often applied because the absence of preexcitation during this arrhythmia results in a normal QRS that lacks a δ wave.

The circus movement less commonly involves anterograde conduction through the bypass tract and retrograde conduction through the AV nodal pathway. In such instances, the QRS has a δ wave and is completely abnormal; the arrhythmia can be mistaken for ventricular tachycardia.

What other mechanisms may be responsible for PSVT?

In addition to the WPW syndrome, PSVT can be caused by AV reentrant tachycardia, AV nodal reentrant tachycardia, and SA node and atrial reentrant tachycardias. Patients with AV reentrant tachycardia have an extranodal bypass tract similar to patients with WPW syndrome, but the bypass tract conducts only retrograde; preexcitation and a δ wave are absent. The PSVT may be initiated either by an APC or a ventricular premature contraction (VPC). A retrograde P wave is usually visible because atrial depolarization always follows ventricular depolarization.

Functional differences in conduction and refractoriness may occur within the AV node, SA node, or atria; a large bypass tract is not necessary. Thus, the circus movement may occur on a smaller scale within the AV node, SA node, or atria, respectively. PSVT is always induced during AV nodal reentry by an APC with a prolonged P–R interval; a retrograde P wave is either absent or buried in the QRS complex. Another APC may terminate the arrhythmia.

PSVT associated with SA node or atrial reentry is always triggered by an APC. The P wave is usually visible and has a prolonged P–R interval. Its morphology is normal with SA nodal reentry and abnormal with atrial reentry.

How does atrial fibrillation in patients with WPW syndrome differ from the arrhythmia in other patients?

Atrial fibrillation can occur when a cardiac impulse is conducted rapidly retrograde up into the atria and arrives to find different parts of the atria out of phase in recovery from the impulse. Once atrial fibrillation is established, conduction into the ventricles most commonly occurs through the bypass tract only; because of the accessory pathway's ability to conduct very rapidly (unlike the AV nodal pathway), the ventricular rate is typically very rapid (180–300 beats/min). The majority of QRS complexes are bizarre, but periodic conduction of an impulse through the AV nodal pathway results in occasional normal-looking QRS complexes. Less commonly, impulses during atrial fibrillation are conducted mainly through the AV nodal pathway (resulting in mostly normal QRS complexes) or through both the bypass tract and the AV nodal pathway (resulting in a mixture of normal, fusion, and bizarre QRS complexes). As stated previously, atrial fibrillation in patients with WPW syndrome is a very dangerous arrhythmia.

What anesthetic agents can safely be used in patients with preexcitation?

Few data are available comparing the use of different anesthetic agents or techniques in patients with preexcitation. Almost all the volatile and intravenous agents have been used with equal success. Volatile anesthetics increase antegrade refractoriness in both normal and accessory pathways and increase the coupling interval (a measure of the ability of an extrasystole to induce tachycardia). Propofol, opioids, and benzodiazepines seem to have little direct electrophysiological effects, but can alter autonomic tone, generally reducing sympathetic outflow. Factors that tend to cause sympathetic stimulation and increased cardiac automaticity are undesirable. Premedication with a benzodiazepine helps reduce high sympathetic tone preoperatively. Agents that can increase sympathetic tone, such as ketamine and perhaps pancuronium in large bolus doses, should generally be avoided. Anticholinergics should be used cautiously; glycopyrrolate may be preferable to atropine. Endotracheal intubation should be carried out only after the patient is deeply anesthetized; pretreatment with a β-adrenergic blocker,

such as esmolol, may be useful. Light anesthesia, hypercapnia, acidosis, and even transient hypoxia will activate the sympathetic system and are to be avoided. A deep extubation and good postoperative analgesia (without respiratory acidosis) may also help prevent the onset of arrhythmias. When patients with preexcitation are anesthetized for electrophysiological study and surgical ablation, opioids, propofol, and benzodiazepines may be the agents least likely to alter conduction characteristics.

How are antiarrhythmic agents selected for tachyarrhythmias?

Most antiarrhythmic agents act by altering myocardial cell conduction (phase 0), repolarization (phase 3), or automaticity (phase 4). Prolongation of repolarization increases the refractoriness of cells. Many antiarrhythmic drugs also exert direct or indirect autonomic effects. Although antiarrhythmic agents are generally classified according to broad mechanisms of action or electrophysiological effects (Table 20–7), the most commonly

TABLE 20–7 Classification of antiarrhythmic agents.[1]

Class	Mechanism of Action	Agents	Intravenous Loading Dose
I	Blocks voltage-gated sodium channels; decreases slope of phase 0 (V_{max})		
Ia	Moderate depression of V_{max}, prolongs APD	Quinidine[2–4] Procainamide (Pronestyl)[1,4] Disopyramide (Norpace)[1,4]	NR 5–10 mg/kg NA
Ib	Minimal effect on V_{max}, shorten APD	Lidocaine Phenytoin Tocainide (Tonocard) Mexiletine (Mexitil) Moricizine (Ethmozine)	1–2 mg/kg 5–15 mg/kg NA NA NA
Ic	Marked depression of V_{max}, minimal effect of APD	Flecainide (Tambacor) Propafenone (Rythmol)	NA NA
II	Blocks β-adrenergic receptors	Esmolol (Brevibloc) Metoprolol (Lopressor)	0.5 mg/kg 5–10 mg
III	Prolongs repolarization	Amiodarone (Cordarone)[5–7] Sotalol (Betapace)[8] Ibutilide (Corvert) Dofetilide (Tikosyn)	150 mg NA 1 mg NA
IV	Blocks slow calcium channels	Verapamil (Calan) Diltiazem (Cardizem)	2.5–10 mg 0.25–0.35 mg/kg
V	Various (miscellaneous agents)	Digoxin Adenosine (Adenocard)	0.5–0.75 mg 6–12 mg

[1] V_{max}, maximum velocity; APD, action potential duration; NR, not recommended; NA, not available for intravenous use.
[2] Also has antimuscarinic (vagolytic activity).
[3] Also blocks α-adrenergic receptors.
[4] Also prolongs repolarization.
[5] Also binds inactivated sodium channels.
[6] Also causes noncompetitive α- and β-adrenergic blockade.
[7] Also blocks slow calcium channels.
[8] Also has nonselective β-adrenergic blocking activity.

used classification system is not perfect because some agents have more than one mechanism of action.

Selection of an antiarrhythmic agent generally depends on whether the arrhythmia is ventricular or supraventricular and whether acute control or chronic therapy is required. Intravenous agents are usually employed in the acute management of arrhythmias, whereas oral agents are reserved for chronic therapy (Table 20–8).

TABLE 20–8 Clinical pharmacological properties of antiarrhythmic drugs.[1]

Drug	Effect on SA Nodal Rate	Effect on AV Nodal Refractory Period	PR Interval	QRS Duration	QT Interval	Usefulness in Arrhythmias		Half-Life
						Supraventricular	Ventricular	
Adenosine	Little	↑↑↑	↑↑↑	0	0	++++	?	<10 s
Amiodarone	↓↓[2]	↑↑	↑↑	↑	↑↑↑↑	+++	+++	(Weeks)
Bretylium	↑↓[3]	↑↓[3]	0	0	0	0	+	4h
Diltiazem	↑↓	↑↑	↑	0	0	+++	–	4–8 h
Disopyramide	↑↓[2,4]	↑↓[4]	↑↓[4]	↑↑	↑↑	+	+++	6–8 h
Dofetilide	↓?	0	0	0	↑↑	++	None	7 h
Esmolol	↓↓	↑↑	↑↑	0	0	+	+	10 min
Flecainide	None	↑	↑	↑↑↑	0	+[5]	++++	20 h
Ibutilide	↓(?)	0	0	0	↑↑	++	?	6 h
Lidocaine	None[2]	None	0	0	0	None[6]	+++	1–2 h
Metopolol	↓↓	↑↑	↑↑	0	0	+	+	8 h
Mexiletine	None[2]	None	0	0	0	None[7]	+++	12 h
Moricizine	None	None	↑	↑↑	0	None	+++	2–6 h[7]
Procainamide	↓[2]	↑↓[4]	↑↓[4]	↑↑	↑↑	+	+++	3–4 h
Propafenone	0	↑	↑	↑↑↑	0	+	+++	5–7 h
Quinidine	↑↓[2,4]	↑↓[4]	↑↓[4]	↑↑	↑↑	+	+++	6 h
Sotalol	↓↓	↑↑	↑↑	0	↑↑↑	+++	+++	7 h
Tocainide	None[2]	None	0	0	0	None[6]	+++	12 h
Verapamil	↓↓	↑↑	↑↑	0	0	+++	–	7 h

[1]Data from Katzung BG: *Basic and Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012.
[2]May suppress diseased sinus nodes.
[3]Initial stimulation by release of endogenous norepinephrine followed by depression.
[4]Anticholingergic effect and direct depressant action.
[5]Particularly in Wolff–Parkinson–White syndrome.
[6]May be effective in atrial arrhythmias caused by digitalis.
[7]Half-life of active metabolites is much longer.

Which agents are most useful for tachyarrhythmias in patients with WPW syndrome?

Cardioversion is the treatment of choice in hemodynamically compromised patients. Adenosine is the drug of choice for PSVT because of its short duration of action. Small doses of phenylephrine (100 mcg), together with vagal maneuvers (carotid massage if not contraindicated by carotid occulsive disease), help support arterial blood pressure and may terminate the arrhythmia. The most useful pharmacological agents are class Ia drugs (eg, procainamide). These agents increase the refractory period and decrease conduction in the accessory pathway. Moreover, class Ia drugs frequently terminate and can suppress the recurrence of PSVT and atrial fibrillation. Class Ic drugs and amiodarone are also useful because they slow conduction and prolong refractoriness in both the AV node and the accessory pathway. β-Adrenergic blocking agents may also be useful, particularly in controlling ventricular rate once these rhythms are established. Verapamil and digoxin are contraindicated during atrial fibrillation or flutter in these patients because they can dangerously accelerate the ventricular response. Both types of agents decrease conduction through the AV node, favoring conduction of impulses down the accessory pathway. The bypass tract is capable of conducting impulses into the ventricles much faster than the AV nodal pathway. Digoxin may also increase the ventricular response by shortening the refractory period and increasing conduction in accessory pathways. Although verapamil can terminate PSVT, its use in this setting may be hazardous because patients can subsequently develop atrial fibrillation or flutter. Moreover, atrial fibrillation may not be readily distinguishable from ventricular tachycardia in these patients if wide-QRS tachycardia develops.

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