4. **Mean arterial pressure**
   - is the average arterial pressure with respect to time.
   - can be calculated approximately as **diastolic pressure plus one-third of pulse pressure.**

H. Venous pressure

- is very low.
- The veins have a high capacitance and, therefore, can hold large volumes of blood at low pressure.

I. Atrial pressure

- is slightly lower than venous pressure.
- Left atrial pressure is estimated by the **pulmonary wedge pressure.** A catheter, inserted into the smallest branches of the pulmonary artery, makes almost direct contact with the pulmonary capillaries. The measured pulmonary capillary pressure is approximately equal to the left atrial pressure.

III. CARDIAC ELECTROPHYSIOLOGY

A. Electrocardiogram (ECG) (Figure 3-3)

1. **P wave**
   - represents atrial depolarization.
   - does not include atrial repolarization, which is "buried" in the QRS complex.
2. **PR interval**
   - is the interval from the beginning of the P wave to the beginning of the Q wave (initial depolarization of the ventricle).

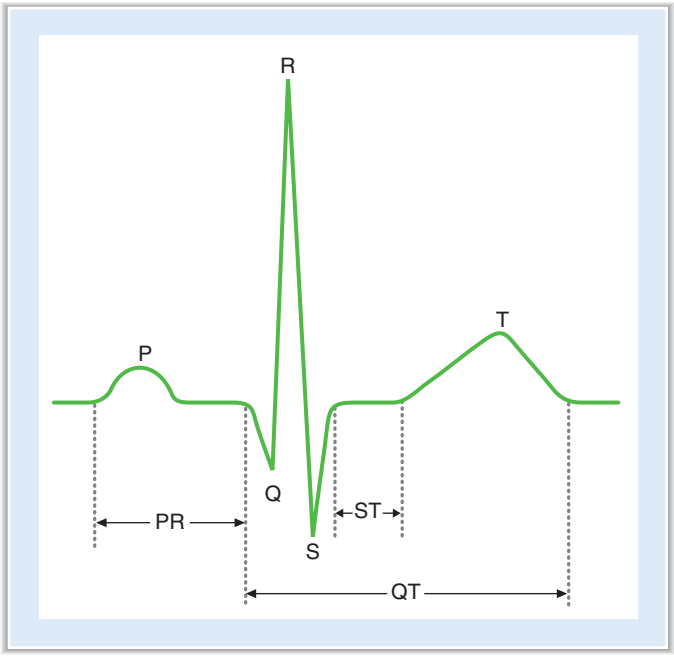

FIGURE 3-3 Normal electrocardiogram measured from lead II.

- varies with **conduction velocity through the atrioventricular (AV) node.** For example, if AV nodal conduction decreases (as in **heart block**), the PR interval increases.
- is decreased (i.e., increased conduction velocity through AV node) by stimulation of the sympathetic nervous system.
- is increased (i.e., decreased conduction velocity through AV node) by stimulation of the parasympathetic nervous system.

3. QRS complex

- represents depolarization of the ventricles.

4. QT interval

- is the interval from the beginning of the Q wave to the end of the T wave.
- represents the entire period of depolarization and repolarization of the ventricles.

5. ST segment

- is the segment from the end of the S wave to the beginning of the T wave.
- is isoelectric.
- represents the period when the ventricles are depolarized.

6. T wave

- represents ventricular repolarization.

B. Cardiac action potentials (see Table 1-3)

- The **resting membrane potential** is determined by the conductance to K^+ and approaches the K^+ equilibrium potential.
- **Inward current** brings positive charge into the cell and **depolarizes** the membrane potential.
- **Outward current** takes positive charge out of the cell and **hyperpolarizes** the membrane potential.
- The role of Na^+,K^+-adenosine triphosphatase (ATPase) is to maintain ionic gradients across cell membranes.

1. Ventricles, atria, and the Purkinje system (Figure 3-4)

- have stable resting membrane potentials of about –90 millivolts (mV). This value approaches the K^+ equilibrium potential.
- Action potentials are of long duration, especially in Purkinje fibers, where they last 300 milliseconds (msec).

a. Phase 0

- is the **upstroke** of the action potential.

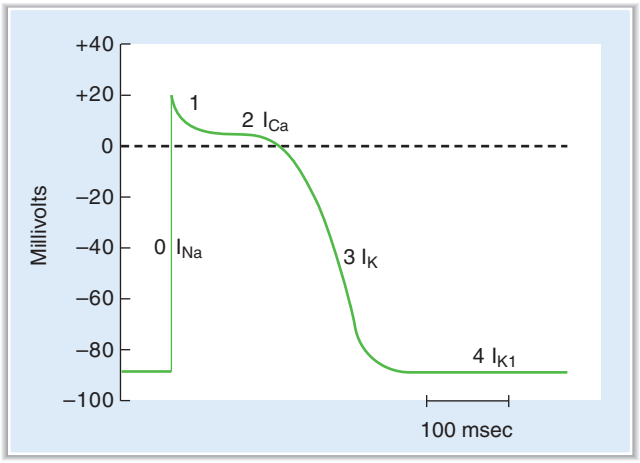

FIGURE 3-4 Ventricular action potential.

- is caused by a transient increase in **Na^+ conductance.** This increase results in an inward Na^+ current that depolarizes the membrane.
- At the peak of the action potential, the membrane potential approaches the Na^+ equilibrium potential.

b. Phase 1

- is a brief period of initial repolarization.
- **Initial repolarization** is caused by an outward current, in part because of the movement of K^+ ions (favored by both chemical and electrical gradients) out of the cell and in part because of a decrease in Na^+ conductance.

c. Phase 2

- is the **plateau** of the action potential.
- is caused by a **transient increase in Ca^{2+} conductance**, which results in an **inward Ca^{2+} current**, and by an increase in K^+ conductance.
- During phase 2, outward and inward currents are approximately equal, so the membrane potential is stable at the plateau level.

d. Phase 3

- is **repolarization.**
- During phase 3, Ca^{2+} conductance decreases, and K^+ conductance increases and therefore predominates.
- The high K^+ conductance results in a large **outward K^+ current (I_K)**, which hyperpolarizes the membrane back toward the K^+ equilibrium potential.

e. Phase 4

- is the **resting membrane potential.**
- is a period during which inward and outward currents (I_{K1}) are equal and the membrane potential approaches the K^+ equilibrium potential.

2. Sinoatrial (SA) node (Figure 3-5)

- is normally the **pacemaker** of the heart.
- has an **unstable resting potential.**
- exhibits phase 4 depolarization, or automaticity.
- The AV node and the His-Purkinje systems are **latent pacemakers** that may exhibit automaticity and override the SA node if it is suppressed.
- The intrinsic rate of phase 4 depolarization (and heart rate) is fastest in the SA node and slowest in the His-Purkinje system:
  SA node > AV node > His-Purkinje

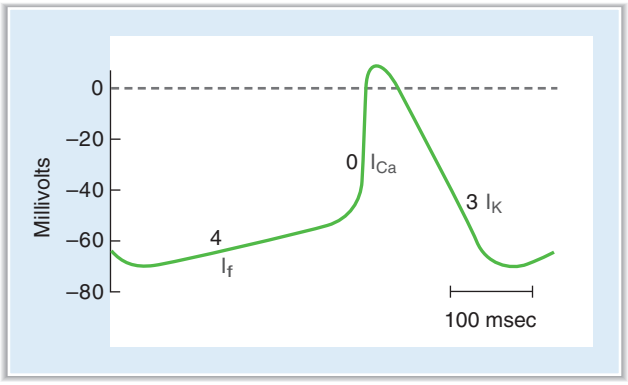

FIGURE 3-5 Sinoatrial nodal action potential.

a. Phase 0

- is the **upstroke** of the action potential.
- is caused by an increase in Ca^{2+} conductance. This increase causes an **inward Ca^{2+} current** that drives the membrane potential toward the Ca^{2+} equilibrium potential.
- The ionic basis for phase 0 in the SA node is different from that in the ventricles, atria, and Purkinje fibers (where it is the result of an inward Na^+ current).

b. Phase 3

- is **repolarization.**
- is caused by an increase in K^+ conductance. This increase results in an **outward K^+ current** that causes repolarization of the membrane potential.

c. Phase 4

- is **slow depolarization.**
- accounts for the pacemaker activity of the SA node (automaticity).
- is caused by an increase in Na^+ conductance, which results in an **inward Na^+ current** called **I_f.**
- **I_f is turned on by repolarization** of the membrane potential during the preceding action potential.

d. Phases 1 and 2

- are not present in the SA node action potential.

3. AV node

- Upstroke of the action potential in the AV node is the result of an **inward Ca^+ current** (as in the SA node).

C. Conduction velocity

- reflects the time required for excitation to spread throughout cardiac tissue.
- depends on the **size of the inward current during the upstroke** of the action potential. The larger the inward current, the higher the conduction velocity.
- is **fastest in the Purkinje system.**
- is **slowest in the AV node** (seen as the PR interval on the ECG), allowing time for **ventricular filling** before ventricular contraction. If conduction velocity through the AV node is increased, ventricular filling may be compromised.

D. Excitability

- is the ability of cardiac cells to initiate action potentials in response to inward, depolarizing current.
- reflects the recovery of channels that carry the inward currents for the upstroke of the action potential.
- changes over the course of the action potential. These changes in excitability are described by **refractory periods** (Figure 3-6).

1. Absolute refractory period (ARP)

- begins with the upstroke of the action potential and ends after the plateau.
- reflects the time during which **no action potential can be initiated**, regardless of how much inward current is supplied.

2. Effective refractory period (ERP)

- is slightly longer than the ARP.
- is the period during which a **conducted action potential cannot be elicited.**

3. Relative refractory period (RRP)

- is the period immediately after the ARP when repolarization is almost complete.

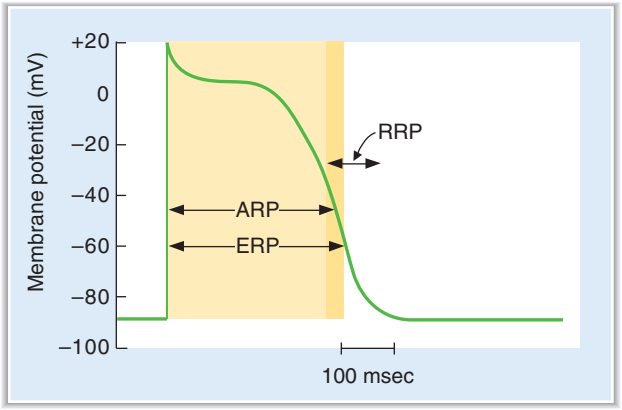

FIGURE 3-6 Absolute (ARP), effective (ERP), and relative refractory periods (RRP) in the ventricle.

- is the period during which an **action potential can be elicited, but more than the usual inward current is required.**

E. Autonomic effects on heart rate and conduction velocity (Table 3-1)

- See IV C for a discussion of inotropic effects.

1. Definitions of chronotropic and dromotropic effects

a. Chronotropic effects

- produce changes in heart rate.
- A **negative chronotropic effect** decreases heart rate by decreasing the firing rate of the SA node.
- A **positive chronotropic effect** increases heart rate by increasing the firing rate of the SA node.

b. Dromotropic effects

- produce changes in conduction velocity, primarily in the AV node.
- A **negative dromotropic effect** decreases conduction velocity through the AV node, slowing the conduction of action potentials from the atria to the ventricles and increasing the PR interval.
- A **positive dromotropic effect** increases conduction velocity through the AV node, speeding the conduction of action potentials from the atria to the ventricles and decreasing the PR interval.

2. Parasympathetic effects on heart rate and conduction velocity

- The SA node, atria, and AV node have parasympathetic vagal innervation, but the ventricles do not. The neurotransmitter is **acetylcholine** (ACh), which acts at **muscarinic receptors.**

table 3-1 Autonomic Effects on the Heart and Blood Vessels

	Sympathetic		Parasympathetic	
	Effect	*Receptor*	*Effect*	*Receptor*
Heart rate	↑	β_1	↓	Muscarinic
Conduction velocity (AV node)	↑	β_1	↓	Muscarinic
Contractility	↑	β_1	↓ (atria only)	Muscarinic
Vascular smooth muscle				
Skin, splanchnic	Constriction	α_1		
Skeletal muscle	Constriction	α_1		
	Relaxation	β_2		

AV = atrioventricular.

a. Negative chronotropic effect

- **decreases heart rate** by decreasing the rate of phase 4 depolarization.
- Fewer action potentials occur per unit time because the threshold potential is reached more slowly and, therefore, less frequently.
- The mechanism of the negative chronotropic effect is **decreased I_f**, the inward Na^+ current that is responsible for phase 4 depolarization in the SA node.

b. Negative dromotropic effect

- **decreases conduction velocity through the AV node.**
- Action potentials are conducted more slowly from the atria to the ventricles.
- **increases the PR interval.**
- The mechanism of the negative dromotropic effect is **decreased inward Ca^{2+} current** and increased outward K^+ current.

3. Sympathetic effects on heart rate and conduction velocity

- **Norepinephrine** is the neurotransmitter, acting at **β_1 receptors.**

a. Positive chronotropic effect

- **increases heart rate** by increasing the rate of phase 4 depolarization.
- More action potentials occur per unit time because the threshold potential is reached more quickly and, therefore, more frequently.
- The mechanism of the positive chronotropic effect is **increased I_f**, the inward Na^+ current that is responsible for phase 4 depolarization in the SA node.

b. Positive dromotropic effect

- **increases conduction velocity through the AV node.**
- Action potentials are conducted more rapidly from the atria to the ventricles, and ventricular filling may be compromised.
- **decreases the PR interval.**
- The mechanism of the positive dromotropic effect is **increased inward Ca^{2+} current.**

IV. CARDIAC MUSCLE AND CARDIAC OUTPUT

A. Myocardial cell structure

1. Sarcomere

- is the contractile unit of the myocardial cell.
- is similar to the contractile unit in skeletal muscle.
- runs from Z line to Z line.
- contains thick filaments (myosin) and thin filaments (actin, troponin, tropomyosin).
- As in skeletal muscle, shortening occurs according to a sliding filament model, which states that thin filaments slide along adjacent thick filaments by forming and breaking cross-bridges between actin and myosin.

2. Intercalated disks

- occur at the ends of the cells.
- maintain cell-to-cell cohesion.

3. Gap junctions

- are present at the intercalated disks.
- are **low-resistance paths** between cells that allow for rapid electrical spread of action potentials.
- account for the observation that the heart behaves as an **electrical syncytium.**

4. **Mitochondria**
   - are more numerous in cardiac muscle than in skeletal muscle.
5. **T tubules**
   - are continuous with the cell membrane.
   - invaginate the cells at the Z lines and **carry action potentials into the cell interior.**
   - are well developed in the ventricles, but poorly developed in the atria.
   - form **dyads** with the sarcoplasmic reticulum.
6. **Sarcoplasmic reticulum (SR)**
   - are small-diameter tubules in close proximity to the contractile elements.
   - are the site of **storage and release of Ca^{2+} for excitation–contraction coupling.**

B. Steps in excitation–contraction coupling

1. The action potential spreads from the cell membrane into the T tubules.
2. During the **plateau** of the action potential, Ca^{2+} conductance is increased and Ca^{2+} enters the cell from the extracellular fluid **(inward Ca^{2+} current)** through L-type Ca^{2+} channels **(dihydropyridine receptors).**
3. This Ca^{2+} entry triggers the release of even more Ca^{2+} from the SR **(Ca^{2+}-induced Ca^{2+} release)** through Ca^{2+} release channels **(ryanodine receptors).**
   - The amount of Ca^{2+} released from the SR depends on the amount of Ca^{2+} previously stored and on the size of the inward Ca^{2+} current during the plateau of the action potential.
4. As a result of this Ca^{2+} release, **intracellular [Ca^{2+}] increases.**
5. Ca^{2+} binds to troponin C, and tropomyosin is moved out of the way, removing the inhibition of actin and myosin binding.
6. Actin and myosin bind, the thick and thin filaments slide past each other, and the myocardial cell contracts. **The magnitude of the tension that develops is proportional to the intracellular [Ca^{2+}].**
7. **Relaxation** occurs when Ca^{2+} is reaccumulated by the SR by an active Ca^{2+}-ATPase pump.

C. Contractility

- is the **intrinsic ability of cardiac muscle to develop force at a given muscle length.**
- is also called **inotropism.**
- is related to the **intracellular Ca^{2+} concentration.**
- can be estimated by the **ejection fraction** (stroke volume/end-diastolic volume), which is normally 0.55 (55%).
- **Positive inotropic agents** produce an increase in contractility.
- **Negative inotropic agents** produce a decrease in contractility.

1. **Factors that increase contractility (positive inotropism)** [see Table 3-1]
   a. **Increased heart rate**
      - When more action potentials occur per unit time, more Ca^{2+} enters the myocardial cells during the action potential plateaus, more Ca^{2+} is released from the SR, and greater tension is produced during contraction.
      - Examples of the effect of increased heart rate are:

      (1) *Positive staircase,* or Bowditch staircase (or Treppe). Increased heart rate increases the force of contraction in a stepwise fashion as the intracellular [Ca^{2+}] increases cumulatively over several beats.

      (2) *Postextrasystolic potentiation.* The beat that occurs after an extrasystolic beat has increased force of contraction because "extra" Ca^{2+} entered the cells during the extrasystole.

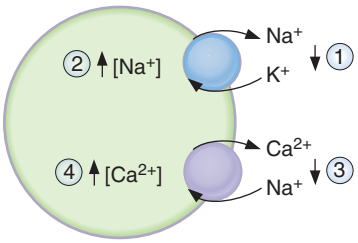

FIGURE 3-7 Stepwise explanation of how ouabain (digitalis) causes an increase in intracellular [Ca^{2+}] and myocardial contractility. The circled numbers show the sequence of events.

b. Sympathetic stimulation (catecholamines) via β_1 receptors (see Table 3-1)

- increases the force of contraction by two mechanisms:

(1) It increases the **inward Ca^{2+} current** during the plateau of each cardiac action potential.
(2) It increases the activity of the Ca^{2+} pump of the SR (by phosphorylation of **phospholamban**); as a result, more Ca^{2+} is accumulated by the SR and thus more Ca^{2+} is available for release in subsequent beats.

c. Cardiac glycosides (digitalis)

- increase the force of contraction by inhibiting Na^+,K^+-ATPase in the myocardial cell membrane (Figure 3-7).
- As a result of this inhibition, the intracellular [Na^+] increases, diminishing the Na^+ gradient across the cell membrane.
- Na^+–Ca^{2+} exchange (a mechanism that extrudes Ca^{2+} from the cell) depends on the size of the Na^+ gradient and thus is diminished, producing an increase in intracellular [Ca^{2+}].

2. Factors that decrease contractility (negative inotropism) [see Table 3-1]

- **Parasympathetic stimulation (ACh) via muscarinic receptors** decreases the force of contraction in the **atria** by decreasing the inward Ca^{2+} current during the plateau of the cardiac action potential.

D. Length–tension relationship in the ventricles (Figure 3-8)

- describes the effect of ventricular muscle cell length on the force of contraction.
- is similar to the relationship in skeletal muscle.

1. Preload

- is **end-diastolic volume**, which is related to **right atrial pressure.**
- When venous return increases, end-diastolic volume increases and stretches or lengthens the ventricular muscle fibers (see Frank–Starling relationship, IV D 5).

2. Afterload

- for the left ventricle is **aortic pressure.** Increases in aortic pressure cause an increase in afterload on the left ventricle.
- for the right ventricle is **pulmonary artery pressure.** Increases in pulmonary artery pressure cause an increase in afterload on the right ventricle.

3. Sarcomere length

- determines the maximum number of cross-bridges that can form between actin and myosin.
- determines the maximum tension, or force of contraction.

4. Velocity of contraction at a fixed muscle length

- is maximal when the afterload is zero.
- is decreased by increases in afterload.

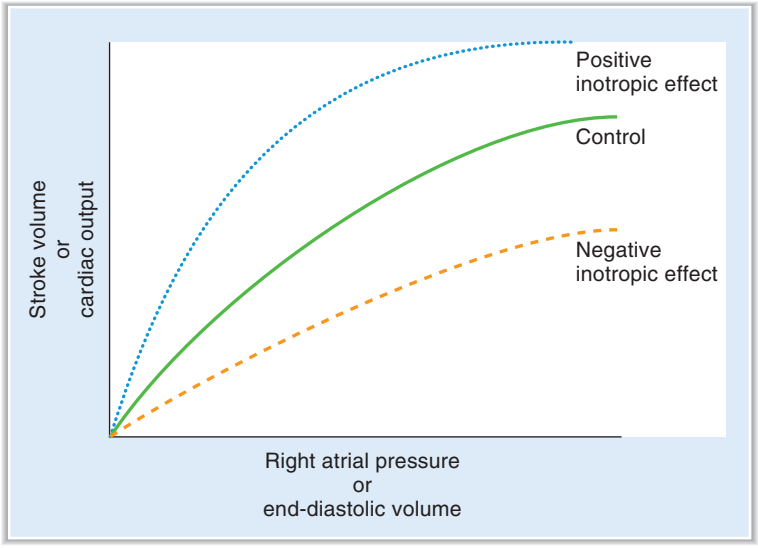

FIGURE 3-8 Frank–Starling relationship and the effect of positive and negative inotropic agents.

5. Frank–Starling relationship

- describes the increases in stroke volume and cardiac output that occur in response to an increase in venous return or end-diastolic volume (see Figure 3-8).
- is based on the length–tension relationship in the ventricle. **Increases in end-diastolic volume cause an increase in ventricular fiber length, which produces an increase in developed tension.**
- is the mechanism that **matches cardiac output to venous return.** The greater the venous return, the greater the cardiac output.
- Changes in contractility shift the Frank–Starling curve upward (increased contractility) or downward (decreased contractility).

a. Increases in contractility cause an increase in cardiac output for any level of right atrial pressure or end-diastolic volume.

b. Decreases in contractility cause a decrease in cardiac output for any level of right atrial pressure or end-diastolic volume.

E. Ventricular pressure–volume loops (Figure 3-9)

- are constructed by combining systolic and diastolic pressure curves.
- The diastolic pressure curve is the relationship between diastolic pressure and diastolic volume in the ventricle.

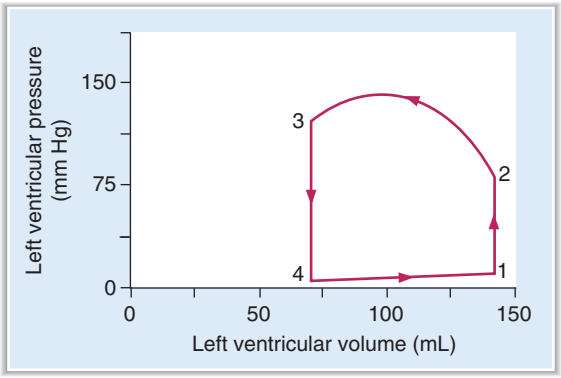

FIGURE 3-9 Left ventricular pressure–volume loop.

- The systolic pressure curve is the corresponding relationship between systolic pressure and systolic volume in the ventricle.
- **A single left ventricular cycle of contraction, ejection, relaxation, and refilling** can be visualized by combining the two curves into a pressure–volume loop.

1. **Steps in the cycle**
   a. **1 → 2 (isovolumetric contraction).** The cycle begins during diastole at point 1. The left ventricle is filled with blood from the left atrium and its volume is about 140 mL (end-diastolic volume). Ventricular pressure is low because the ventricular muscle is relaxed. On excitation, the ventricle contracts and ventricular pressure increases. The mitral valve closes when left ventricular pressure is greater than left atrial pressure. Because all valves are closed, no blood can be ejected from the ventricle (isovolumetric).
   b. **2 → 3 (ventricular ejection).** The aortic valve opens at point 2 when pressure in the left ventricle exceeds pressure in the aorta. Blood is ejected into the aorta, and ventricular volume decreases. The volume that is ejected in this phase is the **stroke volume.** Thus, stroke volume can be measured graphically by the **width of the pressure–volume loop.** The volume remaining in the left ventricle at point 3 is end-systolic volume.
   c. **3 → 4 (isovolumetric relaxation).** At point 3, the ventricle relaxes. When ventricular pressure decreases to less than aortic pressure, the aortic valve closes. Because all of the valves are closed again, ventricular volume is constant (isovolumetric) during this phase.
   d. **4 → 1 (ventricular filling).** Once left ventricular pressure decreases to less than left atrial pressure, the mitral (AV) valve opens and filling of the ventricle begins. During this phase, ventricular volume increases to about 140 mL (the end-diastolic volume).
2. **Changes in the ventricular pressure–volume loop** are caused by several factors (Figure 3-10).
   a. **Increased preload** (see Figure 3-10A)
      - refers to an increase in end-diastolic volume and is the result of increased venous return.
      - causes an **increase in stroke volume** based on the Frank–Starling relationship.
      - The increase in stroke volume is reflected in increased width of the pressure–volume loop.
   b. **Increased afterload** (see Figure 3-10B)
      - refers to an increase in aortic pressure.
      - The ventricle must eject blood against a higher pressure, resulting in a **decrease in stroke volume.**
      - The decrease in stroke volume is reflected in decreased width of the pressure–volume loop.
      - The decrease in stroke volume results in an increase in end-systolic volume.

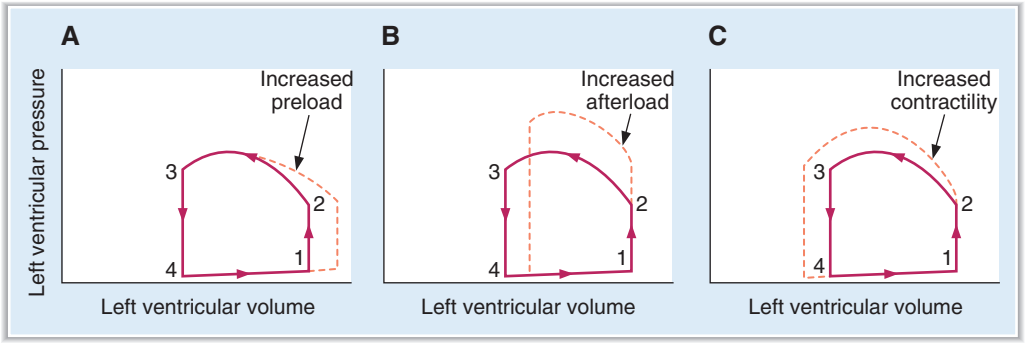

FIGURE 3-10 Effects of changes in **(A)** preload, **(B)** afterload, and **(C)** contractility on the ventricular pressure–volume loop.

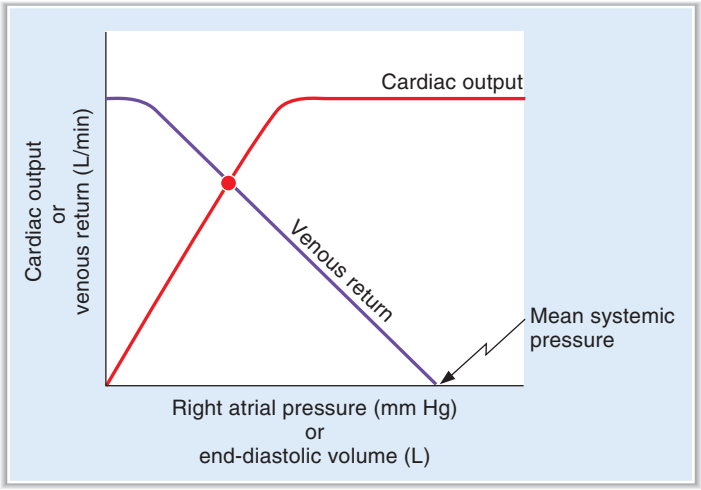

FIGURE 3-11 Simultaneous plots of the cardiac and vascular function curves. The curves cross at the equilibrium point for the cardiovascular system.

c. Increased contractility (see Figure 3-10C)

- The ventricle develops greater tension than usual during systole, causing an **increase in stroke volume.**
- The increase in stroke volume results in a decrease in end-systolic volume.

F. Cardiac and vascular function curves (Figure 3-11)

- are simultaneous plots of cardiac output and venous return as a function of right atrial pressure or end-diastolic volume.

1. The cardiac function (cardiac output) curve

- depicts the Frank–Starling relationship for the ventricle.
- shows that cardiac output is a function of end-diastolic volume.

2. The vascular function (venous return) curve

- depicts the relationship between blood flow through the vascular system (or venous return) and right atrial pressure.

a. Mean systemic pressure

- is the point at which the vascular function curve intersects the x-axis.
- equals right atrial pressure when there is "no flow" in the cardiovascular system.
- is measured when the heart is stopped experimentally. Under these conditions, cardiac output and venous return are zero, and pressure is equal throughout the cardiovascular system.

(1) Mean systemic pressure is increased by an **increase in blood volume** or by a **decrease in venous compliance** (where blood is shifted from the veins to the arteries). An increase in mean systemic pressure is reflected in a **shift of the vascular function** curve to the right (Figure 3-12).

(2) Mean systemic pressure is decreased by a **decrease in blood volume** or by an **increase in venous compliance** (where blood is shifted from the arteries to the veins). A decrease in mean systemic pressure is reflected in a **shift of the vascular function curve to the left.**

b. Slope of the venous return curve

- is determined by the **resistance of the arterioles.**

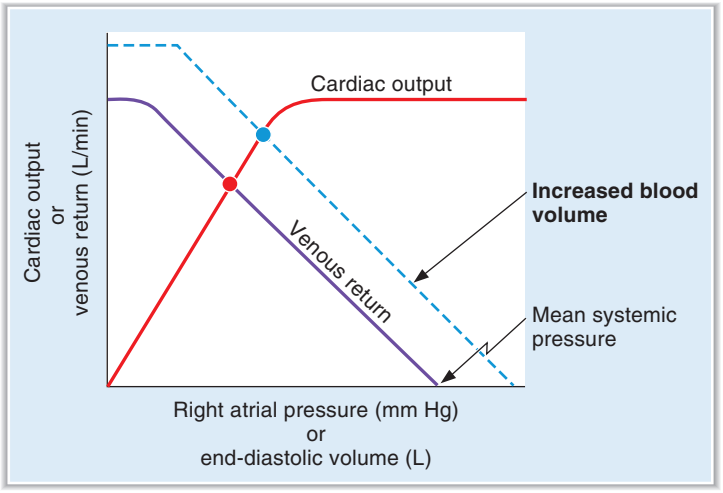

FIGURE 3-12 Effect of increased blood volume on the mean systemic pressure, vascular function curve, cardiac output, and right atrial pressure.

(1) A clockwise rotation of the venous return curve indicates a **decrease in total peripheral resistance (TPR).** When TPR is decreased for a given right atrial pressure, there is an increase in venous return (i.e., vasodilation of the arterioles "allows" more blood to flow from the arteries to the veins and back to the heart).

(2) A counterclockwise rotation of the venous return curve indicates an **increase in TPR** (Figure 3-13). When TPR is increased for a given right atrial pressure, there is a decrease in venous return to the heart (i.e., vasoconstriction of the arterioles decreases blood flow from the arteries to the veins and back to the heart).

3. Combining cardiac output and venous return curves

- When cardiac output and venous return are simultaneously plotted as a function of right atrial pressure, they intersect at a single value of right atrial pressure.
- The point at which the two curves intersect is the **equilibrium, or steady-state, point** (see Figure 3-11). Equilibrium occurs when cardiac output equals venous return.

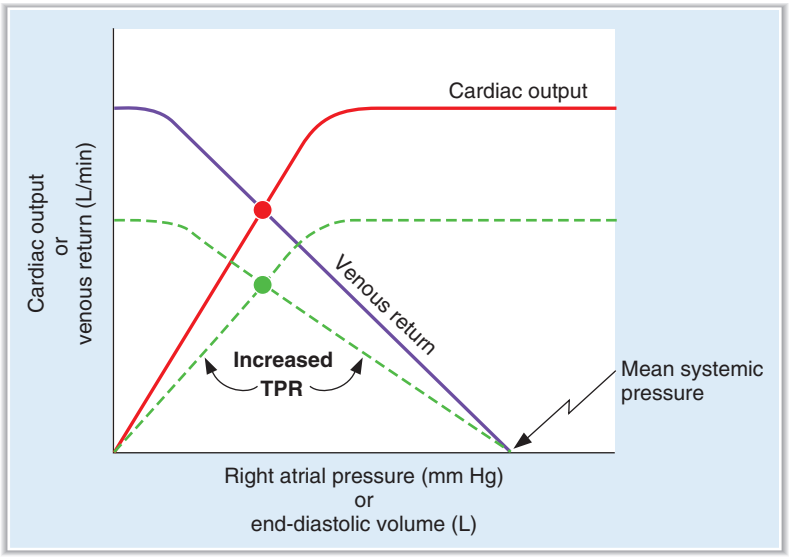

FIGURE 3-13 Effect of increased total peripheral resistance (TPR) on the cardiac and vascular function curves and on cardiac output.

- Cardiac output can be changed by altering the cardiac output curve, the venous return curve, or both curves simultaneously. The superimposed curves can be used to predict the direction and magnitude of changes in cardiac output.

a. Inotropic agents change the cardiac output curve.

(1) *Positive inotropic agents* (e.g., **digitalis**) produce increased contractility and increased cardiac output (Figure 3-14).

- The equilibrium, or intersection, point shifts to a higher cardiac output and a correspondingly lower right atrial pressure.
- Right atrial pressure decreases because more blood is ejected from the heart on each beat (increased stroke volume).

(2) *Negative inotropic agents* produce decreased contractility and decreased cardiac output (not illustrated).

b. Changes in blood volume or venous compliance change the venous return curve.

(1) *Increases in blood volume or decreases in venous compliance* increase mean systemic pressure, shifting the venous return curve to the right in a parallel fashion (see Figure 3-12). A new equilibrium, or intersection, point is established at which **both cardiac output and right atrial pressure are increased.**

(2) *Decreases in blood volume* (e.g., hemorrhage) *or increases in venous compliance* have the opposite effect—decreased mean systemic pressure and a shift of the venous return curve to the left in a parallel fashion. A new equilibrium point is established at which **both cardiac output and right atrial pressure are decreased** (not illustrated).

c. Changes in TPR change both the cardiac output and the venous return curves.

- Changes in TPR alter both curves simultaneously; therefore, the responses are more complicated than those noted in the previous examples.

(1) *Increasing TPR causes a decrease in both cardiac output and venous return* (see Figure 3-13).

(a) A **counterclockwise rotation of the venous return curve** occurs. Increased TPR results in decreased venous return as blood is retained on the arterial side.

(b) A **downward shift of the cardiac output curve** is caused by the increased aortic pressure (increased afterload) as the heart pumps against a higher pressure.

(c) As a result of these simultaneous changes, a new equilibrium point is established at which **both cardiac output and venous return are decreased**, but right atrial pressure is unchanged.

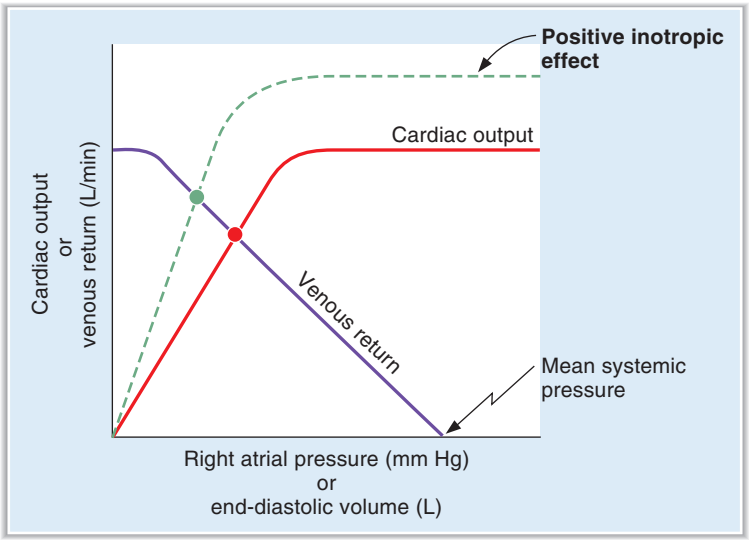

FIGURE 3-14 Effect of a positive inotropic agent on the cardiac function curve, cardiac output, and right atrial pressure.

(2) *Decreasing TPR causes an increase in both cardiac output and venous return* (not illustrated).

(a) A **clockwise rotation of the venous return curve** occurs. Decreased TPR results in increased venous return as more blood is allowed to flow back to the heart from the arterial side.

(b) **An upward shift of the cardiac output curve** is caused by the decreased aortic pressure (decreased afterload) as the heart pumps against a lower pressure.

(c) As a result of these simultaneous changes, a new equilibrium point is established at which **both cardiac output and venous return are increased**, but right atrial pressure is unchanged.

G. Stroke volume, cardiac output, and ejection fraction

1. Stroke volume

- is the volume ejected from the ventricle on each beat.
- is expressed by the following equation:

$$\text{Stroke volume} = \text{End-diastolic volume} - \text{End-systolic volume}$$

2. Cardiac output

- is expressed by the following equation:

$$\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}$$

3. Ejection fraction

- is the fraction of the end-diastolic volume ejected in each stroke volume.
- is related to **contractility.**
- is normally 0.55 or **55%.**
- is expressed by the following equation:

$$\text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End-diastolic volume}}$$

H. Stroke work

- is the work the heart performs on each beat.
- is equal to **pressure × volume.** For the left ventricle, pressure is aortic pressure and volume is stroke volume.
- is expressed by the following equation:

$$\text{Stroke work} = \text{Aortic pressure} \times \text{Stroke volume}$$

- Fatty acids are the primary energy source for stroke work.

I. Cardiac oxygen (O_2) consumption

- is directly related to the amount of tension developed by the ventricles.
- is increased by:

1. Increased **afterload** (increased aortic pressure)
2. Increased **size of the heart** (Laplace's law states that tension is proportional to the radius of a sphere.)
3. Increased **contractility**
4. Increased **heart rate**

J. Measurement of cardiac output by the Fick principle

- The Fick principle for measuring cardiac output is expressed by the following equation:

$$\text{Cardiac output} = \frac{O_2 \text{ consumption}}{[O_2]_{\text{pulmonary vein}} - [O_2]_{\text{pulmonary artery}}}$$

- The equation is solved as follows:

1. O_2 consumption for the whole body is measured.
2. Pulmonary vein $[O_2]$ is measured in a peripheral artery.
3. Pulmonary artery $[O_2]$ is measured in systemic mixed venous blood.

- **For example**, a 70-kg man has a resting O_2 consumption of 250 mL/min, a peripheral arterial O_2 content of 0.20 mL O_2/mL of blood, a mixed venous O_2 content of 0.15 mL O_2/mL of blood, and a heart rate of 72 beats/min. What is his cardiac output? What is his stroke volume?

$$\text{Cardiac output} = \frac{250 \text{ mL/min}}{0.20 \text{ mL } O_2/\text{mL} - 0.15 \text{ mL } O_2/\text{mL}}$$
$$= 5000 \text{ mL/min, or } 5.0 \text{ L/min}$$

$$\text{Stroke volume} = \frac{\text{Cardiac output}}{\text{Heart rate}}$$
$$= \frac{5000 \text{ mL/min}}{72 \text{ beats/min}}$$
$$= 69.4 \text{ mL/beat}$$

V. CARDIAC CYCLE

- Figure 3-15 shows the mechanical and electrical events of a single cardiac cycle. The seven phases are separated by vertical lines.
- Use the **ECG** as an event marker.
- Opening and closing of valves causes the physiologic **heart sounds.**
- When all valves are closed, ventricular volume is constant, and the phase is called **isovolumetric.**

A. Atrial systole

- is preceded by the P wave, which represents electrical activation of the atria.
- contributes to, but is not essential for, ventricular filling.
- The increase in atrial pressure (venous pressure) caused by atrial systole is the **a wave** on the venous pulse curve.
- Filling of the ventricle by atrial systole causes the **fourth heart sound**, which is not audible in normal adults.

B. Isovolumetric ventricular contraction

- begins after the onset of the QRS wave, which represents electrical activation of the ventricles.
- When ventricular pressure becomes greater than atrial pressure, the AV valves close. Their closure corresponds to the **first heart sound.** Because the mitral valve closes before the tricuspid valve, the first heart sound may be split.

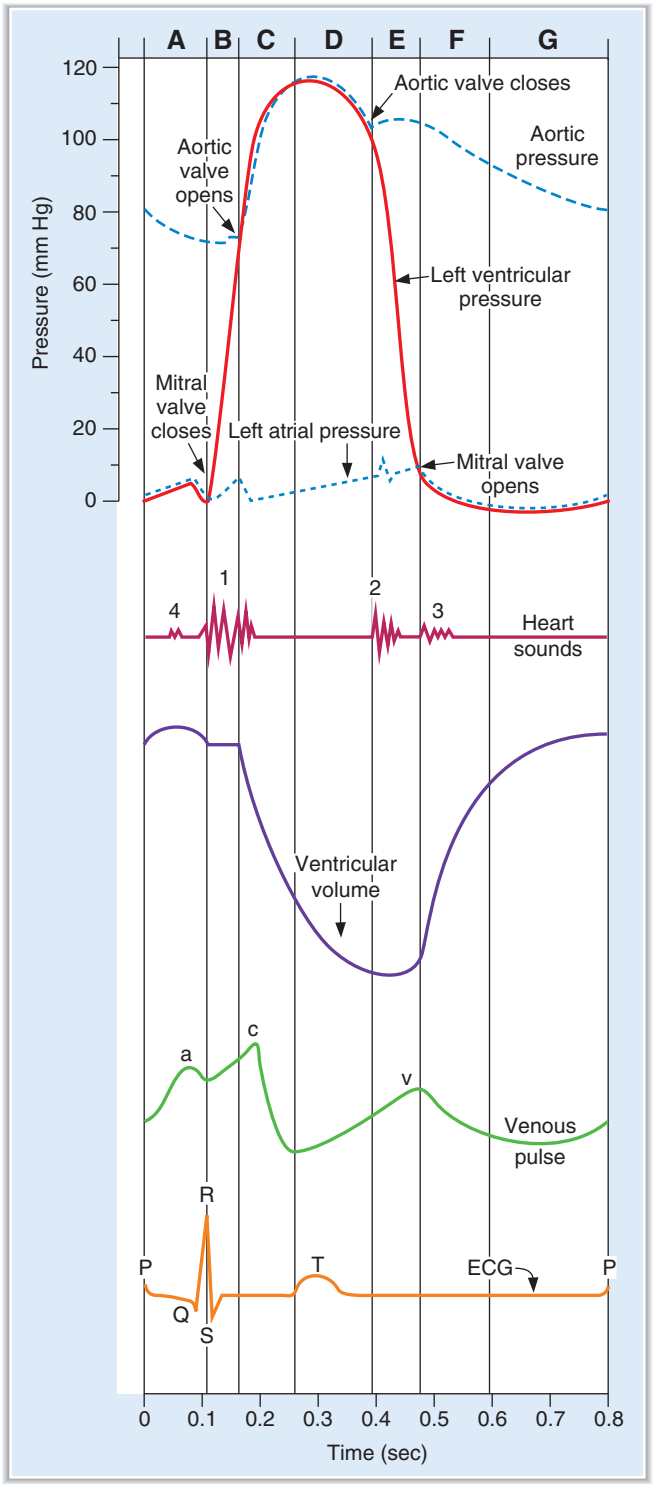

FIGURE 3-15 The cardiac cycle. ECG = electrocardiogram; A = atrial systole; B = isovolumetric ventricular contraction; C = rapid ventricular ejection; D = reduced ventricular ejection; E = isovolumetric ventricular relaxation; F = rapid ventricular filling; G = reduced ventricular filling.

- Ventricular pressure increases isovolumetrically as a result of ventricular contraction. However, no blood leaves the ventricle during this phase because the **aortic valve is closed.**

C. Rapid ventricular ejection

- Ventricular pressure reaches its maximum value during this phase.
- When ventricular pressure becomes greater than aortic pressure, the **aortic valve opens.**
- Rapid ejection of blood into the aorta occurs because of the pressure gradient between the ventricle and the aorta.
- Ventricular volume decreases dramatically because **most of the stroke volume is ejected** during this phase.
- Atrial filling begins.
- The onset of the T wave, which represents repolarization of the ventricles, marks the end of both ventricular contraction and rapid ventricular ejection.

D. Reduced ventricular ejection

- Ejection of blood from the ventricle continues, but is slower.
- Ventricular pressure begins to decrease.
- Aortic pressure also decreases because of the runoff of blood from large arteries into smaller arteries.
- Atrial filling continues.

E. Isovolumetric ventricular relaxation

- Repolarization of the ventricles is now complete (end of the T wave).
- The aortic valve closes, followed by closure of the pulmonic valve. Closure of the semilunar valves corresponds to the **second heart sound.** Inspiration causes splitting of the second heart sound.
- The AV valves remain closed during most of this phase.
- Ventricular pressure decreases rapidly because the ventricle is now relaxed.
- Ventricular volume is constant (isovolumetric) because all of the valves are closed.
- The "blip" in the aortic pressure tracing occurs after closure of the aortic valve and is called the **dicrotic notch, or incisura.**
- When ventricular pressure becomes less than atrial pressure, the **mitral valve opens.**

F. Rapid ventricular filling

- The mitral valve is open and ventricular filling from the atrium begins.
- Aortic pressure continues to decrease because blood continues to run off into the smaller arteries.
- Rapid flow of blood from the atria into the ventricles causes the **third heart sound**, which is normal in children but, in adults, is associated with disease.

G. Reduced ventricular filling (diastasis)

- is the longest phase of the cardiac cycle.
- Ventricular filling continues, but at a slower rate.
- The time required for diastasis and ventricular filling depends on heart rate. Increases in heart rate decrease the time available for ventricular refilling.

VI. REGULATION OF ARTERIAL PRESSURE

- The most important mechanisms for regulating arterial pressure are a fast, neurally mediated baroreceptor mechanism and a slower, hormonally regulated renin–angiotensin–aldosterone mechanism.