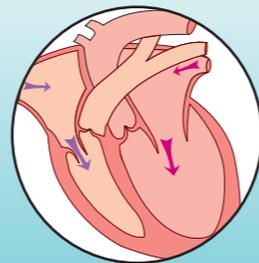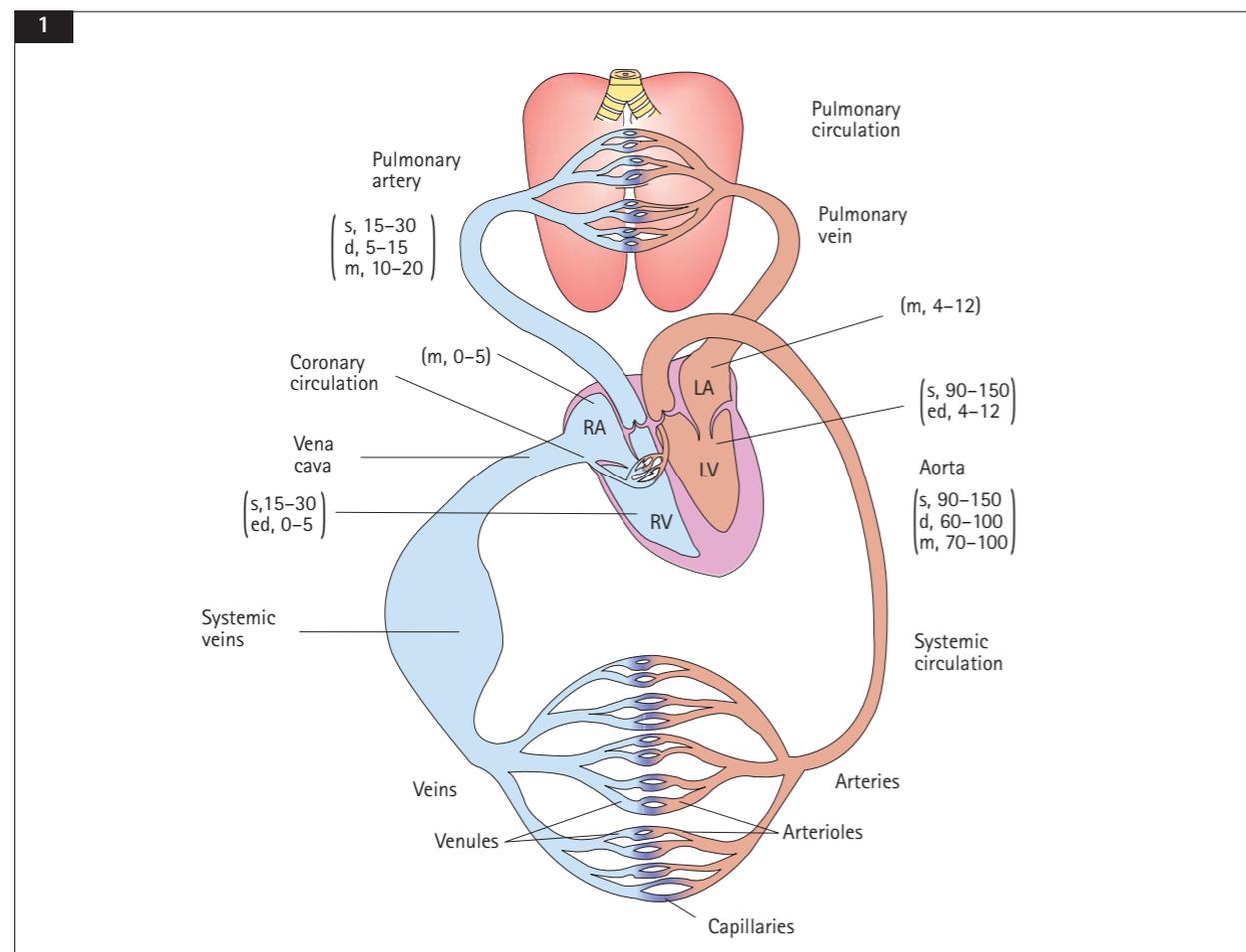# 1

# The Normal Cardiovascular System

The cardiovascular (CV) system provides nutrient delivery and metabolic waste removal throughout the body. Its two component circulations (pulmonary and systemic) are linked in series. The normal path of blood flow is schematically illustrated (**1**), along with approximate normal pressures. The systemic circulation contains about 75% of the total blood volume, compared with 25% in the pulmonary circulation. Systemic veins act as storage (capacitance) vessels and contain about 67–80% of the systemic blood volume; 11–15% is held within arteries and 5% within the capillaries[1, 2]. Blood in the pulmonary circulation is distributed evenly among arterial, capillary, and venous vessels. Mean blood pressure in the pulmonary circulation is about one seventh of that in the systemic circuit.

## THE HEART

### EXTERNAL FEATURES
The pericardial sac surrounds the heart. This sac, or pericardium, consists of a thin visceral (epicardial) layer of mesothelial cells that is closely adhered to the heart and reflects back at the heartbase into the serous lining of the fibrous outer parietal layer[3, 4]. The left and right coronary arteries arise from sinuses of Valsalva behind valve leaflets at the aortic root. These arteries course over the external surface of the heart before their branches penetrate into the myocardium (**2**). Smaller coronary veins flow into the great coronary (cardiac) vein, which empties into the coronary sinus in the caudal right atrium (RA). Blood from the body enters the RA through the cranial vena cava, caudal vena cava, and azygous vein (**3**). Inflow to the left heart enters the dorsal left atrium (LA) from several pulmonary veins.
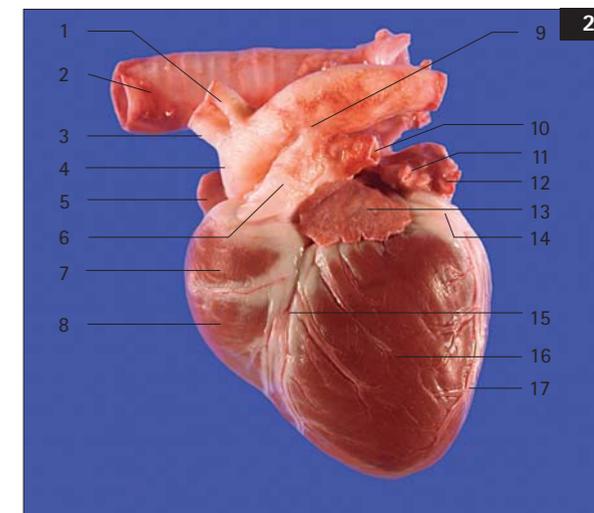
    The left ventricle (LV) forms the caudoventral aspect of the heart; its point forms the cardiac apex. The LV is cone-shaped, and is surrounded on the right, cranial, and craniodorsal left sides by the 'U-shaped' right ventricle (RV). The LA is in a dorsocaudal location, above the LV. The aorta exits cranial to the LA, in a central location. The RA occupies the dorsal right aspect, above the RV inflow tract. The pulmonary artery exits the RV on the dorsal left side of the heart.

### INTERNAL FEATURES
An endothelial layer covers the internal cardiac surface (endocardium). The valves are thin, flexible fibrous flaps covered with endothelium. Each is attached to a fibrous valve ring (annulus).

#### Left heart
The LV endocardial surface is fairly smooth. A continuum of myocardial fibers arrayed in varying orientations from epicardium to endocardium and base to apex forms the LV wall. Contraction causes longitudinal shortening as well as reduced circumference of the LV chamber, as blood is pushed toward the outflow region[1]. The mitral (left atrioventricular, AV) valve has two leaflets: septal (anterior; cranioventral) and parietal (posterior; caudodorsal)[4].



**1** Schematic diagram of the cardiovascular system. Examples of normal pressures (mm Hg) in different regions are noted in parentheses:
ed = end-diastolic; d = diastolic; m = mean; s = systolic; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.



**2** Canine heart: external view from the left. a = artery; v = vein; L = left; R = right.
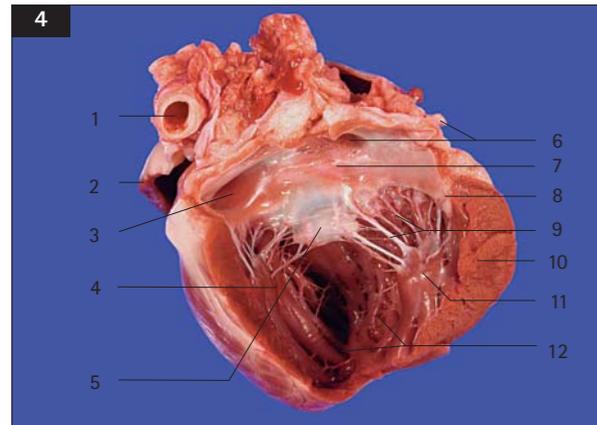1. L. subclavian a.  2. Trachea  3. Brachiocephalic trunk  4. Aorta
5. R. auricle  6. Pulmonary trunk  7. Conus arteriosus 8. R. ventricle
9. Ligamentum arteriosum  10. L. pulmonary a.  11. Pulmonary v.
12. L. atrium  13. L. auricle  14. Coronary groove (with circumflex branch of L. coronary a.)  15. Cranial (paraconal) interventricular branch of L. coronary a.  16. L. ventricle  17. Caudal (subsinuosal) interventricular branch of L. coronary a.
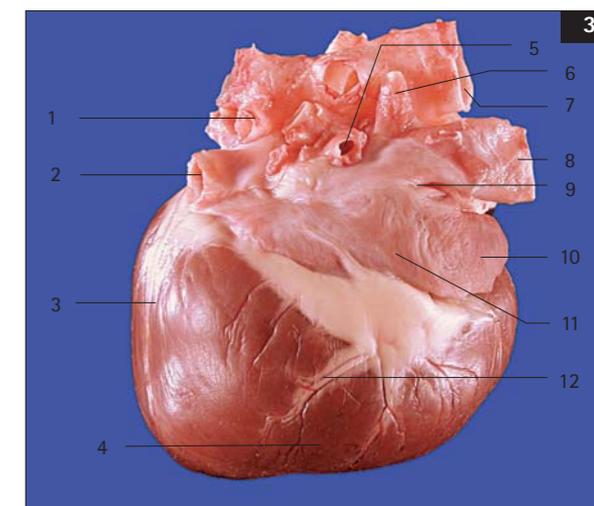


**3** Canine heart: external view from the right. a = artery; v = vein; L = left; R = right.
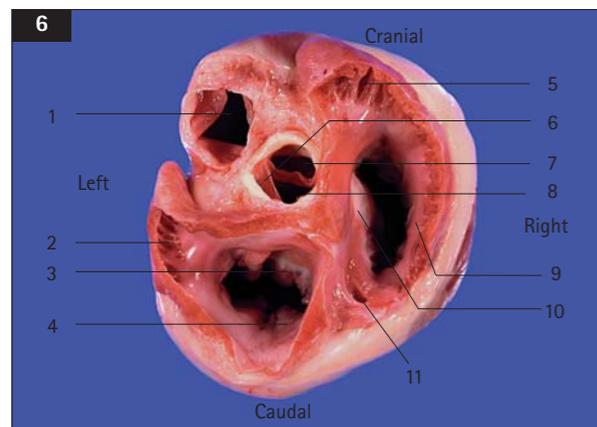1. Pulmonary v. ostium  2. Caudal vena cava  3. Caudal (subsinuosal) interventricular sulcus  4. R. ventricle  5. R. pulmonary a.  6. Azygous v.
7. Trachea  8. Cranial vena cava  9. Region of sinoatrial node  10. R. auricle  11. R. atrium  12. Branches of R. coronary a.

Stout chordae tendineae attach these leaflets to two large papillary muscles, which arise near the apical region (**4**). The anterior mitral leaflet originates at the caudal aspect of the aortic root. This leaflet functionally separates the LV inflow and outflow tracts (**5**). The 3-cusped (semilunar) aortic valve is located centrally in the heart's fibrous skeleton (**6**). The cranial aspect of the aortic root abuts the interventricular septum (IVS).

### Right heart

The RV wall thickness is normally about one third of that of the LV wall, reflecting the much lower systolic pressure here. Muscular ridges (*trabeculae carneae*) characterize the inner RV surface (**7**). A muscular band (septomarginal trabecula, moderator band), which carries conduction system fibers, extends from the IVS to the RV free wall[4].

The tricuspid (right AV) valve has two main leaflets in dogs and cats. The lateral (parietal) leaflet is larger; the smaller septal (medial) leaflet lies close to the IVS in the area of the membranous septum. Generally, there are three main papillary muscles, but their number and configuration are variable[5]. Inflow and outflow areas of the RV are separated by the muscular supraventricular crest, so that the right AV and semilunar valves are not adjacent as they are in the left heart. The semilunar pulmonary valve is similar in appearance but thinner than the aortic valve (**8**). There are no coronary ostia behind pulmonary valve cusps.

## CONDUCTION SYSTEM

The sinoatrial (SA) node is the normal pacemaker of the heart because the specialized muscle cells here have the fastest intrinsic rate of automaticity (spontaneous diastolic depolarization). The SA node is located at the cranial aspect of the RA, near its junction with the cranial vena cava. Electrical impulses originating from SA nodal cells spread into the RA, LA, and via the AV conduction system into the ventricles (**9**). Specialized fibers (internodal pathways) facilitate conduction through the RA and LA to the AV node.



**4** Canine heart: left ventricular inflow tract. L = left; R = right; m = muscle; v,=vein.
1. Descending aorta 2. R. ventricular wall (cut) 3. L. auricle 4. Ventral (subauricular) papillary m. 5. Septal (anterior) mitral cusp 6. Pulmonary v. 7. Interatrial septum 8. Parietal (posterior) mitral cusp (cut) 9. Chordae tendineae 10. L. ventricular freewall 11. Dorsal (subatrial) papillary m. 12. Trabeculae carneae



**5** Canine heart: left ventricular outflow tract. L = left; R= right; m = muscle.
1. Pulmonary trunk 2. R. ventricular outflow region (conus) 3. Interventricular septum 4. Trabeculae carneae 5. Ascending aorta 6. L. auricle 7. Aortic valve cusps 8. Septal (anterior) mitral cusp 9. Dorsal (subatrial) papillary m. 10. L. ventricle
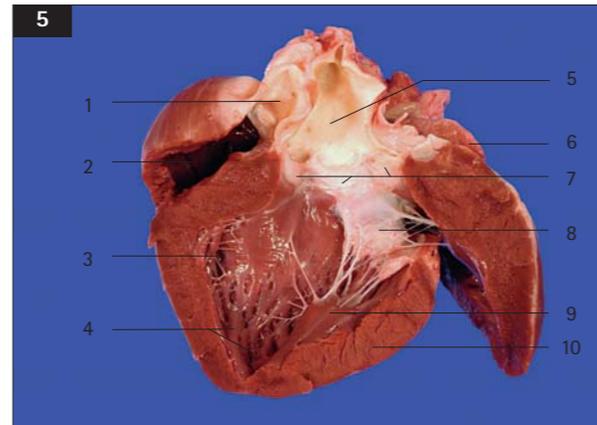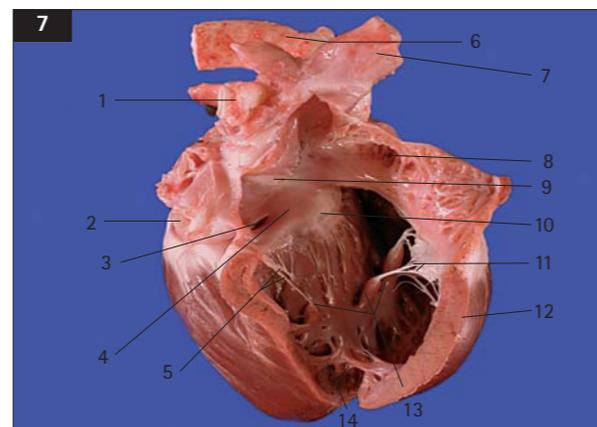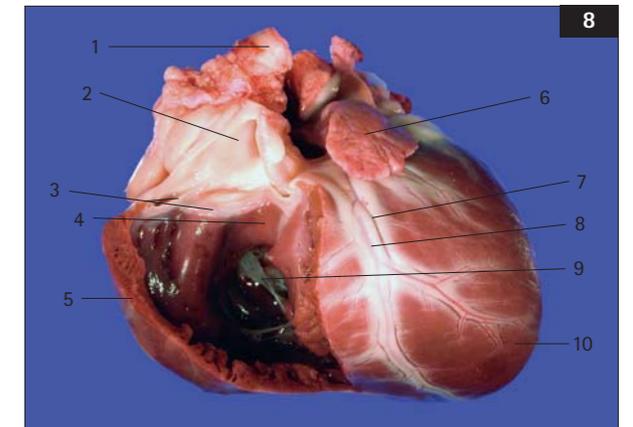


**6** Canine heart: dorsal view showing orientation of cardiac valves. L = left; R = right.
1. Pulmonary valve 2. Pectinate mm in L. auricle 3. Mitral valve: septal (anterior) leaflet 4. Mitral valve: parietal (posterior) leaflet 5. Pectinate mm in R. auricle 6. Aortic valve: left cusp 7. Aortic valve: right cusp 8. Caudal (non coronary) cusp 9. Tricuspid valve: parietal leaflet 10. Tricuspid valve: septal leaflet 11. Coronary sinus



**7** Canine heart: right ventricular inflow tract. mm = muscles; R = right.
1. R. pulmonary a. 2. Caudal vena cava 3. Coronary sinus 4. Region of AV node 5. Chordae tendineae 6. Aorta 7. Cranial vena cava 8. R. auricle 9. Interatrial septum 10. Septal tricuspid leaflet 11. Parietal tricuspid leaflet (cut) 12. R. ventricular free wall 13. Papillary mm 14. Trabeculae carneae



**8** Canine heart: right ventricular outflow tract. L = left; R = right; a = artery; v = vein.
1. Aorta 2. Pulmonary trunk (main pulmonary a.) 3. Pulmonary valve 4. Supraventricular crest 5. R. ventricle 6. L. auricle 7. Great coronary v. 8. Cranial interventricular branch of L. coronary a. in cranial (paraconal) interventricular groove 9. Tricuspid valve 10. L. ventricle
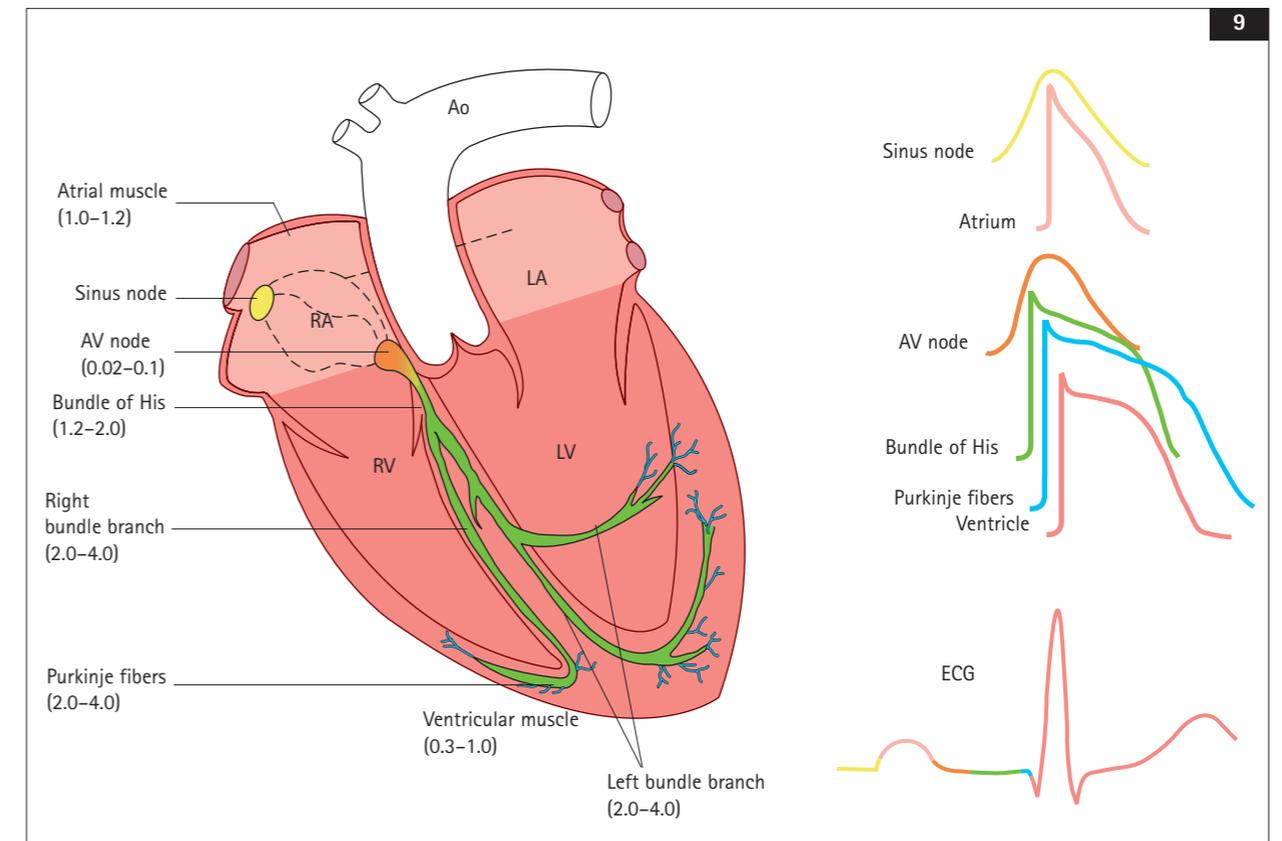


**9** Cardiac conduction system. Major components of the cardiac conduction system are indicated on the left, with approximate conduction speed (m/sec) in parentheses. On the right, representative action potentials are color coded to the conduction system components. A composite ECG (below) illustrates the activation sequence of these structures.

The AV node is the electrical 'gatekeeper' to the ventricles. Normally, there is no other pathway for electrical impulses to pass from the atria to the ventricles. The AV node is located in the ventral right side of the interatrial septum, near the septal tricuspid leaflet. AV nodal cells are small and branching. This causes slowed (decremental) conduction of electrical impulses, allowing time for atrial contraction before ventricular activation.

Electrical impulses enter the bundle of His after passing through the AV node. Conduction is rapid through the His bundle and into the left and right bundle branches. The right bundle branch courses down the right side of the IVS and branches distally to activate the RV free wall[6]. The left bundle branch divides into a septal fascicle, a posterior (caudal) fascicle serving the ventrocaudal aspect of the LV wall, and an anterior fascicle serving the craniolateral LV wall. A branching system of Purkinje fibers transmits electrical impulses from the bundle branches into the ventricular myocardium.

## CARDIAC ELECTROPHYSIOLOGY

Cardiac action potentials occur in association with changes in cell membrane permeability to sodium (Na^{+}), potassium (K^{+}), and calcium (Ca^{++}) ions. Transmembrane movement of these ions depends on the opening and closing of ion-specific channels[7]. The duration of cardiac action potentials is longer than that of noncardiac tissues. Cardiac action potentials also differ among types of heart cells, depending on cellular location and function. There are two main types of cardiac action potentials: 'fast-response' (typical of atrial and ventricular muscle cells, and Purkinje fibers) and 'slow-response' (characteristic of SA and AV nodal cells).

### Resting membrane potential

The cardiac cell membrane (sarcolemma) maintains a gradient of certain ions and enzymes between the intra- and extracellular environment. In normal myocardial cells at rest the electrical potential difference across the sarcolemma is about −90 mV; inside the cell is negative compared with the outside[7]. This resting membrane potential (RMP) is largely determined by the equilibrium between chemical and electrostatic forces for K^{+} (as described by the Nernst equation[a]). The concentration of K^{+} inside the cell is much greater than that outside; conversely, extracellular Na^{+} and Ca^{++} concentrations far exceed intracellular concentrations. The resting sarcolemma is relatively permeable to K^{+}, but not to Na^{+} and Ca^{++} as well as negatively charged intracellular proteins. K^{+} tends to diffuse outward along its concentration gradient through K^{+}-specific channels despite an opposing electrostatic force attracting the positive ions into the cell. A very small inward leak of Na^{+} also occurs. Normal RMP is maintained by the membrane's electrogenic Na^{+}, K^{+}-ATPase pump, which moves three Na^{+} ions out for every two K^{+} ions in.

### Fast-response action potential

When a stimulus reduces the membrane potential to a less negative 'threshold' level, activation of Na^{+}-specific membrane channels allows a rapid Na^{+} influx, which initiates an action potential (phase 0; 10)[7, 8]. Activation (as well as subsequent inactivation) of these channels depends on the level of membrane potential (i.e. is voltage-dependent), and the inward Na^{+} current occurs only briefly. Inactivation (closure) of the Na^{+} channels results in an effective refractory period. A return toward RMP, as well as time, is necessary for Na^{+} channels to recover from inactivation and become responsive to another stimulus. The steepness of the phase 0 upstroke, as well as its amplitude, influences the velocity of impulse conduction along the myocardial membranes. If the cells are stimulated when membrane potential is less negative than normal RMP, Na^{+} channels are partially inactivated and conduction velocity of the resulting action potential is slowed. This predisposes to certain (reentrant) arrhythmias.

The rapid upstroke of the fast-response action potential is followed by a brief partial repolarization in some fibers (phase 1). Voltage-activated membrane Ca^{++} channels (L-type) slowly open during the latter part of phase 0, allowing an inward Ca^{++} current, which is responsible for phase 2 (the plateau). The Ca^{++} that enters the myocardial cells during phase 2 induces electrical–mechanical coupling. As the Ca^{++} channels slowly inactivate, the inward Ca^{++} flux decreases and outward movement of K^{+} (through several types of K^{+} channels) increases. This leads to repolarization (phase 3).

The effective refractory period (from phase 0 until membrane potential reaches about −50 mV during phase 3) is a time when the cell cannot be reexcited. Immediately following is the relative refractory period, when a stronger than normal stimulus may elicit another action potential, although conduction velocity may be slowed because of partial Na^{+} channel inactivation. Normal excitability is achieved only after full repolarization.
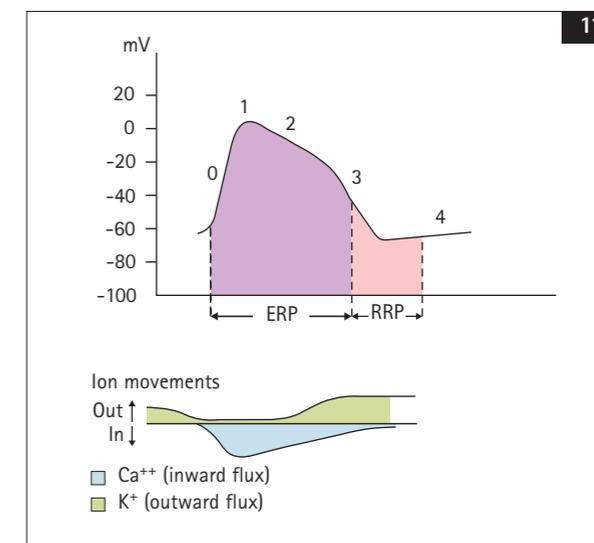
### Slow-response action potential

Two important properties of the heart are automaticity (the ability to initiate a heartbeat) and rhythmicity (the regularity of this activity). Cells with slow-response action potentials allow the heart to beat spontaneously because, instead of a consistent RMP, they undergo spontaneous diastolic (phase 4) depolarization (11). Typically, these cells are in the SA or AV node. They cells have a less negative diastolic membrane potential, and their action potential upstroke (phase 0) depends on slow Ca^{++} channel activation[7, 8]. Conduction velocity in slow-response fibers is much less than in normal fast-response cells, and the refractory period is longer. Consequently, conduction is more easily blocked in these cells.

The SA nodal cells normally have the most rapid intrinsic rate of spontaneous diastolic depolarization. Therefore, they reach threshold first and control the heartbeat. If the sinus rate slows or stops, other slow-response fibers lower in the conduction system (so-called subsidiary pacemakers) can initiate a heartbeat. The rate at which SA cells (or other automatic fibers) activate the heart depends on the slope of their spontaneous phase 4 depolarization, as well as maximal diastolic potential and threshold potential.
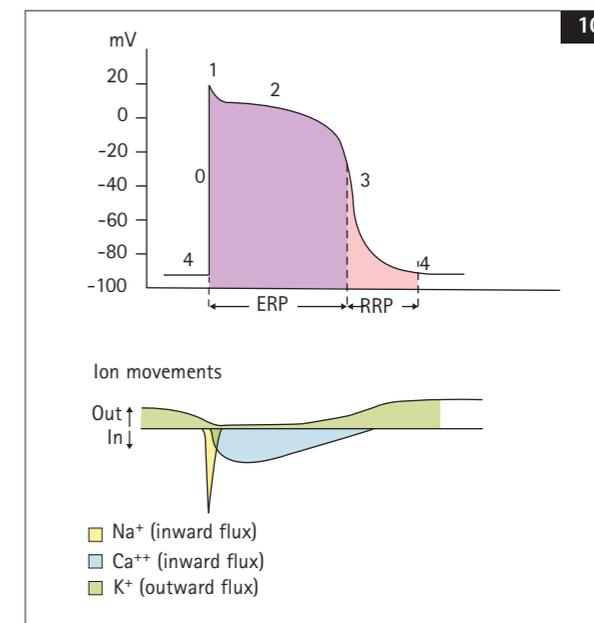


10 Fast-response action potential. Phases of the action potential are indicated (see text for further explanation). Major fluxes of ions into and out of the cell during the action potential are schematically indicated below. ERP = effective refractory period; RRP = relative refractory period; Na^{+} = sodium ion; Ca^{++} = calcium ion; K^{+} = potassium ion.



11 Slow-response action potential. Phases of the action potential are indicated (see text for further explanation). Major fluxes of ions into and out of the cell during the action potential are schematically indicated below. ERP = effective refractory period; RRP = relative refractory period; Ca^{++} = calcium ion; K^{+} = potassium ion.
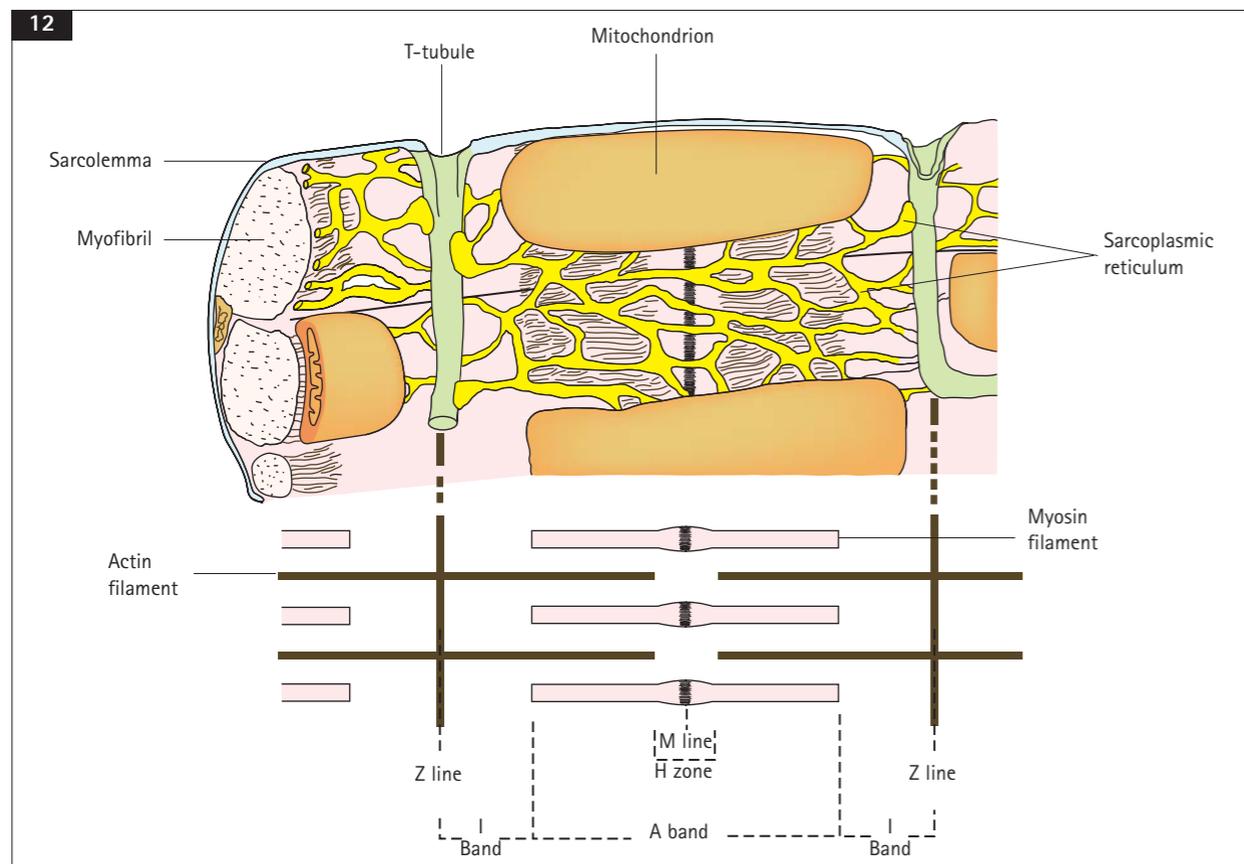
**12** Diagram of myocardial cell components involved with excitation and contraction (above) and schematic illustration of the contractile elements (below) (see text for more information).

### Electrical–mechanical coupling

The $Ca^{++}$ influx during phase 2 of cardiac cell activation triggers the intracellular release of more $Ca^{++}$ from the sarcoplasmic reticulum (SR). The increase in free intracellular $Ca^{++}$ leads to contraction[1, 2]. This process is known as electrical–mechanical or excitation–contraction coupling. The SR is an intracellular network of tubules surrounding the myofibrils; it sequesters and releases the $Ca^{++}$ necessary for contraction (**12**). Invaginations of the cell membrane (T tubule system) facilitate action potential propagation along the cells. Coupling of electrical excitation to mechanical contraction is enhanced by the close proximity of T tubules to parts of the SR.

### MYOCARDIAL CONTRACTION

Cardiac myocytes function as a syncytium. Cell to cell conduction and communication are facilitated by gap junctions within the intercalated disks that separate adjacent myocytes[1, 2]. At the subcellular level, sarcomeres (demarcated by Z lines) are the basic
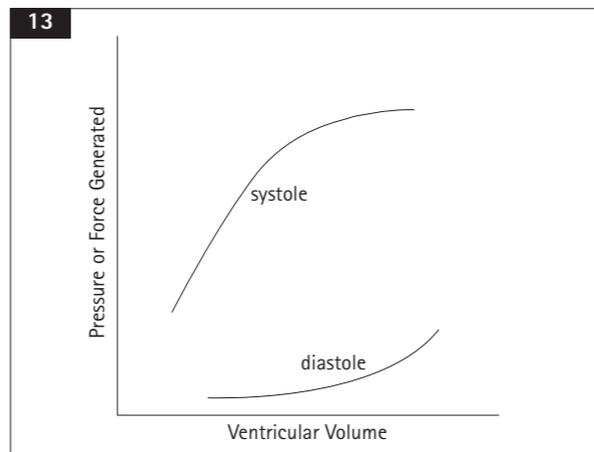


**13** Systole: illustration of the effect of increasing ventricular volume (or preload) on the force generated (and stroke output) in systole. This is the Frank–Starling relationship. Diastole: the effect of increasing ventricular volume on filling pressure.

contractile units within myocytes. Thin actin filaments attach to the Z lines and interdigitate with thick myosin filaments. Contraction (sarcomere shortening) occurs as these filaments slide along each other by the cycling of cross-bridges (formed by heavy meromyosin heads interacting with sites on the actin filaments). The actin filaments are composed of two helical chains attached to a twisting tropomyosin support molecule. The troponin complexes consist of proteins (troponins I, C, and T), which regulate contraction; they are attached to the tropomyosin backbone of the actin filaments[9, 10]. Troponin I, in conjunction with the conformation of tropomyosin, inhibits cross-bridge formation during diastole when intracellular free $Ca^{++}$ is low. When $Ca^{++}$ is available (systole), it activates troponin C, which then binds to troponin I. This reduces the inhibitory effect of troponin I and subsequently allows interaction between adjacent actin and myosin filaments[10]. Myocardial injury causes leakage of troponin proteins; clinical assays for circulating troponin I and T can provide a sensitive test for cardiac damage.

### Loading conditions

Diastolic stretch of the sarcomeres (to an optimal length) will increase the force of the subsequent contraction by increasing myofilament $Ca^{++}$ affinity. This is the Frank–Starling relationship or Starling's law of the heart (**13**)[1, 9]. The level of diastolic stretch, or end-diastolic ventricular volume, is known as 'preload'. In the intact heart, as end-diastolic volume (preload) increases, the volume ejected with each contraction increases. But a high preload also raises the (filling) pressure within the chamber (**13**). Excessive filling pressure leads to venous congestion and edema upstream from that chamber.

'Afterload' refers to the contractile force that must be achieved in order for the sarcomeres to shorten (and for the ventricle to eject blood). It is the force that opposes contraction. In the animal, afterload is largely related to arterial blood pressure, unless there is obstruction to ventricular outflow (e.g. valvular or subvalvular stenosis). The afterload presents opposition to ventricular ejection. Reduced afterload facilitates ejection; increased afterload requires greater force generation for ejection of a given volume of blood.

### Contractility

The term 'contractility' refers to the intrinsic strength of contraction at a given preload and afterload. Contractility primarily depends on the amount of free intracellular $Ca^{++}$ available during systole, although adenosine triphosphate (ATP) availability is also important. By increasing intracellular $Ca^{++}$, positive inotropic agents (e.g. catecholamines, digoxin) increase the peak force of contraction and

reduce ventricular end-systolic volume. Negative inotropic agents (e.g. beta-blockers, calcium channel-blockers) reduce available $Ca^{++}$ and contractility. Indices of myocardial contractility include the maximal rate of pressure generation in the LV during isovolumic contraction ($dP/dt_{max}$), the slope of the end-systolic pressure-volume relationship (Es, $E_{max}$, maximal end-systolic elastance), the percent of diastolic volume ejected during systole (ejection fraction, EF), and the percent reduction in LV diameter from diastole to systole (fractional shortening, FS). Other indices are also used sometimes, but all are imperfect. The so-called ejection phase indices (EF, FS) are especially influenced by loading conditions.

### MYOCARDIAL RELAXATION

At the end of systole, $Ca^{++}$ influx stops and the SR is not stimulated to release further intracellular $Ca^{++}$. The SR actively takes up $Ca^{++}$ (via a phospholamban-stimulated $Ca^{++}$ pump in its membrane), which makes it unavailable to the contractile apparatus and leads to inhibition of cross-bridge formation. Although the SR is the major site of $Ca^{++}$ reuptake, some $Ca^{++}$ is transported out of the cell via membrane Na/Ca exchange and $Ca^{++}$ pump mechanisms[10]. Mitochondrial uptake of free $Ca^{++}$ becomes important with pathologically high intracellular $Ca^{++}$ levels. Slowed or incomplete reuptake of $Ca^{++}$ in diastole increases cardiac stiffness and adversely affects filling; impaired myocardial relaxation can contribute to heart failure[10]. Catecholamines accelerate relaxation as well as enhance contractility.

Indices of relaxation include the maximal rate and time constant of LV pressure decline during isovolumic relaxation ($-dP/dt_{max}$ and tau, respectively), and the Doppler echocardiography-derived isovolumic relaxation time (IVRT) and mitral inflow patterns.

### THE HEART AS A PUMP

The heart's ability to function as a pump is based on interrelationships between synchronous electrical activation, the level of ventricular contractility, loading conditions (preload and afterload) imposed on the myofibers, and the degree of filling in diastole. Ventricular filling is determined by several factors. Active relaxation of the myocardium is important early in diastole. The amount of venous return to the heart, ventricular compliance, the duration of diastole, and atrial contraction also contribute to ventricular end-diastolic volume (preload). As the heart rate increases, diastole shortens and atrial contraction contributes relatively more to final filling. The loss of atrial contraction (e.g. with atrial fibrillation) may have serious negative effects on cardiac performance.

Ventricular compliance (1/stiffness) affects how much blood flows in during diastole. Filling is