Failure in Cardiac Action: Comparing Humans, Dogs, Cats, and Horses

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Contents

Abstract

The heart is a central organ keeping the blood flow going, thereby providing oxygenation of peripheral tissues. An overview is given here on the most important heart diseases, comparing among humans and animals, especially cats and dogs. Whereas in humans cardiac diseases due to long-standing arterial hypertension and atherosclerosis represent the well-known most important death causes, in animals the disease is less recognized by the public and often occurs

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silent. In humans, the prevalence of diseases of the cardiovascular system varies according to the socioeconomic conditions of a geographic region: Whereas rheumatic heart diseases and cardiomyopathies due to infection and malnutrition are more prevalent in developing countries, arterial hypertension and atherosclerosis are more prevalent in industrial countries. In animals, the most frequent diseases of the cardiovascular system comprise chronic degenerative valve disease (endocardiosis), dilated cardiomyopathy in dogs, and hypertrophic cardiomyopathy in cats. In humans, arterial hypertension is frequently primary, whereas in animals secondary hypertension due to underlying systemic diseases is more frequent than primary hypertension.

1.1 Cardiac Disease: Number One of Death Causes in Humans

The most frequent cardiovascular diseases in humans (Fig. 1.1) comprise arterial hypertension, atherosclerotic vascular disease, cardiomyopathies, valvular heart disease, and Takotsubo cardiomyopathy. Since arterial hypertension is also one of the most important risk factors for the development of atherosclerosis, a high interdependence between these diseases exists. The most devastating manifestation of atherosclerosis is myocardial infarction, which may lead to stroke, potentially leading to lifelong disability or sudden death. Sedentary lifestyle, food composition, nicotine abuse, and environmental factors play a role in the development of hypertension and atherosclerosis. In the pathogenesis of cardiomyopathies, arterial hypertension but also genetic and metabolic factors, alcohol abuse, malnutrition, and infections may play a role in human patients. Valvular heart disease may either be congenital or caused by infections, rheumatic, autoimmune, or atherosclerotic mechanisms. Psychic as well as physic stress and emotional factors, which are difficult to measure and quantify, play an important role in the development of Takotsubo cardiomyopathy. These emotional factors, as well as sleep deprivation, are also assumed to be important risk factors for arterial hypertension and atherosclerosis.

The prevalence of the diseases of the cardiovascular system varies according to the socioeconomic conditions of a geographic region: Whereas rheumatic heart diseases and cardiomyopathies due to infection and malnutrition are more prevalent in developing countries, arterial hypertension and atherosclerosis are more prevalent in industrial countries.

1.1.1 Arterial Hypertension

The prevalence of elevated blood pressure, i.e., arterial hypertension in middle Europe is about 10–50 % of the human population with a steep increase with aging (Mancia et al. 2013). According to measurement results of the systolic and diastolic blood pressure, a classification has been established (Table 1.1).

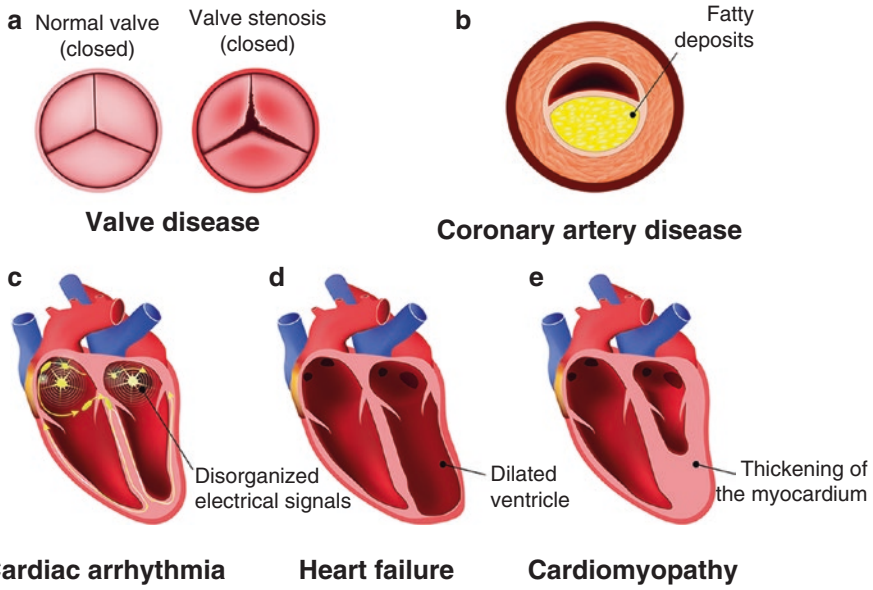

Fig. 1.1 Most frequent heart diseases in humans and animals. (**a**) Inflammation, for instance, through bacterial infections, may damage the ventile function of heart valves and result in functional insufficiency. Chronic degenerative valve disease (CDVD) is the most common acquired heart disease, for instance, in dogs, mostly affecting the *mitral valve* between the left atrium and ventricle; (**b**) arteriosclerosis, in contrast, is a disease mostly seen in humans associated with metabolic syndrome. Thereby, fatty deposits (plaques) are formed in endothelia, macrophages activated to phagocytose them. Coronary artery disease may present as reversible stenocardia or infarct. The latter occurs when an instabile plaque suddenly causes vessel obstruction. (**c**) Transient or stable obstructions of coronary arteries are typically associated with disorganized electric signals resulting in arrhythmia, which can be monitored in an electrocardiogram; (**d**) chronic insufficiency or inflammation of the heart muscle may lead to heart dilatation, associated with output failure due to decreased contractility; (**e**) cardiomyopathy as illustrated here is associated with thickening of the heart muscle, being, for instance, a consequence of constant overload in hypertonia (Fotolia.com-© designua)

Table 1.1 Classification of hypertension in humans

Classification	Systolic mmHg	Diastolic mmHg
Normal	90–119	60–79
Prehypertension	120–139	80–89
Stage 1 hypertension	140–159	90–99
Stage 2 hypertension	≥160	≥100
Isolated systolic hypertension	≥140	<90

In 90–95 % of humans with arterial hypertension, the cause remains unidentified, prompting the classification "primary arterial hypertension." The development of arterial hypertension is assumed to be a complex interaction between genetic,

environmental, and lifestyle factors, including sleep deprivation (Kohansieh and Makaryus 2015).

In contrast, in "secondary arterial hypertension," a specific cause can be identified. It may, for instance, occur in a minority of cases in patients with renal diseases, congenital vascular abnormalities, or hormonal diseases like Cushing syndrome, thyroid disorders, or pheochromocytoma.

Arterial hypertension is a silent offender. It causes no symptoms in the beginning of the disease, and blood pressure measurements are only occasionally performed in healthy adults. Hypertension, however, is the most important risk factor for atherosclerosis. When symptoms occur, hypertension has frequently already led to organ damage involving the brain, eye, heart, kidneys, and blood vessel walls.

The following lifestyle factors have been identified to lower the blood pressure: reduced salt intake, increased consumption of fruits, exercise, weight loss, and reduced alcohol intake (Mancia et al. 2013; Börjesson et al. 2016). When the blood pressure remains elevated despite modifications of lifestyle, long-term antihypertensive drug therapy is indicated.

1.1.2 Experimental Animal Models in Hypertension

An animal model for hypertension is sought-after in small animals, able to predict the potential antihypertensive properties of an agent, consume minimal quantities of compounds, simple to perform and uniformly reproducible, and comparable to some form of human hypertension. Unfortunately, there are no adequate models for primary hypertension (Dornas and Silva 2011). The animal models of hypertension are mainly models for secondary hypertension, which is rare among humans (Table 1.2). Natural history of the disease and observations of therapeutic effects can be only translated with caution from animal experiments to humans. Therefore, the concept of comparative medicine, i.e., comparison of human disease to veterinary patients, is highly attractive. Intriguingly, animals and owners share many of the environmental and lifestyle factors.

1.1.3 Atherosclerosis

Atherosclerosis is characterized by an accumulation of deposits of lipid, fibrous tissue, and calcium in the arterial walls, which eventually results in luminal narrowing. Atherosclerosis is induced by chronic endothelial injury. Several factors like arterial hypertension, nicotine abuse, hyperlipidemia, diabetes mellitus, and toxic, inflammatory, and immunologic reactions are involved in the process of endothelial injury.

Table 1.2 Experimental animal models of genetic hypertension

Phenotype driven	Genotype driven
Spontaneously hypertensive rat (SHR)	Renin-angiotensin system
SHR stroke prone	Sympathetic nervous system
Dahl salt-sensitive rat	Atrial natriuretic peptide
Genetically hypertensive rat	Nitric oxide
Sabra model	Endothelin
Lyon hypertensive rat	Neuropeptide Y
Obesity related	Vasopressin
	Prostaglandin
	Kallikrein-kinin

Clinical consequences of atherosclerosis depend on the affected arteries. When the coronary arteries are affected, atherosclerosis might cause angina pectoris. In the case atherosclerosis leads to an occlusion of a coronary artery, myocardial infarction may occur. Affection of the cerebral arteries may lead to stroke, and of the peripheral arteries to intermittent claudication and gangrene.

Acute myocardial infarction is characterized by oppressing chest pain lasting >30 min, dyspnea, nausea, vomiting, palpitations, sweating, and anxiety. If one or more of these symptoms occur, the emergency service should be called immediately since life-threatening arrhythmias like ventricular fibrillation are frequent. Ventricular fibrillation will lead to cerebral hypoxia and, if untreated, to the patient's death. Ventricular fibrillation can be treated by defibrillators. Furthermore, the patient with myocardial infarction should be transported to the hospital as soon as possible for acute intervention to open the occluded coronary artery (Fig. 1.2). The shorter the artery remains occluded, the lower will be the consecutive damage of the myocardium. Reperfusion therapy by acute coronary intervention in patients with acute myocardial infarction saves life and the myocardium (Bainey and Armstrong 2016).

1.1.4 Experimental Models in Atherosclerosis

Atherosclerosis rarely occurs in animals. Atherosclerotic lesions have been detected in aged pigs and parrots and in dogs with hypothyroidism and diabetes mellitus. Animals used for atherosclerosis research comprise rabbits, mice, rats, guinea pigs, hamsters, swine, and nonhuman primates (Fuster et al. 2012). In these animals, atherosclerosis is induced by either cholesterol feeding or mechanical endothelial injury. Furthermore, genetically engineered mice are used.

Pigs, rabbits, and chicken are susceptible to the experimental disease produced by feeding of a high-cholesterol diet, whereas dogs, cats, cows, goats, mice, and rats are resistant. Rabbit models of atherosclerosis have the advantages that they are easy to maintain and handle and have low costs, that the animals are highly

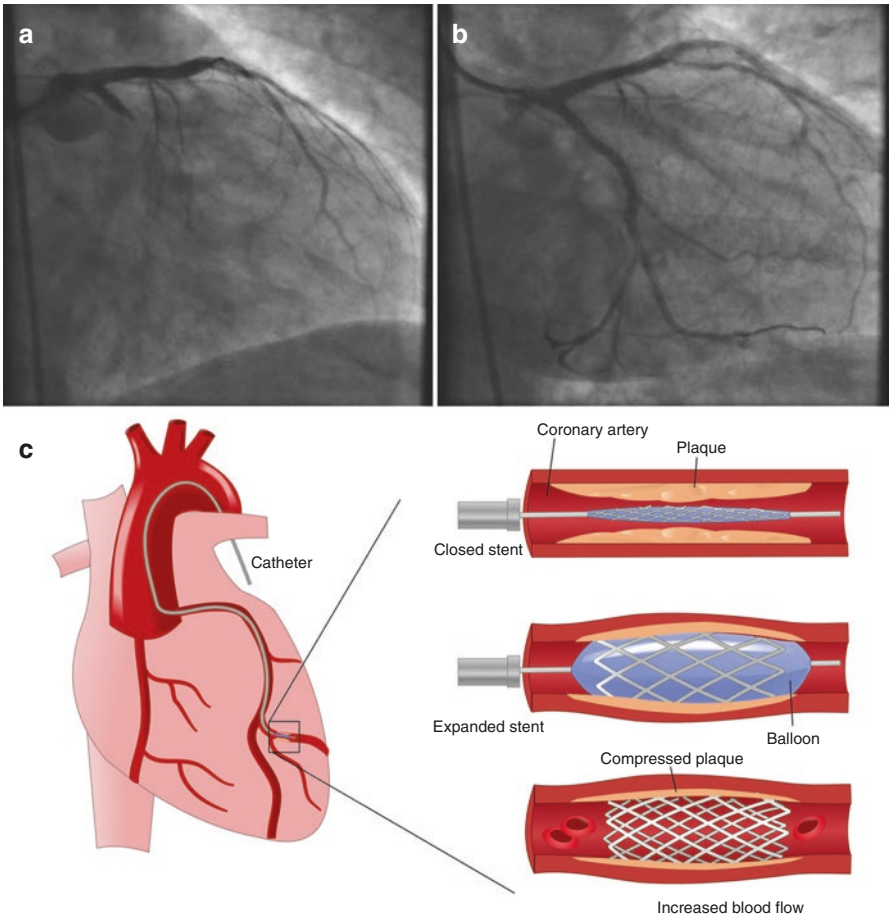

Fig. 1.2 Acute myocardial infarction in a human patient and stent therapy. (**a**) Acute coronary angiography showing an occlusion of the circumflex branch of the left coronary artery in a patient with acute myocardial infarction; (**b**) after recanalization and implantation of a stent within the narrowed coronary artery, a normal blood flow is seen in the artery, which had been occluded in the beginning of the procedure; (**c**) in case of blockage of the arteria coronaria, e.g., by arteriosclerotic plaques, via cardiac catheterization a ballon stent can be introduced that enlarges the diameter of the vessel by compressing the plaque. The balloon is removed after the manipulation, whereas the stent remains (Fotolia.com-©ellepigrafica)

available, that their lipoprotein metabolism is similar to humans, and that they show a good response to dietary cholesterol. Disadvantages of rabbits in animal experiments of atherosclerosis are the highly abnormal diet and that long-term cholesterol feeding induces hepatic toxicity and massive inflammation. Pig models of atherosclerosis have the following advantages: cardiovascular anatomy similar to humans, spontaneous formation of atherosclerotic lesions, morphology of lesions, and lipoprotein metabolism similar to humans. Disadvantages of pig models are high cost of purchase and maintenance, difficulty in handling, and that atheroma formation

requires time. Advantages of nonhuman primates as animal model for atherosclerosis are that they are phylogenetically close to humans and show spontaneous formation of atherosclerotic lesions and that these vascular lesions are similar to humans. Disadvantages of nonhuman primate models are high costs of purchase and maintenance, limited availability, requirement of special animal facilities, and ethical concerns. Mouse models of atherosclerosis have the advantages of easy breeding and handling, short generation time, well-defined genetics, and well-established protocols for genetic manipulation. Disadvantages of mouse models are a high resistance to atherosclerosis development in wild-type mice, a plasma lipid profile different to humans, differences in the morphology of vessel wall, and the absence of plaque rupture and luminal thrombosis.

1.2 Cardiac Diseases in Dog and Cat Patients

The common cardiovascular diseases in veterinary medicine include chronic degenerative valve disease (endocardiosis), dilated cardiomyopathy in dogs, hypertrophic cardiomyopathy in cats, and systemic hypertension.

Acute myocardial infarctions are uncommon in veterinary medicine and are most commonly associated with concurrent systemic or cardiac disease that leads to a thromboembolic state. Endocarditis, neoplasia, renal disease, immune-mediated hemolytic anemia, and pancreatic disease are the most frequent conditions. In human medicine there is a high incidence of infarcts associated with atherosclerosis, whereas in veterinary medicine, the patients with infarcts are very rarely diagnosed with atherosclerosis (Meurs 2010).

1.2.1 Chronic Degenerative Valve Disease (CDVD) Mostly Affects *Mitral Valve*

Endocardiosis, also known as chronic degenerative valve disease (CDVD), is the most common acquired heart disease of dogs accounting for 75–80 % of all cases. The mitral valve is the one most commonly affected, but the tricuspid valve may be affected concurrently and/or preferentially in individuals. The disease is characterized by the accumulation of glycosaminoglycans (myxomatous proliferation) within the spongiosa and fibrosa layers creating a vegetative nodular appearance. Small breed dogs such as Cavalier King Charles spaniel, Chihuahua, dachshund, poodle, and papillon are frequently affected (Egenvall et al. 2006). The disease is uncommon in young dogs. In older dogs the condition is frequent, with a prevalence >90 % in dogs over 10 years of age.

CDVD has a strong resemblance to primary mitral valve prolapse (MVP) in humans. Knowledge about the canine disease may thus help to increase the understanding of the disease in humans.

The disease appears to be inherited in the dog as well as in man. It is known that most dogs develop myxomatous mitral valve disease with age and this disease is very similar macroscopically as well as microscopically to primary MVP in humans

(Pomerance 1981). In affected patients of both species, the most frequent macroscopic changes are enlarged, thickened leaflets, interchordal hooding, and elongated chordae tendineae. Furthermore, the involvement of the tricuspid valve, secondary leaflet fibrosis, ruptured chordae tendineae, jet lesions, dilatation of the left ventricle, left atrium, and mitral annulus can develop (Pomerance 1981; Kogure 1980).

A major difference in pathological findings among human and canine species is the risk for endocarditis. Whereas humans are more prone to develop endocarditis, in dogs this condition occurs rarely only, and large breed dogs, which typically have no risk for CDVD, are more affected (Calvert 1982).

It is speculated that primary MVP is a part of a generalized connective tissue abnormality. Similarly, the dogs predisposed to CDVD have a risk of developing connective tissue disorders such as intervertebral disk disease, collapsing trachea, and ruptured cruciate ligaments.

The myxomatous changes start along the line of apposition of the leaflets and progress in severity with advancing age. One study including 190 clinically healthy dachshunds showed a positive correlation of an increase of valvular changes (with positively correlation) with age. Dachshunds are often affected, and 50 % typically develop a regurgitation murmur before 10 years of age (Olsen et al. 1999).

The prevalence and severity are clearly age dependent in dogs suffering from CDVD and in humans with MVP (Whitney 1974; Davies et al. 1978).

In some dog breeds, almost all dogs are affected. For example, in Cavalier King Charles (CKC) spaniels, a typical murmur of mitral regurgitation can be found in 50 % of dogs at the age of 5–6 years and in all dogs at 10 years of age. Most of the dogs of this breed showed a typical MVP in the ultrasound (Häggström et al. 1992).

In both species the myxomatous mitral valve disease is a slowly progressing disease which in most cases has a benign course, and the severe form usually develops in old age (Pedersen et al. 1999; Häggström et al. 1992).

According to the studies in humans with MVP following for a mean period of 6–13 years, 5–10 % of the patients developed severe mitral regurgitation requiring surgery (Duren et al. 1988). Another study followed 250 patients for an average period of 40 years have found that after the age of 50, about one fourth will undergo some form of surgical therapy (Chapman 1994). In CKC spaniels aged less than 10 years, the mitral regurgitation becomes severe enough leading to the spontaneous death or to the euthanasia in 15–20 % of cases (Häggström 1996).

In dogs, as well as in humans, males have almost twice the risk to develop a severe disease in old age (Agozzino et al. 1992; Swenson et al. 1996).

A strong positive correlation exists between the murmur intensity and the degree of mitral regurgitation in patient affected by MVP in both species (Pedersen et al. 1999; Häggström 1996). In mild disease a heart murmur with short duration can be detected, and in cases with severe mitral regurgitation, a holosystolic murmur can be heard. Mild mitral regurgitation in dogs is characterized by typically early systolic murmurs, and seldom is a late systolic murmur found. In contrast, in humans with mild mitral regurgitation, short murmurs appear mostly late systolic (Ranganathan et al. 1976; Pedersen et al. 1999).

Echocardiography is the method of choice to diagnose and assess the degree of mitral regurgitation. Using this procedure a different 2D-Echo test changes

including leaflet thickness, degree of leaflet protrusion, and recognition of regurgitation jet on spectral or color flow Doppler can be detected.

Typical signs of remodeling secondary to mitral regurgitation involve progressively increasing dimensions of the left atrium and ventricle (Brown et al. 2007). The systolic left ventricle diameter is initially preserved, and its increase in late stage disease has been interpreted as a sign of myocardial dysfunction.

1.2.2 Systemic Hypertension: An Increasing Problem in Dogs and Cats

Persistent elevation of systemic blood pressure is increasingly recognized in dogs and cats. In most cases it presents a complication of other systemic diseases and is defined as a secondary hypertension.

If the cause for systemic hypertension cannot be found, the condition is classified as a primary hypertension. Secondary hypertension occurs more often than a primary (idiopathic, i.e., without detectable reason) hypertension, accounting for approximately 18–20 % cases in cats (Brown et al. 2007).

Systemic hypertension may be recognized in animals with systemic disease associated with the development of hypertension. The other scenario could occur when blood pressure measurement is performed in patients with clinical signs of hypertension-related target organ damage.

Stress-induced systemic hypertension should be excluded, and single value cannot be used for the diagnosis of elevated blood pressure in the absence of other clinical data.

According to current recommendations, a systolic blood pressure exceeding 160 mmHg indicates hypertension, and over a long term, a persistent damage of the effector organs such as the eyes, the central nervous system (CNS), the heart, and kidneys is expected.

Systemic hypertension in animals is often clinically silent. The most common signs are the ophthalmologic changes with a prevalence rate nearly 100 %. They include intraocular hemorrhage, hypertensive retinopathy, hypertensive choroidopathy, and hypertensive optic neuropathy. Dogs and cats may be presented due to an acute onset of blindness from complete, bilateral exudative retinal detachment. Antihypertensive treatment can lead to retinal reattachment, but the restoration of vision generally occurs seldom (Magio et al. 2000).

Hypertensive encephalopathy has been reported in dogs (Jakob et al. 2006), in cats (Magio et al. 2000), as well as in people (Kletzmayr et al. 2003). CNS signs have been reported in 29 % (Magio et al. 2000) and 46 % of hypertensive cats (Littman 1994) and include seizures, vascular accident, and changes in mentation. Other central nervous system abnormalities, including hemorrhage and infarction, which accompany chronic hypertension in people (Manolio et al. 2003), are also observed in dogs and cats.

The most reported cardiac changes following systemic hypertension are cardiac gallop, systolic heart murmurs, and left ventricular hypertrophy. In contrast to humans, the congestive heart failure secondary to hypertension occurs seldom. The

hypertensive cats may be less tolerant to fluid administration, and in rare cases, the intensive fluid therapy can lead to congestive heart failure.

As a consequence of systemic hypertension, an epistaxis (bleeding from the nose) can occur due to hypertension-induced vascular abnormalities (Brown et al. 2007).

1.2.3 Frequent Cardiac Problems in Horses

Mitral regurgitation, atrial fibrillation, aortic regurgitation, and tricuspid regurgitation are commonly reported cardiac disease in horses, whereas pulmonary regurgitation, ventricular arrhythmia, ventricular septal defect, and congestive heart failure are less frequently reported.

Mitral regurgitation is the most common cardiac disease with a prevalence of 4.4 %. In this setting, the cardiac output with oxygenized blood is reduced due to insufficiency of the mitral valve between the left atrium and left ventricle of the heart (Fig. 1.1). atrial fibrillation has a prevalence of 2.3 % and in some studies is considered as only lone or paroxysmal atrial fibrillation (Reef et al. 1998). According to another study, atrial fibrillation is most often occurring secondary to underlying cardiac disease like mitral regurgitation, tricuspid regurgitation (affecting the valve between the right atrium and ventricle, before the pulmonary passage of the venous blood), and pulmonary regurgitation. Moreover, the authors report that heavier and larger horses have a higher risk of developing atrial fibrillation and thus arrhythmia. In accordance with previous studies, in horses with a larger left atrium, the reflux of blood occurs easier and represents an underlying mechanism of atrial fibrillation. Whereas horses, large breed dogs (i.e., Irish wolfhound), and humans predominantly suffer from primary atrial fibrillation without atrial enlargement, small dogs and cats develop atrial fibrillation secondary to severe atrial (mostly left atrium) enlargement. The prevalence of atrial fibrillation is 2.1 % in horses with a cutoff level of 13.5 years of age from which on horses have a higher risk to develop atrial fibrillation. The prevalence for tricuspid regurgitation is 1.7 %. Congestive heart failure has a prevalence of 1 %. Taken together, atrial fibrillation and all valvular regurgitation except aortic regurgitation are risk factors for congestive heart failure in horses, whereas the body weight and age are not (Leroux et al. 2013).

1.3 Synopsis

An overview is given on the most important cardiovascular diseases. In humans, cardiac diseases due to long-standing arterial hypertension and atherosclerosis are frequent. In animals, the most frequent diseases of the cardiovascular system comprise chronic degenerative valve disease (endocardiosis), dilated cardiomyopathy in dogs, and hypertrophic cardiomyopathy in cats. In humans, arterial hypertension is frequently primary, whereas in animals, secondary hypertension due to underlying systemic diseases is more frequent than primary hypertension.

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