1 Cardiovascular system

M. Grant Maxie and Wayne F. Robinson

Diseases of the heart

Diseases of the vascular system

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The pathologic and functional changes observed in an organ or organ system are intimately related to the biology of the organ affected. We therefore first consider the normal form and function of the heart, and then its reaction to injury, under the anatomic units of the pericardium, endocardium, and myocardium.

NORMAL CARDIAC STRUCTURE AND FUNCTION

Gross anatomy

The heart is a **muscular pump** that sends oxygenated, nutrient-rich arterial blood throughout the body via the systemic circulation, and pumps de-oxygenated blood into the pulmonary circulation. Located within the mediastinum, the heart is enclosed in the fibroserous **pericardial sac**, which is lined by a serosal membrane and contains several milliliters of clear serous fluid that acts as a lubricant. **Heart weight** varies with species, age, sex, nutritional status, and fitness level of the animal, and averages about 1% of body weight in newborns, and decreases to 0.3–0.8% in juveniles and adults.

The heart consists of a right and left side; each side consists of an atrium and a ventricle. The ventricles function as two pumps in series. Venous blood from the body enters the **right atrium**, passes into the **right ventricle**, and is pumped through the pulmonary artery into the lungs to be oxygenated and to give up its carbon dioxide. Oxygenated blood returns via the pulmonary veins to the **left atrium**, enters the **left ventricle**, and is then pumped to the body via the aorta. Ventricular thickness varies greatly. Left ventricular free wall and interventricular septum are normally 2–4 times thicker than the right ventricular free wall. *An increase in myocardial mass is termed* **hypertrophy**; *an increase in chamber volume is termed* **dilation**. *An overall increase in cardiac size is termed* **cardiomegaly**.

The four cardiac valves are structured to allow unimpeded unidirectional blood flow, to prevent backflow, and to withstand high pressure. The **atrioventricular (AV) valves**, supported by tendinous cords (chordae tendineae) and papillary muscles of the ventricles, allow flow from the atria into the ventricles and prevent backflow into the atria. The right AV (RAV, tricuspid) valve has 3 valve cusps; the separation into 3 cusps may be difficult to discern. The left AV (LAV, bicuspid) valve consists of 2 cusps. The **pulmonic and aortic semilunar** (crescent moon-shaped) **valves** each have 3 cusps, and they allow flow into the pulmonary artery and aorta respectively and prevent backflow into the ventricles. The nodules (*nodules of Arantius*) in the center of the free edges of the semilunar valve cusps are normal structures. Valve cusps are normally thin and translucent. The free edges of the valve cusps (*cooptation region*) normally overlap during closure, and therefore fenestrations of the valve edges are usually insignificant. Normal valvular function depends on coordinated actions of the respective annulus and leaflets, and in the case of AV valves, the tendinous cords, papillary muscles, and ventricular walls.

The cardiac muscle and valves are supported at the base of the heart by the **cardiac skeleton**, *which consists of four fibrous rings, the fibrous triangle, and the fibrous or membranous part of the ventricular septum*. The fibrous triangle fills the space between the atrioventricular openings and the base of the aorta – it consists of dense fibrous connective tissue in pigs and cats, fibrocartilage in dogs, hyaline cartilage in horses, and bone (*os cordis*) in large ruminants.

The **blood supply to the heart** is primarily via two major coronary arteries. The *left and right coronary arteries* arise, respectively, behind the left and right cusps of the aortic valve at the base of the aorta. The left coronary artery gives rise to the left descending and the left circumflex coronary arteries. The epicardial coronary arteries give rise to the intramural arteries that penetrate the myocardium. Most coronary arterial blood flow occurs during ventricular diastole, when the coronary microcirculation is not compressed by myocardial contraction.

The **conduction system of the heart** consists of specialized conduction fibers that initiate and conduct an electrical impulse. The **sinus node** (sinoatrial node, SA node) is located subepicardially at the junction of the cranial vena cava and the right auricle. The impulse from this pacemaker causes atrial depolarization and contraction, and travels through internodal bundles to the **atrioventricular (AV) node** located in the interatrial septum just cranial to the coronary sinus. The impulse is delayed in the AV node before traveling via the **AV bundle** (bundle of His) to the **left and right bundle branches**,

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or crura, before terminating in **Purkinje fibers**. These modified myocardial cells ramify within the myocardium and transmit the depolarizing impulse to ventricular myocytes.

The components of the conduction system have different rates of diastolic depolarization, with the sinus node the most frequent and dominant. The frequency of depolarization of the sinus node is in turn modified by the autonomic nervous system. Atrial and ventricular myocytes do not normally exhibit the property of automaticity. When injured, however, the myocytes may repeatedly depolarize independent of a stimulus from the conduction system and may become dominant pacemakers. There are diseases that specifically affect the conduction system, but in domestic animals dysrhythmias are usually the result of disease involving the atrial and ventricular myocytes.

Histology

The cardiac wall has three layers:

1. the **epicardium**, the outermost layer;
2. the **myocardium**, the thick muscular middle layer; and
3. the **endocardium**, the innermost layer, which is continuous with the tunica intima of the great vessels entering and leaving the heart.

The **epicardium**, or visceral pericardium, consists of a thin layer of mesothelium resting on elastic fiber-rich connective tissue that merges with that of the myocardium. The epicardium is continuous with the **parietal pericardium**, which consists of an inner mesothelial layer and a thick layer of collagen and elastic fibers. The cavity between the visceral and parietal pericardium contains serous fluid that lubricates the surfaces and provides frictionless cardiac motion. Although the **pericardial sac** is not a vital organ, its proper function includes prevention of sudden cardiac dilation; assurance of equal end-diastolic transmural pressures throughout the ventricles; limitation of right ventricular stroke work; hydrostatic compensation for gravitational or inertial forces; reduction of friction; and maintenance of cardiac alignment and streamlined cardiac flow.

The **myocardium** consists of unique striated muscle cells – **cardiac myocytes** – embedded in a well-vascularized connective tissue framework. Individual myocytes are intimately joined at intercalated discs in order to function as a unit, and account for about 2/3 of the myocardial volume. Each myocyte consists of a single, central nucleus; mitochondria; contractile myofibrils composed of actin and myosin; sarcoplasmic reticulum that stores calcium needed for contraction; and the cell membrane (sarcolemma) and T tubules needed for impulse conduction. Myocytes may be binucleate in some species, e.g., dogs, and are commonly multinucleate in pigs (4–16 nuclei per cell). The actin and myosin filaments comprise contractile units called **sarcomeres**, which are demarcated by Z lines. Mitochondria occupy about 20–30% of the volume of cardiac myocytes versus 2% in skeletal muscle, reflective of the great dependence of cardiac muscle on aerobic metabolism. Sarcomere length varies from 1.6 to 2.2 μm; *ventricular dilation increases sarcomere length, which enhances contractility* (*Frank–Starling relationship*). Atrial cardiac myocytes are typically smaller than ventricular cardiac myocytes; specific granules in atrial myocytes contain the hormone **atrial natriuretic factor** (ANF).

The cardiac **interstitium** contains blood vessels and fibroblasts in a diverse extracellular matrix that consists of collagens, proteoglycans, noncollagenous glycoproteins, growth factors and cytokines, and extracellular proteases. The collagen network of the heart is arranged into 3 interconnected regions: the collagenous weave of the *endomysium* around individual fibers, the *perimysium* around groups of fibers, and the *epimysium* around the whole muscle. This fibrillar collagenous network of the myocardium prevents over-stretching of myofibers, transmits myofiber-generated force to the chamber, and provides tensile strength and stiffness to the chamber. The collagenous struts that connect adjacent myofibers provide proper alignment during contraction. Struts that connect myocytes to capillaries help to maintain capillary patency during high intraventricular pressure.

As do all tissues, the myocardium has a limited set of *reactions to injury*, but the pattern and distribution of lesions may aid in arriving at a morphologic and etiologic diagnosis. The stage of irreversible damage to a myocyte, at least in ischemia, is determined by structural and functional changes in the mitochondria. Irreversible damage occurs after only 30 min of ischemia, whether or not flow is restored.

Only in neonatal hearts are cardiac myocytes able to *regenerate*. Once the neonatal period passes and a particular myocyte or group of myocytes is lost, there is no replacement. There is progressive scavenging of the necrotic remnants of the myocytes and replacement by fibrosis. Remaining myocytes do have the capacity for *compensatory hypertrophy*.

Myocardial injury may be functionally manifest as either irregularities in the rate or rhythm of impulse formation and conduction (dysrhythmias), or as depression in the force of myocardial contraction. **Dysrhythmias** are usually associated with acute, often focal myocardial injury. **Contractility disturbances** occur when there are either insufficient numbers of ventricular myocytes for effective contraction, or when there is ineffectual contraction of normal numbers of myocytes. Generalized, ineffective myocardial contraction is most commonly seen as a feature of dilated cardiomyopathies.

The **endocardium** lines the heart and consists of a monolayer of *endothelium* on a continuous basement membrane, covering the *inner subendothelial layer* of dense collagen, and the *outer subendothelial layer* composed of collagen, elastin, and blood and lymph vessels. The **atrioventricular (AV) valves** are endocardial infoldings with a central layer (*fibrosa*) of dense irregular connective tissue covered by layers of elastic fibers and, on the ventricular side, loose connective tissue (*spongiosa*). The central collagen of the AV valves is continuous with the dense collagen of the *chordae tendineae*, which are attached to the ventricular papillary muscles. The **aortic and pulmonic semilunar valves** consist of a *ventricularis* layer of collagen and radially aligned elastin on the ventricular side, a central *spongiosa* layer of water and glycosaminoglycans, and a *fibrosa* layer of collagen and elastin arranged in a circumferential direction on the great vessel side of the valves to resist back pressure of blood. Valve cusps are predominantly avascular.

Valvular abnormality from any cause can lead to disturbances of blood flow through the heart either by altering the normal unidirectional pattern of flow, or by impeding the chamber inflow or outflow. Alterations in hemodynamics reflect changes in systolic workloads characterized by changed pressure loading during contraction (*afterload*), or changed volume loading during diastole (*preload*). Most

disorders have only a single preload or afterload change imposed. This encompasses all of the valvular disorders that cause either **insufficiency** (*failure to close*) or **stenosis** (*narrowing, failure to open*). Some of the congenital heart abnormalities, such as tetralogy of Fallot, have multiple preload and afterload effects. The general rules are:

1. valvular insufficiency increases the preload on the ventricle;
2. semilunar valvular stenosis, outflow tract stenosis, and hypertension increase the afterload on the ventricle
3. AV valvular stenoses and pericardial disorders decrease the preload on the ventricles.

The **coronary arteries** feed a dense capillary network that supplies the myocardium, endocardium, epicardium, cardiac skeleton, and bases of the cardiac valves. Blood collected by venules and veins is drained into the right atrium via the *coronary sinus*. Lymphatic capillaries draining the cardiac connective tissue, and are continuous with larger lymph vessels in the endocardium and epicardium. Sympathetic and parasympathetic innervation is extensive in the atria, and particularly around the SA and AV nodes.

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HEART FAILURE

Heart failure *is the end-point of a number of causes, rather than a specific disease*, and denotes a situation in which all compensatory mechanisms have been exhausted, and the heart is unable to meet the demands of the animal. The syndrome is characterized by *diminished cardiac output* (*"forward failure"*), or *damming back of blood in the venous system* (*"backward failure"*), or both. The heart can fail because of **impaired pump function** or because of **increased cardiac work demands** – both mechanisms may be operative in some cases. The heart can fail as a pump because of

1. decreased myocardial contractility, or loss or replacement of myofibers, or
2. decreased distensibility (*compliance*), or
3. dysrhythmia (abnormal heart rate and/or rhythm).

Increased cardiac work demands on one or both ventricles result from disturbed hemodynamics, in the form of sustained *pressure overload* (e.g., obstructed flow in aortic valvular stenosis) or *volume overload* (e.g., regurgitant flow in mitral valvular regurgitation).

Congestive heart failure *is characterized by vascular congestion and edema fluid within the interstitium and body cavities.* Not all cases of heart failure are of the congestive type. While in congestive heart failure the clinical manifestations are more or less constant, in **acute heart failure** there may be intermittent weakness and syncope caused by a substantial change in heart rate or rhythm resulting in a precipitous drop in cardiac output. The effect of acute heart failure is often sudden unexpected death, often with minimal lesions. **Circulatory failure, or shock**, *denotes a state of inadequate peripheral vascular perfusion* and is used to describe a state that may or may not be the result of heart failure. It is characterized by a drop in effective circulating blood volume. Common causes are acute internal or external hemorrhage, dehydration, or endotoxic shock. Shock can of course lead to acute heart failure.

Based on clinical manifestations, heart failure may be predominantly either left-sided failure or right-sided failure. **Left-sided failure** *results in left atrial dilation, pulmonary congestion and edema*, and clinical signs of dyspnea and cough. A prominent feature of chronic left-sided heart failure is the presence of hemosiderin-laden macrophages (*"heart failure cells"*) in pulmonary alveoli, the result of diapedesis of red cells into the alveoli. **Right-sided failure** *results in excessive right atrial pressure and systemic venous congestion*, expressed as jugular distension, hepatic and splenic enlargement, ascites, and peripheral edema. **Cor pulmonale** *is defined as right heart failure secondary to pulmonary disease*, such as chronic obstructive pulmonary disease, dirofilariasis, or pulmonary thromboembolism. Because the cardiovascular system is closed, failure of one ventricle will ultimately lead to failure of the other, culminating in global or **biventricular failure**.

While there are many causes that lead to intermittent or permanent lowering of effective cardiac output, there is a limited set of responses to this by the animal. The major compensatory mechanisms include the **intrinsic cardiac responses** *of dilation and hypertrophy*, and the **systemic responses**, *which include increased heart rate and peripheral resistance, redistribution of blood flow, venular constriction, and increased blood volume*. In each case, the compensatory responses are at least temporarily beneficial and are directed toward increasing cardiac output to meet the metabolic needs of the animal. The range within which the compensatory mechanisms result in an increase in cardiac output is wide. Indeed, the increase may be up to five times the basal rate. As cardiac output falls below the requirements of the animal, signs of congestive heart failure appear.

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These may be intermittent or prolonged, depending on the nature of the defect.

An untoward side effect of the systemic responses is increased capillary hydrostatic pressure that leads to the accumulation of **edema fluid**. This can involve the systemic or pulmonary veins. *Right-sided lesions*, such as right atrioventricular valvular insufficiency, pulmonic stenosis, or pulmonary hypertension, result in peripheral dependent edema [e.g., submandibular edema ("bottle-jaw"), brisket edema], ascites, hydrothorax, and hydropericardium. *Left-sided defects*, such as left atrioventricular or aortic valvular insufficiency cause pulmonary edema as the predominant finding.

Intrinsic cardiac responses in heart failure

Cardiac dilation

Dilation is a response to an increased workload in both physiologic and pathologic states. Increasing the end-diastolic volume, and hence stretching the myofibers, can increase the contractile force of the heart and increase the stroke volume and cardiac output. This is known as the **Frank–Starling relationship**, or heterometric autoregulation. Transient cardiac dilation is an acute response to increased demands, e.g., increased exercise. Continued stretch increases contractile force to a limit, after which increased stretch will result in a decrease in tension developed. The limit of stretch in most species appears to be a sarcomere length of 2.2–2.4 μm. Chronic dilation of a ventricle can occur through addition of sarcomeres and hence lengthening of myocytes.

Various disease conditions can cause an increased diastolic workload (preload) and hence dilation of the heart, such as arteriovenous shunts, and atrioventricular and semilunar valvular insufficiencies. *Acute volume overload of a chamber is expected to lead to physiologic dilation*, whereas chronic volume overload is one stimulus to the development of cardiac hypertrophy.

Cardiac hypertrophy

Cardiac hypertrophy is a reversible increase in the mass, but not the number, of myocardial cells. In general, **chronic pressure overload** *leads to myocardial hypertrophy*, whereas **chronic volume overload** *leads to combined ventricular dilation and hypertrophy*. Hyperplasia, or increase in the number of cells, is not an option as a myocardial response to workload given that the capacity of the myocyte to divide decreases rapidly prior to birth, and little mitotic activity is observed after the first few weeks of life. Cardiac hypertrophy is a compensatory response to an increase in mechanical work or to trophic signals, e.g., stimulation of β-adrenergic receptors in hyperthyroidism. The following discussion will be concerned only with the process of hypertrophy following a defined change in workload or stimulation. The presence of hypertrophy in the absence of an observable increase in workload will be considered to be primary and is discussed under the cardiomyopathies.

For hypertrophy to occur, there are requirements of **time, a healthy myocardium, and adequacy of nutrition of the myocardium**. The mass and size of the heart are increased through the actions of mechanical stimuli (stretch) and trophic stimuli (polypeptide growth factors; vasoactive agents such as angiotensin II and α-adrenergic agonists) that increase the rate of protein synthesis, the amount of protein in each cell, the size of myocytes, and the number of sarcomeres and mitochondria. The hypertrophic response is accompanied by selective up-regulation of several immediate early-response genes and embryonic forms of contractile and other proteins. The phenotype of the hypertrophic myocyte may be changed by this expression of embryonic genes, e.g., induction of atrial natriuretic factor occurs in ventricular myocytes, and late response genes such as β-myosin heavy chain and skeletal α-actin may be expressed (a switch from adult to fetal/neonatal forms). Other genes are also activated and selectively regulated in hypertrophy, including immediate early genes or proto-oncogenes that encode early regulatory factors (*c-jun*, *c-fos*, *egr-1*); growth factors (transforming factor-β, insulin-like growth factor, fibroblast growth factor), vasoactive agents (α-adrenergic agonists, endothelin-1, angiotensin II), and components involved in receptor-mediated signaling pathways, such as protein kinase C.

Physiologic hypertrophy of the myocardium in response to strenuous exercise is an extension of the normal growth process, and is usually without deleterious effect. However, *in pathologic states, hypertrophy is an adaptive response of limited benefit.* Hypertrophic myocytes have impaired intrinsic contractility and relaxation; impaired ventricular relaxation and compliance cause increased end-diastolic pressure and limited exercise performance. Once further muscle mass cannot meet the demands posed by increased workload, heart failure ensues. Degenerative changes occur in myofibers, including loss of myocardial contractile elements. Limitations to continued hypertrophy and the reasons for eventual myocardial failure include inadequacy of the vascular supply to the enlarged fibers, diminished oxidative capacity of mitochondria, altered protein synthesis and degradation, and cytoskeletal alterations. The capillary density in hypertrophic myocardium typically does not keep pace with myofiber size, intercapillary distances increase, and fibrous tissue is deposited in the interstitium ("*reactive interstitial fibrosis*"). Also, the altered isoforms of proteins produced by expression of fetal genes may be less functional than adult forms. Myocyte hypertrophy occurs only if increased protein synthesis exceeds the rate of degradation. Similarly, hypertrophy of the ventricle occurs only if growth of individual myocytes exceeds the apoptotic loss of myocytes; excessive apoptosis can contribute to failure of a hypertrophic heart. This postulate is supported by experimental work with receptor-mediated Gαq signaling of cultured rat cardiac myocytes (Gαq is the α subunit of the Gq family of G proteins, guanine nucleotide-binding proteins, which transduce signals) – moderate levels of Gq signaling stimulate cardiac hypertrophy, whereas high-level Gq activation results in cardiac myocyte apoptosis.

There are distinctive anatomic patterns of hypertrophy that accompany the increase in workload. **Concentric cardiac hypertrophy**, *that is, an increase in mass of the ventricle without accompanying increase in end-diastolic volume*, characterizes increased systolic loads (*increased afterloads*), such as aortic stenosis, pulmonic stenosis, and pulmonary hypertension in patent ductus arteriosus. There is often a decrease in the volume of the ventricular lumen. An increase in diastolic load (*increased preload*), typically produced by atrioventricular or semilunar valvular insufficiencies or by arteriovenous shunts, results in **eccentric cardiac hypertrophy**, *which is an increase in myocardial mass accompanied by increased end-diastolic volume (dilated chamber)*. Because of dilation, the thickness of the involved ventricular wall is usually no more than normal and may be less.

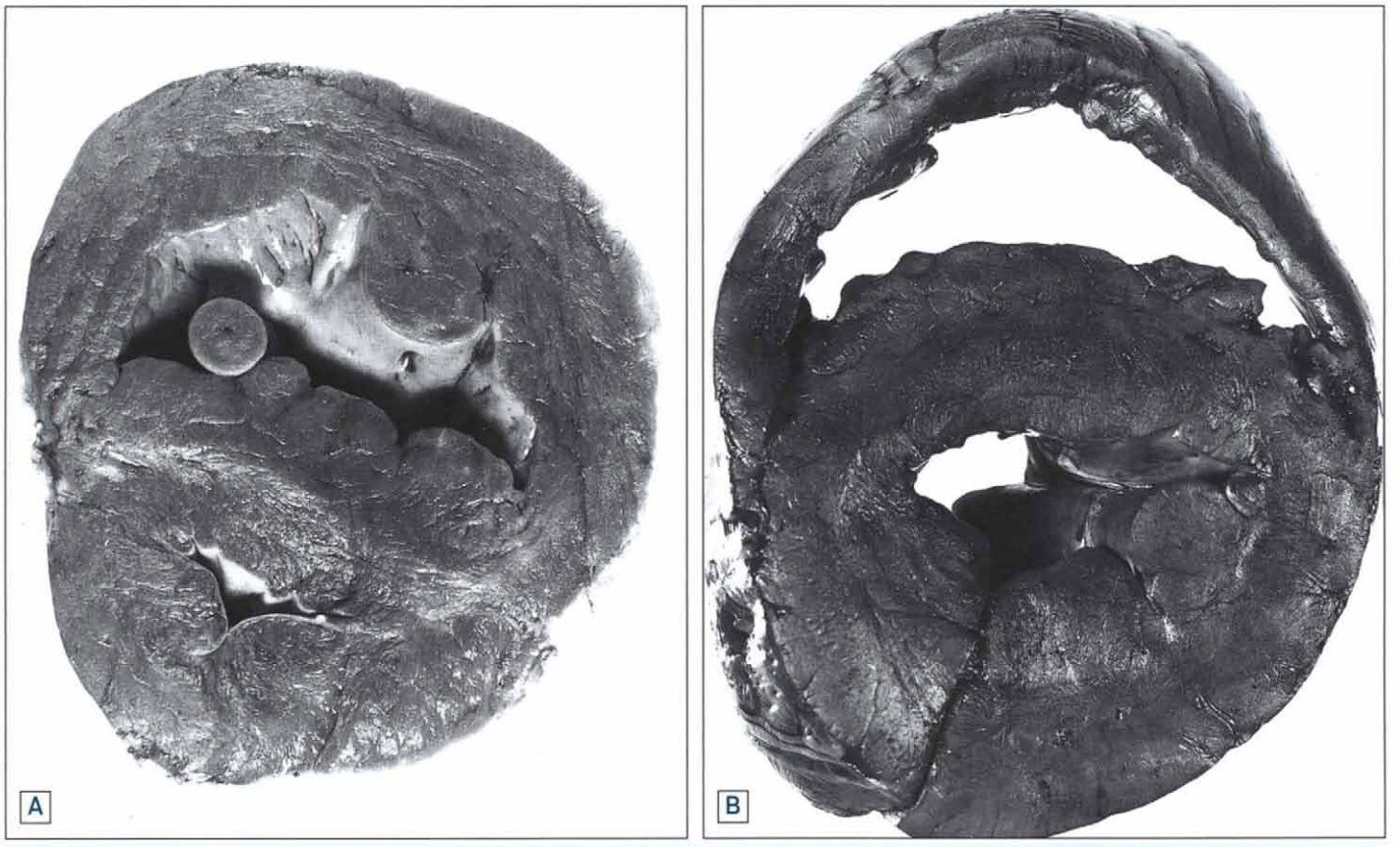

Figure 1.1 Myocardial hypertrophy. A. Cross-section of heart of a cow with chronic interstitial pneumonia. The **right ventricle** is greatly hypertrophied. Note marked increase in size of trabecula septomarginalis (moderator band). **B.** Cross section of heart of a dog with chronic glomerulonephritis. The **left ventricle** is hypertrophic and encroaching on the diastolic capacity of the right ventricle.

The gross appearance of the hypertrophic heart depends on the chamber affected and the nature of the insult. In general, hypertrophy of the right side of the heart makes the heart broader at its base; hypertrophy of the left side increases the organ length; bilateral hypertrophy produces a more rounded shape than normal.

In *concentric hypertrophy*, there is increased thickness of the wall of the affected chamber, and a marked increase in the size of the papillary muscles and the trabeculae carneae. Although the hypertrophy may emphasize one or other chamber, the whole heart is involved. When the right ventricle is involved, the moderator band (trabecula septomarginalis) may be much thickened (Fig. 1.1A). Extreme hypertrophy of one chamber may encroach on the diastolic capacity of its opposite number (Fig. 1.1B). Microscopically, the myocytes are enlarged, but the increase in the size of fibers is not uniform and is not always easy to discern on routine microscopy.

In *eccentric hypertrophy and dilation*, the heart tends to be globose, and even though the mass is increased, the wall is usually thin. The papillary muscles may also be attenuated.

In both types of hypertrophy and dilation, the endocardium may be diffusely opaque as a result of subendocardial fibrosis, and this alteration may be the best indication of dilation in the atria, in which dilation and hypertrophy can be difficult to assess.

An example of concentric cardiac hypertrophy occurs in cats with **hyperthyroidism** (thyrotoxicosis), a condition usually due to the presence of thyroid hyperplasia or adenoma. The thyroid glands in these cases are unilaterally or bilaterally enlarged, nodular, pink to dark-brown, and may contain cysts. Microscopically, the thyroids usually exhibit a mixture of hyperplastic areas, adenomatous nodules, and normal follicles (see also disorders of the thyroid gland in Vol. 3, Endocrine glands). The pathogenesis of ventricular hypertrophy in this disease is not clear, but may involve the direct action of thyroid hormones on myocardium, enhanced myocardial adrenergic receptor number or affinity, peripheral vasodilation, and work hypertrophy in response to increased peripheral tissue demands for oxygen and dissipation of heat. The hearts in most cases are symmetrically hypertrophied; however, some exhibit asymmetric hypertrophy. The left ventricular lumen is usually reduced in size. Affected myofibers are enlarged, but are not in disarray in the great majority of cases. The hypertrophy is reversible on return to euthyroidism.

Systemic responses in heart failure

The *extracardiac features of heart failure* stem from two basic pathophysiologic changes: **fluid accumulation** and **tissue or organ ischemia**. Depending on the cause of the heart failure, both effects may be present, but it is more usual for one to predominate.

Fluid accumulation results from the retention of sodium and water, which primarily involves the kidneys, and also involves atrial natriuretic factor released from the heart. The influence of the failing heart on the kidneys stems from its inability to supply them with an adequate flow of blood. Blood flow through different parts of the kidneys depends on the vasomotor tone of blood vessels

within the parenchyma. It is considered that many, if not all, of the intrarenal blood flow changes in heart failure follow increased activity of the sympathetic nervous system.

The kidneys receive approximately 20% of the output of the left ventricle, almost all of which flows through the renal cortices. One of the earliest changes following a drop in cardiac output is redistribution of blood flow within the kidney. There is reduced flow through the outer renal cortex and increased flow within the outer renal medulla. This results in readjustment of the *filtration fraction*, which is the ratio of glomerular filtration rate (GFR) to renal blood flow. Contrary to expectations, there is a *less* than proportionate drop in GFR compared with renal blood flow resulting in an *increased* filtration fraction. As a consequence, proportionally more sodium moves through the glomerular filter, leading to proportionally more sodium being delivered into the proximal convoluted tubule. Because the rate of sodium resorption remains constant, a greater number of sodium ions are resorbed. Also, because of the increased filtration fraction, local plasma osmotic pressure in the efferent arteriole increases, causing greater resorption of sodium and water.

The alteration in renal blood flow in heart failure also increases the activity of the **renin–angiotensin–aldosterone** system, producing more sodium resorption from the distal convoluted tubule. There is also increased water-retaining activity by **antidiuretic hormone**.

A mechanism within the heart also regulates blood volume complementing the activity of aldosterone and the renin–angiotensin system. **Atrial natriuretic factor** (ANF), with natriuretic and diuretic properties, is present in granules in some of the atrial myocytes. If the atrial pressure is elevated or the atria are distended, ANF is released and causes natriuresis, vasodilation, suppression of the renin–angiotensin–aldosterone axis, and decreased arterial blood pressure. *In terms of homeostasis, ANF has effects opposite to those of aldosterone, thus providing a balance to fluid regulation.* Although plasma ANF is significantly increased in dogs with chronic left AV valvular insufficiency, it is not clear whether the metabolic effects of aldosterone or ANF predominate, but it would appear that the effects of aldosterone override those of ANF.

It should be noted that none of the hormones mentioned produce the edema of congestive heart failure if administered alone. In addition, once a new steady state has been reached, the hormonal state returns to relatively normal limits. Lastly, *the mechanisms that are brought into play are not exclusive to the syndrome of heart failure.* Any situation that leads to a drop in effective circulating blood volume will activate the sodium- and water-retaining mechanism. The fundamental difference between these states and congestive heart failure is that the total blood volume in heart failure is already more than adequate, but the *effective blood volume* is much diminished because of the poor cardiac output. The volume changes in heart failure should be viewed as an integrated response by the body to compensate for the inability of the heart to respond to the normal hemodynamic needs of the body.

The expansion of blood volume has both a beneficial and a detrimental effect. By increasing blood volume, venous return is enhanced and, in turn, cardiac output and tissue perfusion are improved. However, this is to the detriment of the balance between capillary hydrostatic pressure and plasma osmotic pressure. This leads to an increase in the amount of fluid in the interstitial spaces and body cavities.

Syndromes of circulatory failure

Circulatory failure, the term implying severe systemic consequences, falls into three general categories: cardiac syncope, peripheral circulatory failure, and congestive heart failure.

Cardiac syncope

Cardiac syncope is characterized clinically by profound changes in blood pressure and heart rate with bradycardia or tachycardia, either of which may result in inadequate output of blood. Both may occur in the presence or absence of organic heart disease.

In one form of cardiac syncope, hypersensitive or hyperactive reflexes, for which the vagus nerve is the efferent limb, may result in reflex inhibition of the heart, manifest as extreme bradycardia or as asystole. The sudden deaths that result from acute pleural irritation or the tracheal irritation of aspirated vomitus fall into this group, and obviously there may be no organic heart lesion.

In a second form of cardiac syncope, the heart rate is extremely rapid, and the cardiac output severely reduced. Such may occur in paroxysmal tachycardia, atrial flutter or fibrillation, and ventricular fibrillation.

Third, in organic heart disease with complete obstruction of impulse conduction from the atrium to the ventricle (complete heart block), syncope may occur if there is sufficient delay before the ventricle assumes an independent rhythm.

Finally, cardiac syncope may terminate a syndrome of congestive cardiac failure when the cardiac reserve is depleted and the heart cannot increase its output sufficiently to meet sudden increases in peripheral needs.

Peripheral circulatory failure

Peripheral circulatory failure is characterized by reduction in the effective circulating blood volume with insufficient venous return and reduced cardiac output. Acute hemorrhage and shock are examples of this form of circulatory failure.

Congestive heart failure

The combination of compensatory mechanisms, brought into play to maintain cardiac output, is in general successful. However, there is also the planting of the seeds of destruction. Both the local increase in venous hydrostatic pressure and the increased sodium and water retention by the kidneys tend to promote the development of interstitial edema. Depending on the inciting abnormality, it is usual for one side of the heart to fail before the other, but it must be remembered that the cardiovascular system is a closed circuit and that failure of one side will eventually embarrass the other.

Left-sided heart failure is ushered in by progressive dilation of the left ventricle and atrium, although this progression may be marked by exacerbations and remissions if hypertrophy is given time to develop. The major extracardiac manifestations of left-sided failure arise from the damming back of blood in the lungs and the diminution in cardiac output. The *pulmonary venous congestion* is transmitted back to the capillaries of the alveolar wall, and edema fluid accumulates in the interstitial tissue and the alveolar spaces. The consequent reduction in pulmonary vital capacity and impaired

gaseous exchange of cardiogenic pulmonary edema result in hypoxic stimulation of the carotid sinus and medullary respiratory centers so that *reflex dyspnea* occurs. A *wheezing bronchial cough* is common and is presumed to be due to irritation of the respiratory mucosae by the edema fluid. Cyanosis may be present but is more often the rule in right ventricular failure.

At necropsy the **lungs** are usually of normal color, but may be light brown, and are heavy and wet. Stable, white froth is present in the airways, and fluid exudes from the cut surface. There is little evidence of the abundant fluid on microscopic examination, because of its low protein content. The alveoli contain erythrocytes and a scattering of macrophages, some of which contain hemosiderin. It may be necessary to use a differential stain for iron to confirm the presence of these so-called "*heart-failure cells*" or siderophages. They are more numerous in chronic disease, and hemosiderin within their cytoplasm may be sufficient to produce tawny discoloration of the lungs.

In **right-sided heart failure**, the major extracardiac manifestations depend on increased hydrostatic pressure in the systemic and portal venous systems, and the reduction of flow from the lungs to the left ventricle. Renal complications occur more frequently in right-sided than in left-sided heart failure, leading to increased blood volume, peripheral edema, and more marked azotemia.

There is some species difference in the **distribution of edema** in congestive heart failure. In ruminants and horses, *dependent subcutaneous edema* is expected; in the other species, excess subcutaneous fluid is scant or absent. In dogs, the predominant accumulation of fluid is in the *peritoneal cavity*. In cats, it is in the *thorax*.

Grossly the **liver** is enlarged and congested and has a "nutmeg" appearance on section due to *chronic passive congestion*. Microscopically the sinusoids are dilated, with atrophy of the parenchyma about the central veins. In more severe or acute cases, the parenchyma in this location may undergo degeneration or necrosis. It is exceptional for an animal with congestive failure to live long enough for severe fibrosis and nodularity to occur. Impaired hepatic function is not usually a significant part of the clinical course, although jaundice may be observed.

Congestion of the **stomach and intestines** is evident and this may impair their function, which is manifest usually as diarrhea. In horses, the subserosal lymphatics, particularly of the large bowel, are often readily discernible, dilated, and filled with edema fluid. The systemic and portal veins are distended and the **spleen** is enlarged and congested. However, this latter finding is masked if the animal in question has been euthanized using barbiturates.

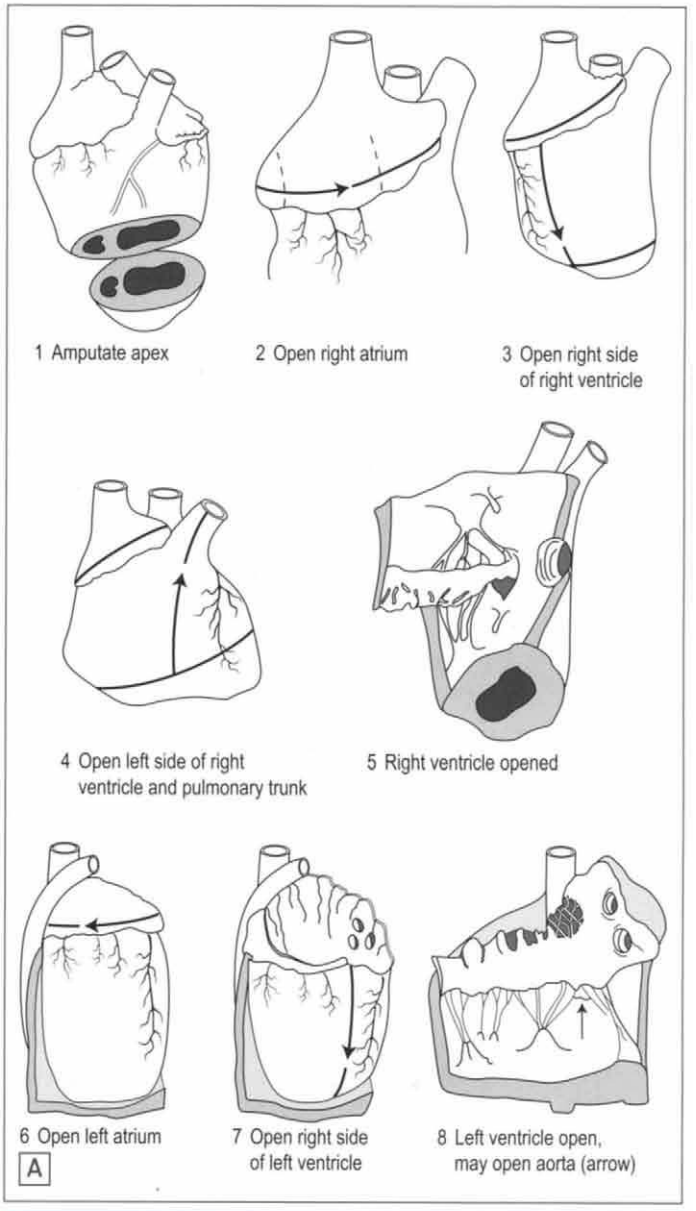

Figure 1.2 A. Gross examination of the heart (see text for details). (1) Transect apex of heart and examine ventricular walls. (2) Open right atrium from caudal vena cava to the tip of the right atrial appendage. (3) Follow blood flow through right ventricle. (4) Cut right ventricular free wall adjacent to septum and out pulmonic valve. (5) Right ventricle and pulmonary trunk opened; moderator band transected. (6) Open left atrium. (7) Open left ventricle towards the apex. (8) Left ventricle opened and left atrioventricular valve exposed; aorta may be opened as indicated by arrow.

EXAMINATION OF THE HEART

In a **gross postmortem examination** of the heart, it is important to examine four major areas: pericardium, myocardium, mural and valvular endocardium, and the great vessels. A useful system is to follow the route of blood flow through the heart, that is, an inflow–outflow method of dissection (Fig. 1.2A). This technique may require modification in the case of cardiac anomalies. Examination of the heart in the planes used for echocardiographic examination could be beneficial.

- The initial examination of the heart and great vessels is best made with the organs in situ to assess abnormalities of size and position.
- Incise the pericardial sac and examine the pericardial fluid before the thoracic viscera are removed; note the volume and color of the fluid, the presence of fibrin, etc.
- Remove the thoracic viscera and examine the external surfaces of pericardium, epicardium, and great vessels.
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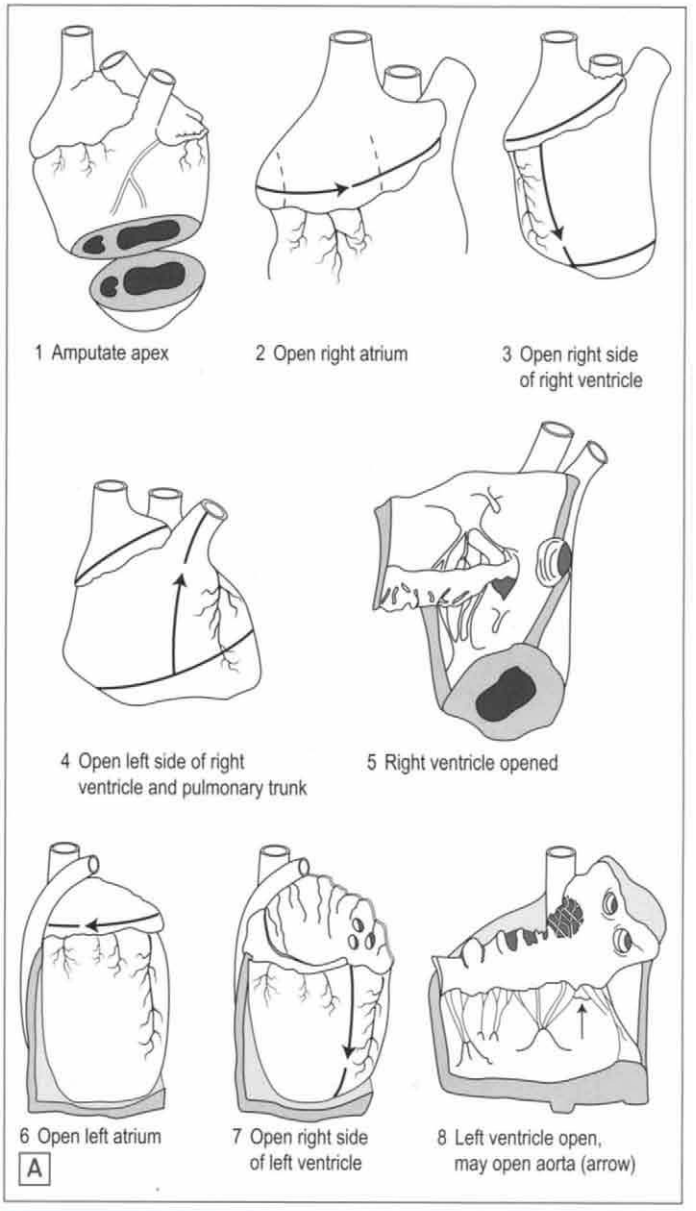

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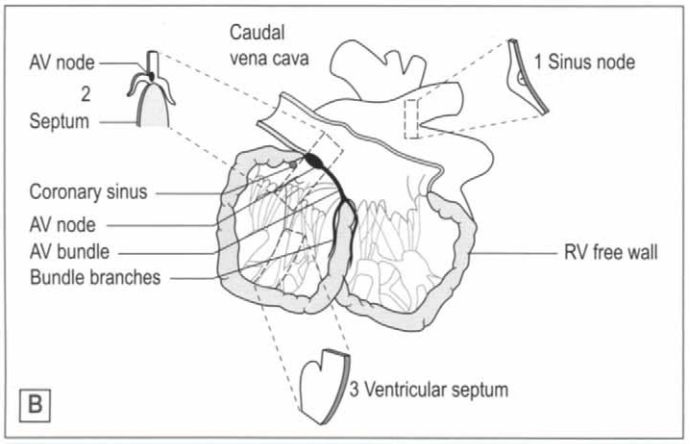

Figure 1.2 B. Tissue sampling from the heart. The cardiac conduction system can be assessed via **block 1**, in which the *sinus node* is located subepicardially in the terminal groove at the junction of cranial vena cava and right atrial appendage, and **block 2**, in which the *atrioventricular node* is located subendocardially on the right side of the interatrial septum, just cranial to the coronary sinus; serial sections through this block will reveal the AV node, the common bundle, and the origins of the bundle branches. A block through the *left ventricular free wall including papillary muscle*, or **block 3** through the ventricular septum, is the minimal representative sample to take from a grossly normal heart.

Table 1.1 Heart weight:body weight (HW/BW) ratios and left ventricular free wall plus septum:right ventricular free wall [(LV + S)/RV] ratios in necropsy accessions of cattle without significant cardiovascular disease

Age	HW/BW (%) (*n*)	(LV + S)/RV (*n*)
<7 days	0.91 (5)	1.69 (5)
7–30 days	0.90 (6)	2.13 (6)
3–365 days	0.48 (9)	2.78 (10)
>1 year	0.48 (11)	2.78 (15)

- The heart may be detached from the lungs if anomalies are absent, but it is usually better left attached to allow careful examination of vessels, e.g., pulmonary artery for thrombi.
- Examine the atria, ventricles, and coronary arteries externally, and confirm normal relationships.
- *When opening the heart, always inspect structures before cutting, and try to preserve a stenotic or dilated valve or vessel.*
- Transect the ventricles in their lower third perpendicular to the long axis of the heart, and check for hypertrophy and/or dilation, myodegeneration or necrosis, mineralization, fibrosis, and mural thrombosis. The apex may remain hinged to the remaining heart. Do not transect the apex if an apical ventricular septal defect is suspected.
- Open the *right atrium*, from the caudal vena cava to the tip of the atrial appendage. Note any thrombus, and check the tricuspid valve and the foramen ovale/fossa ovalis. Leave the cranial vena cava unopened, as a block of tissue to include the *sinus node* may be taken at the junction of the cranial vena cava and the right auricle. Examine the right atrioventricular valve (RAV, tricuspid valve) before cutting.
- Open the lateral side of the *right ventricle* adjacent to the ventricular septum. Examine the RAV and chordae tendineae. The septal leaflet of the RAV is normally thicker than the free leaflets. Transect the moderator band (trabecula septomarginalis).
- Cut through the rostral wall of the right ventricle, and open the *pulmonic valve* if there is no stenosis. Check the pulmonary arteries for thrombi, especially in animals with indwelling jugular catheters. Note the patency or closure of the ductus arteriosus (bear to the right when opening the pulmonary artery in neonates to avoid cutting through a patent ductus arteriosus and creating a false anomaly).
- Open the *left atrium* by cutting into the atrial appendage and then parallel to the ventricular groove. Examine the interatrial septum, foramen ovale/fossa ovalis, and the left atrioventricular valve (LAV, mitral valve).
- Open the *left ventricle* by cutting along the caudal border of the left ventricle adjacent to the ventricular septum, examining the LAV before cutting it. Chordae tendineae should be carefully examined before opening the LAV to ensure that pre-existing ruptures of the chordae are detected.
- Continue to follow the blood flow by cutting through the *aortic valve* and cutting along the aorta – note that the pulmonary artery will be transected by this action.
- The circumference of the four cardiac valves may be measured at this time with a flexible ruler. Normal LAV/RAV valve ratio for dogs is 0.66.

The right ventricle is responsible for systemic circulation in the fetus. Hence, in neonatal hearts, the wall thickness of the left and right ventricles is approximately equal; it is not until a month or more after birth that the mature proportions are attained. Ventricular wall thickness is poorly correlated with ventricular mass, and heart weights provide more valid information about ventricular hypertrophy than do thickness measurements, especially in cases of dilation and eccentric hypertrophy. *To accurately assess cardiac mass, the heart should be weighed and the weights compared to body weight.* After removing the pericardial sac and post-mortem blood clots, weigh the whole heart, right ventricular free wall, and left ventricular free wall plus septum.

- The ratio of normal heart weight to body weight (HW:BW) ranges from 0.5 to 1.0%, depending on age and species (Tables 1.1 and 1.2).
- The HW:BW ratio is higher in neonates than in adults; the more athletic species (horses, dogs) have higher HW:BW ratios; HW:BW ratio is increased by training or exercise; and males typically have greater HW:BW ratios than do females of the same species.
- The ratio of the weight of the left ventricle plus septum divided by the weight of right ventricular free wall [(LV +S)/RV] is 2.8–4.0 in mature animals; (LV +S)/RV >4.0 indicates *left ventricular hypertrophy*; (LV +S)/RV <2.8 is consistent with *right ventricular hypertrophy*.

The usual tissue block taken for routine **histology** is of left ventricular papillary muscle, as this area is one of the most susceptible to damage and most representative in cases of generalized disease. Detailed examination of the heart, including the conduction system, requires collection of tissue blocks (Fig. 1.2B) from the junction of the cranial vena cava and right auricle (sinus node), both atria, the interatrial septum/dorsum of the ventricular septum at

Table 1.2 Reference values for heart weight:body weight (HW/BW) ratio and ventricular ratio [(LV + S)/RV] in normal mature animals at necropsy

Species	*n*	HW/BW (%)		(LV + S)/RV	
		$\bar{x}$	$\bar{x} \pm 2$ SD	$\bar{x}$	$\bar{x} \pm 2$ SD
Dog	21	0.71	0.43–0.99	3.26	2.39–5.12
Horse	12	0.69	0.41–0.97	3.12	2.43–4.34
Cat	9	0.58	0.28–0.88	3.45	2.94–4.17
Cow	15	0.48	0.30–0.66	2.78	2.43–4.00
Goat	11	0.46	0.26–0.66	3.12	2.50–4.17
Sheep	8	0.41	0.17–0.65	3.33	2.63–4.54
Pig	8	0.40	0.32–0.48	2.94	2.38–3.84

HW, heart weight; BW, body weight; LV + S, left ventricular free wall + septum; RV, right ventricular free wall; $\bar{x}$, mean; SD, standard deviation.

the base of the heart just cranial to the coronary sinus (atrioventricular node), right ventricular free wall and AV valve, ventricular septum, left ventricular free wall/papillary muscle and AV valve, great vessels, plus any grossly evident lesions.

The selection of sections to study the **specialized conduction system** should include the sinus node, the atrioventricular node, the common bundle (bundle of His), left and right crura (bundle branches), and conducting fibers. The **sinus node** lies subepicardially in the terminal groove (sulcus terminalis) at the junction of the cranial vena cava and the right atrium. Sections should include either side of that site, to incorporate tissue in the sulcus terminalis region. The **atrioventricular node** is obtained by removing a block of tissue from the coronary sinus to the cranial edge of the septal leaflet of the right AV valve. The block includes interatrial septum and dorsal ventricular septum, and will then contain the atrioventricular node, which is located subendocardially on the right side of the interatrial septum, the common bundle, and the left and right crura. The specimen should be serially sectioned into samples 3 mm thick, and all samples should be processed.

In routine cases, there are no special requirements for fixation. Stains of particular use are hematoxylin and eosin, Masson's trichrome, phosphotungstic acid hematoxylin, Luxol fast blue, and Gomori's aldehyde fuchsin.

Note that *rigor mortis* begins earlier in myocardial than in skeletal musculature, and reaches greater development in the more powerful left ventricle. Rigor should completely express the blood from the left ventricle; rigor of the right ventricle is less efficient, and emptying is incomplete. The presence of some clotted blood in the right ventricle is normal, whereas if present in the left ventricle it is indicative of incomplete rigor and therefore perhaps of severe myocardial degeneration. The presence of unclotted blood in the left ventricle some hours after death is more difficult to interpret. Unclotted blood – the result of fibrinolysis – may flow back into the ventricle when rigor passes.

Blood usually clots slowly after death and permits erythrocytes to sediment. Where blood is present in volume, as in the heart and arterial trunks, this process of sedimentation and subsequent clotting leads to the formation of "currant jelly" and "*chicken fat*" *clots*, the former containing erythrocytes, and the latter largely devoid of them. "Chicken fat" clots are to be expected in horses, which normally have a rapid erythrocyte sedimentation rate, and are in relative excess in anemia. Postmortem **clots** are to be distinguished from **thrombi**; clots are not attached to the endocardium.

Biopsy of the heart in not commonly undertaken in vivo, but is possible via transvenous **endomyocardial biopsy**. Multiple biopsy samples of the right ventricular myocardium may be obtained by this means, and may be used, for example, to monitor the cardiotoxic effects of anthracycline therapy.

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CONGENITAL ABNORMALITIES OF THE HEART AND LARGE VESSELS

In the transition from fetal to neonatal life, substantial adjustments occur within the cardiovascular system: there are alterations in the pressures in cardiac chambers and great vessels, the pattern of blood flow, and the volume of blood flow. Because of these changes, the retention postnatally of fetal vascular communications, such as the ductus arteriosus, may place an excessive load on the heart in the postnatal period and beyond. There are also congenital heart defects, such as pulmonic stenosis, which compromise the fetus, the newborn, and the adult. It is typically only those defects that allow adequate in utero development and a reasonably successful perinatal life that are recognized; anomalies sufficiently severe to cause death in utero, or in the neonatal period, often are not.

As with most diseases, there is a spectrum of change. *The variation in severity of a particular lesion may be wide and will necessarily influence whether clinical signs are observed.* As such, there is a higher incidence of congenital heart disease than is recognized clinically. There is also a group of congenital heart diseases that do not produce clinical signs of heart failure, but which are manifested by upper alimentary dysfunction. Although little is known of the causes of many cardiac malformations in domestic mammals, there is no doubt that, especially in dogs, *some are genetically determined.* The demonstration that some congenital heart diseases are genetically determined arose from the observation that the incidence of defects was higher in purebred populations. It has been thought that both patent ductus arteriosus and conotruncal defects have a polygenic inheritance pattern, where the full expression of these diseases depends on the inheritance of a number of genes from different loci. However, studies on Keeshonds with conotruncal defects indicate that the inheritance pattern is most compatible with a single autosomal locus. The data suggest the presence of a mutant allele that is partially penetrant in heterozygotes and fully penetrant in homozygotes. Congenital subaortic stenosis in the Newfoundland dog is also genetically determined; it may either be polygenic or a single dominant gene that is variably expressed. Table 1.3 outlines the breed-specific predisposition to congenital heart disease in the dog.

There may be other as yet undefined factors that contribute to the development of congenital heart disease in domestic animals. In humans, cardiac and vascular anomalies are common features of several syndromes produced by chromosomal abnormalities and viral infections such as rubella. There is little evidence to suggest the presence of similar abnormalities or infections associated with congenital heart disease in domestic animals.

Table 1.3 Breed-specific predispositions to congenital heart disease in dogs

Defect	Breed
Patent ductus arteriosus	Bichon Frise, Chihuahua, Cocker Spaniel, Collie, English Springer Spaniel, German Shepherd, Keeshond, Kerry Blue Terrier, Maltese Terrier, Pomeranian, Poodle, Shetland Sheepdog, Yorkshire Terrier
Pulmonic stenosis	Airedale Terrier, Beagle, Chihuahua, English Bulldog, Fox Terrier, Mastiff, Miniature Schnauzer, Samoyed, Scottish Terrier, West Highland White Terrier
Subaortic stenosis	Boxer, English Bulldog, German Shepherd, German Shorthaired Pointer, Golden Retriever, Great Dane, Newfoundland, Rottweiler, Samoyed
Persistent right aortic arch	German Shepherd, Great Dane, Irish Setter
Tetralogy of Fallot	English Bulldog, Keeshond
Atrial septal defect	Doberman Pinscher, Samoyed
Ventricular septal defect	English Bulldog
Tricuspid insufficiency or dysplasia	German Shepherd, Golden Retriever, Great Dane, Labrador Retriever, Weimaraner
Mitral insufficiency or dysplasia	Bull Terrier, English Bulldog, Chihuahua, German Shepherd, Great Dane

The pattern and incidence of congenital cardiac disease varies with the species examined. In **dogs**, patent ductus arteriosus, pulmonic stenosis, and subaortic stenosis are common (Table 1.4). In **cattle**, atrial and ventricular septal defects and transpositions of the main vessels are most frequently diagnosed. Subaortic stenosis and endocardial cushion defects are the most frequent anomalies in **pigs**. In **cats**, endocardial cushion defects and congenital mitral insufficiency appear to be common. Congenital cardiovascular disease is quite uncommon in **horses**.

In cases of suspected cardiac abnormality, it is essential to examine the heart and large vessels in situ because relations are difficult to trace once the organ is removed. Some animals are born with hearts that, although of normal arrangement, are very small. In the majority of cases of cardiac abnormality, the anomaly is reflected in gross enlargement of the organ and in alteration of the size or disposition of the large vessels. Cardiac malformations are extremely variable, and their analysis can be perplexing if it is not remembered that they do follow fairly simple basic patterns. The recognition of the primary abnormality is an essential first step. This then assists in the recognition of secondary abnormalities, which develop as adjustments to allow blood to circulate through the heart. An understanding of the mechanics of abnormal development is necessarily based on an understanding of the normal development of the organ, for which reference should be made to a standard text of embryology.

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Table 1.4 Proportions (%) of canine congenital cardiac anomalies in four surveys

Anomaly[a]	Patterson (1953–65), $n = 248$	Mulvihill, Priester (1964–71), $n = 700$	Hunt et al. (1977–89), $n = 100$	Tidholm (1989–96), $n = 151$
Patent ductus arteriosus	30	36	34	11
AV valve dysplasia	4	9	18	15
Pulmonic stenosis	21	11	18	20
Aortic stenosis	15	6	10	35
Persistent right aortic arch	8	12	7	–
Ventricular septal defect	7	10[b]	7	12
Tetralogy of Fallot	4	–	3	0.6
Atrial septal defect	4	3	0	3
Other	7	13	3	3
Total (%)	100	100	100	100

[a] *~7–9% of dogs had more than one anomaly.*
[b] *Includes tetralogy of Fallot.*

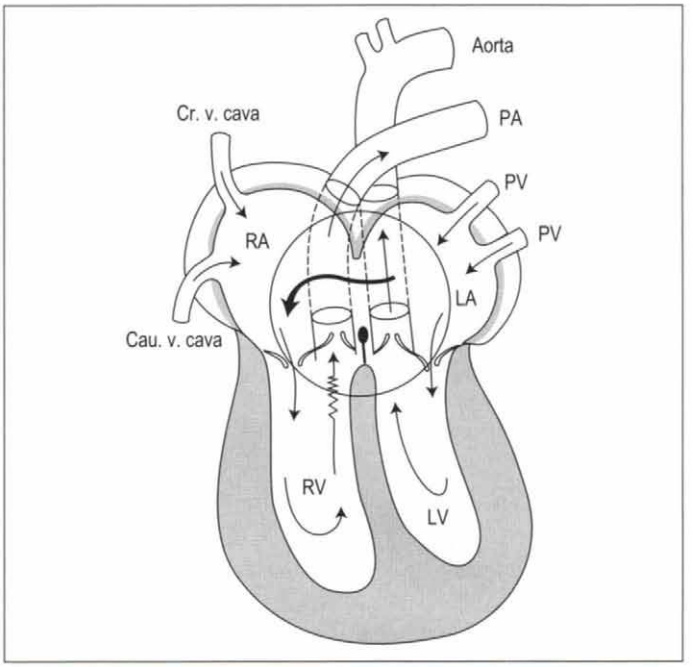

Figure 1.3 Atrial septal defect. Blood flows through the defect from the left atrium to the right atrium. The right ventricle dilates and hypertrophies under increased preload. A relative pulmonic stenosis is induced because of the increased volume in the right ventricle. Both atria also dilate following increased volume loads. Reverse shunts may occur with blood flowing from the right to the left atrium. (Figures 1.3, 1.5, 1.6, 1.7, 1.8, 1.10 from Robinson WF, Huxtable CRR, eds. Clinicopathologic Principles for Veterinary Medicine. Cambridge: Cambridge University Press, 1988, with permission. Abbreviations in these figures: LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; PA, pulmonary artery; PV, pulmonary veins; Cr. v. cava, cranial vena cava; Cau. v. cava, caudal vena cava.)

part of a spectrum. Based on a combination of anatomical defects and functional effects, they may be classified as:

- malformations causing systemic to pulmonary (left-to-right) shunting,
- malformations of cardiac valves,
- transposition complexes,
- miscellaneous cardiac anomalies, and
- vascular anomalies.

Malformations causing systemic to pulmonary (left-to-right) shunting

In the development of the heart, there are three major arteriovenous communications: between the atria, the ventricles, and the great vessels. These connections are necessary for shunting of blood in the fetus. The atrial and ventricular septa close in utero; the foramen ovale and the ductus arteriosus close early in the neonatal period. Failure of closure results in *atrial septal defect, ventricular septal defect, or patent ductus arteriosus*, three of the more common congenital cardiac defects in domestic animals. Less common defects in this group include *atrioventricular septal defect, persistent truncus arteriosus, aorticopulmonary window*, and *anomalous pulmonary venous return*.

Atrial septal defect

In the fetus, separation of the left and right atria commences with the downgrowth of the *septum primum*, which grows toward the atrioventricular junction, where the developing endocardial cushions begin to form the atrioventricular valves and separate the ventricles. The septum fuses with the endocardial cushions, obliterating the *ostium primum*, and then begins to fenestrate in its middle. The fenestration is destined to become the *ostium secundum*. A second septum (*septum secundum*) develops downward and to the right of the septum primum. With its semilunar edge, the septum secundum and the remains of the septum primum form the **foramen ovale**. Within the left atrium, the septum primum forms the flap valve of the foramen ovale that allows blood flow from right atrium to left atrium in the fetus. In the majority of animals, anatomic closure of the foramen ovale follows functional closure postnatally. A *probe-patent foramen ovale* postnatally is not an atrial septal defect, for although the foramen ovale may not be anatomically closed, it is functionally closed (*valvular competent*) because left atrial pressure exceeds right atrial pressure.

An atrial septal defect can result from:

- defects of the septum between the right upper pulmonary veins and the cranial vena cava (**sinus venosus defect**),
- failure of fusion of septum primum with the endocardial cushions (**ostium primum defect**, low in the atrial septum adjacent to the atrioventricular valves, a form of atrioventricular septal defect), or
- an excessively large ostium secundum or inadequate development of the septum secundum (**ostium secundum defect**, in midseptum at the site of the fossa ovalis, the most common type).

The consequence of an atrial septal defect in the neonate is excessive flow from the left to right atrium, with resultant volume overload on the right ventricle and elevated central venous pressure (Fig. 1.3). In some cases, following the development of pulmonary hypertension, the flow through the defect is reversed, leading to cyanosis.

Figure 1.4 Ventricular septal defect in a goat. The defect is just below the aortic valve and the left ventricle is dilated. (5 cm between arrows.)

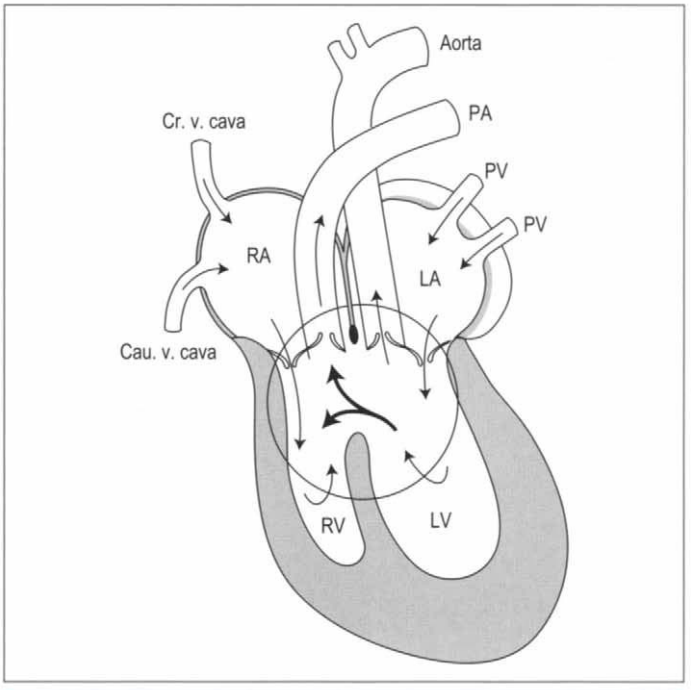

Figure 1.5 Ventricular septal defect. Both increased preload and afterload are imposed on the right ventricle by a VSD. The increased volume of blood returning from the pulmonary circuit also places increased preload on the left atrium and ventricle.

Atrioventricular (AV) septal defect

Also known as *endocardial cushion defects* or *atrioventricular canal defects*, these malformations arise from deficiency of the AV septum that separates the left ventricular inlet from the right atrium. The atrial septum primum must fuse with the endocardial cushions, which in turn contribute to the development of the atrial and ventricular septa, and to the medial leaflets of the left and right atrioventricular valves. Anomalous development may result in a range of anatomic defects, including *ostium primum defect (partial AV canal), ventricular septal defect with a cleft in the tricuspid valve*, or *common atrioventricular canal*. The common or complete AV septal defect consists of an ostium primum defect, a ventricular septal defect, and a common AV orifice.

Defects of the atrioventricular canal are among the most common defects in the pig. In the largest series examined, 40% of pigs with congenital heart disease had this defect. It is also a frequent finding in *cats*.

Ventricular septal defect

Ventricular septal defect (VSD) is one of the most common defects encountered in domestic animals. The separation of the left and right ventricles is completed by three parts of the embryonic heart: the muscular portion of the septum, the downward growth of the conotruncal ridges, and the membranous portion of the septum derived from the endocardial cushions. Defects can be related to defective development of any of the three parts. VSDs are usually single (Fig. 1.4), but may be multiple, and *most commonly involve the membranous septum.* This type of VSD is termed *paramembranous* or *perimembranous*, as they exceed the bounds of the membranous septum and involve a muscular defect at their periphery; they may also be referred to as subaortic or infracristal. Less common sites of VSD are *subpulmonary* (infundibular, conal, supracristal), *below the septal leaflet of the tricuspid valve*, or *in the muscular portion of the ventricular septum* towards the apex of the heart. While occurring most commonly as an isolated defect, VSD is also seen as part of a number of other defects, such as tetralogy of Fallot or persistent truncus arteriosus. There appears to be a high incidence of *spontaneous postnatal closure* of small VSDs in humans, and a similar phenomenon has been reported in dogs.

The presence of a VSD has no deleterious effect on the fetus because left and right ventricular pressures are equal and there is therefore little flow across the defect. *Postnatally, the effects of VSDs are related to the size of the defect and the level of pulmonic vascular resistance relative to the systemic resistance.* Pulmonary vascular resistance normally drops postnatally, leading to a *left-to-right shunt*. Left ventricular output is maintained by an increase in end-diastolic volume and augmentation of contractility by the Frank–Starling mechanism. Since right ventricular pressure equals left ventricular pressure, the right ventricle is confronted with a large systolic and diastolic load. *Both ventricles undergo hypertrophy*, the left being more obviously eccentric in nature (Figs 1.4 and 1.5).

Eventually, pulmonary hypertension can lead to shunt reversal (right-to-left), cyanosis, and death. The term **Eisenmenger complex** is applied to VSD cases in which, instead of the usual left-to-right