There are numerous forms of cardiovascular disease, and there are animal models for the vast majority of these diseases, with thousands of published papers describing studies performed on animal models. Many of the naturally occurring congenital cardiovascular malformations found in humans have been identified in one or more species of animals. The development of sophisticated genetic testing has made the identification of the causative gene(s) for specific defects more practical, and this has led to the creation of specific transgenic animal (rodent) models (Gross 2009). The relative ease with which specifically engineered models can be created has resulted in an explosion of their use in cardiovascular research (Gross 2009); however, there are clearly significant differences between rodent and human hearts.
Generally, dog and other large animal models of heart disease allow the study of left ventricular function and volumes more accurately than rodent models, and they are better for chronic instrumentation (Hasenfuss 1998). Furthermore, in canine, like in human myocardium, the $\beta$-myosin heavy-chain isoform predominates and excitation-contraction coupling processes appear more like those of the human myocardium (Hasenfuss 1998). Large animals also have more diverse genetic backgrounds than rodent models, and they therefore may be more reflective of what is present in humans. Large animal heart rates are also much closer to those of humans (Pleger et al. 2011). Models of myocardial infarction/ischemia, ischemic cardiomyopathy, ventricular pressure and volume overload, and pacing-induced dilated cardiomyopathy have been created in dogs, pigs, and sheep for investigation of heart failure and potential therapies (Dixon and Spinale 2009). However, large animal models are costly and require substantial resources with respect to housing and care compared to rodent models.

Because many naturally occurring cardiovascular diseases occur in dogs and cats, there is great interest in developing clinical trials that use the diseased pet population (Duda et al. 2009). Diseases in these pet species provide spontaneous models that more closely mimic human diseases than most commonly available experimental models (Duda et al. 2009). Moreover, pets and people share common environments, and their diseases often are parallel in pathophysiology and outcome. These animals are also particularly useful for genetic analysis of congenital heart diseases that occur in human populations. These studies in humans are difficult because of small family size, long generation time, locus heterogeneity, and reduced penetrance (Andelfinger et al. 2003). By comparison, domestic dog breeds offer more than 300 well-defined, isolated breeding populations, which are suited to these studies (Andelfinger et al. 2003). However, at this time, most studies do not utilize pet populations, in large part because these spontaneous models are not well known. Table 3.1 lists animal models of heart failure (dilated cardiomyopathy or volume overload models), and Table 3.2 lists animal models of cardiac hypertrophy or pressure overload. This chapter will focus on naturally occurring canine and feline models of human heart disease (listed in bold font in Tables 3.1 and 3.2); however, iatrogenic models (and naturally occurring models in other species) will be briefly described for completeness.

**NATURALLY OCCURRING LARGE ANIMAL MODELS OF INHERITED DISEASES AFFECTING THE HEART**

There are over 30 molecularly characterized forms of muscular dystrophy in humans (Shelton and Engvall 2005). Of those affecting the heart, muscular dystrophy associated with a deficiency of dystrophin is the most common. The dystrophin gene is one of the largest in the human genome (approximately 2.5 million base pairs), and many thousands of mutations have been recorded. Mutations resulting in loss of dystrophin in striated muscle result in a disease, which is severely debilitating and ultimately fatal (Duchenne muscular dystrophy (DMD)). It is an X-linked disease, with most boys wheelchair bound by the time they are in their teenage years. Death occurs as a result of respiratory failure or dilated cardiomyopathy in the late teens to twenties. Several naturally occurring animal models have been recognized, with some being utilized extensively in DMD research. These include a family of cats (Gaschen et al. 1992, 1999), Golden Retriever (Golden Retriever muscular dystrophy (GRMD)) (Valentine et al. 1989b, 1992; Cooper et al. 1988), German Shorthaired Pointers (Olby et al. 2011; Schatzberg et al. 1999), Cavalier King Charles Spaniels (Piercy and Walmsley 2009), the Japanese Spitz (Jones et al. 2004), and various sporadic reports (Baltzer et al. 2007; Bergman et al. 2002). Additionally, the mutation was bred into a colony of beagles in Japan (Yugeta et al. 2006; Shelton and Engvall 2005; Shimatsu et al. 2003, 2005). The GRMD model has been used most frequently in research, and the phenotype in these affected dogs has been well described (Valentine et al. 1986, 1988, 1989a, 1989b; Schatzberg et al. 1999; Brumitt
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<tr>
<th>Animal Models of Heart Failure</th>
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<td><strong>Rat</strong></td>
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<tr>
<td>Coronary ligation</td>
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<td>Spontaneous hypertensive heart failure</td>
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<td>SH-HF/Mccc-facp</td>
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<td>Aortocaval fistula</td>
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<td>Toxic cardiomyopathy</td>
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<td><strong>Dog</strong></td>
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<td>Pacing tachycardia</td>
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<tr>
<td>Coronary ligation</td>
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<td>Microemboli</td>
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<td>Direct current shock</td>
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<td>Volume overload</td>
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<tr>
<td>Aortocaval fistula</td>
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<td>Mitral regurgitation</td>
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<tr>
<td>Toxic cardiomyopathy</td>
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<tr>
<td><strong>Genetic</strong></td>
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<tr>
<td>X-linked muscular dystrophy</td>
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<td>Lysosomal storage disease</td>
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<td><strong>Dilated cardiomyopathy</strong></td>
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<td>Adult and juvenile onset</td>
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<tr>
<td><strong>Degenerative valve disease</strong></td>
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<td>Arrhythmogenic right ventricular cardiomyopathy</td>
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<td>Tricuspid valve dysplasia</td>
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<td><strong>Pig</strong></td>
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<tr>
<td>Pacing tachycardia</td>
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<td>Coronary artery ligation</td>
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<td>Microemboli</td>
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<tr>
<td><strong>Rabbit</strong></td>
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<td>Volume overload</td>
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<td>Pacing tachycardia</td>
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<td>Toxic cardiomyopathy</td>
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<td><strong>Guinea pig</strong></td>
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<td><strong>Syrian hamster</strong></td>
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<td>Genetic</td>
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<td>Hypertrophy and failure</td>
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<td><strong>Cat</strong></td>
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<td>Genetic</td>
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<td>Lysosomal storage disease</td>
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<td><strong>Turkey</strong></td>
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<td>Toxic cardiomyopathy</td>
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<td><strong>Bovine</strong></td>
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<td>Genetic</td>
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<td><strong>Sheep</strong></td>
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<td>Pacing tachycardia</td>
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<tr>
<td>Microemboli</td>
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<td><strong>Transgenic animals</strong></td>
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### Table 3.2 Animal Models of Cardiac Hypertrophy

<table>
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<tr>
<th>Animal</th>
<th>Model</th>
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<tbody>
<tr>
<td>Rat</td>
<td>Aortic constriction</td>
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<td>Pulmonary artery constriction</td>
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<td>Hypertension</td>
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<td>Renal ischemia</td>
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<td>Deoxycorticosterone acetate (DOCA)</td>
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<td>Dahl salt sensitive</td>
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<td>Spontaneous hypertensive ( SHR)</td>
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<td>Arteriovenous fistula</td>
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<td>Hyperthyroidism</td>
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<td>Hypoxia</td>
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<td>Catecholamines</td>
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<td>Exercise</td>
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<tr>
<td>Rabbit</td>
<td>Aortic insufficiency/constriction</td>
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<tr>
<td></td>
<td>Pulmonary constriction</td>
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<td></td>
<td>Hyperthyroidism</td>
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<tr>
<td>Dog</td>
<td>Aortic constriction</td>
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<td></td>
<td>Valvular aortic stenosis</td>
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<tr>
<td>Pig</td>
<td>Pulmonary artery constriction</td>
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<td>Cat</td>
<td>Pulmonary artery constriction</td>
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<td></td>
<td>Hyperthyroidism</td>
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<td></td>
<td>Genetic</td>
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<td></td>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td>Hamster</td>
<td>Genetic</td>
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<tr>
<td>Ferret</td>
<td>Pulmonary artery constriction</td>
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<td>Sheep</td>
<td>Aortic constriction</td>
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<tr>
<td>Baboon</td>
<td>Hyperthyroidism</td>
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<td></td>
<td>Renal ischemia</td>
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<td>Guinea pig</td>
<td>Aortic constriction</td>
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<tr>
<td>Mouse</td>
<td>Aortic constriction</td>
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<td></td>
<td>Renal ischemia</td>
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<td></td>
<td>Exercise</td>
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<td></td>
<td>Aortic constriction</td>
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<td>Transgenic animals</td>
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A mouse model (the mdx mouse) was identified in 1984 (Shelton and Engvall 2005). Although the life span in affected mice is shortened, the clinical phenotype is much more benign than that of affected boys (Shelton and Engvall 2005). Because the disease in affected dogs (particularly the Golden Retriever) closely resembles that seen in humans, and the GRMD phenotype has been well described, the GRMD model has been widely used in various therapeutic trials (Howell et al. 1997, 1998; Bretag 2007; Bartlett et al. 2000; Liu et al. 2004; McClorey et al. 2006; Rando 2002; Bish et al. 2011, 2012). Interestingly, the feline disease results in a different phenotype with cardiac hypertrophy rather than dilation (Shelton and Engvall 2005). Affected cats develop shoulder and neck muscle hypertrophy as well as tongue enlargement (Shelton and Engvall 2005; Gaschen et al. 1992). Pathologic findings are similar to those described for dystrophic dogs and include muscle fiber degeneration and regeneration and fibrosis (Shelton and Engvall 2005). The interested reader is referred to one of the many review articles on animal models of DMD (Shelton and Engvall 2002, 2005; Collins and Morgan 2003; Wells and Wells 2005; Nonaka 1998; Cooper 1989; Kornegay et al. 2012; De Luca 2012).

Lysosomal storage diseases (LSDs) are genetic diseases that result in abnormal degradation of various molecules within the lysosomes of affected animals. More than 50 different forms of inherited LSDs are known to occur in humans, most of which result in high morbidity and mortality. The aggregate incidence is approximately 1 in 7000 live births (Ellinwood et al. 2004). Most LSDs are caused by loss of normal function of a specific lysosomal acid hydrolase, resulting in the lysosome’s inability to degrade large complex substrates that have been targeted for degradation after endocytosis or autophagy. Lysosomal accumulation of the substrate affects architecture and function of cells, tissues, and organs. LSDs that affect the heart include mucopolysaccharidosis (MPS), Pompe disease, and Fabry disease. MPS is due to deficiency in any of several enzymes involved in degradation of glycosaminoglycans, and results in mitral and aortic valve thickening and regurgitation, and aortic dilation (Haskins et al. 1979a, 1980b, 1981, 1982, 1983a, 1991, 2002; Ponder et al. 2002). Pompe disease is due to deficiency in acid a-glucosidase, and results in weakness of cardiac muscle due to the accumulation of glycogen (Geel et al. 2007). Fabry disease is due to deficiency of α-galactosidase A and results in accumulation of globotriaosylceramide, a glycosphingolipid. The result is vascular disease, left ventricular hypertrophy, and cardiac conduction defects (Seino et al., 2005).

Naturally occurring animal homologues of LSDs have been described in the mouse, rat, dog, cat, guinea pig, emu, quail, goat, cow, sheep, and pig (Ellinwood et al. 2004). The mouse, canine, and feline models have been used most extensively in research (Haskins et al. 1992, 2002; Ponder et al. 2002, 2006; Metcalf et al. 2010; Sleeper et al. 2005, 2008; Tessitore et al. 2008; Traas et al. 2007; Wang et al. 2006; Simonaro et al. 2001, 2005; Walkley et al. 2005; Mango et al. 2004; Zhang et al. 2004; Mazrier et al. 2003; Xu et al. 2002; Kakkis et al. 2001; Gao et al. 2000; Sammarco et al. 2000; Wolfe et al. 2000; Daly et al. 1999a, 1999b, 1999c). Mouse models have the advantage of

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<th>Table 3.3</th>
<th>Large Animal Models of Dysrhythmias</th>
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<tr>
<td>Ventricular tachycardia</td>
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<td>German Shepherds</td>
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<td>Boxers</td>
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<td>Doberman Pinschers</td>
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<td>Atrial fibrillation</td>
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<td>Irish Wolfhounds</td>
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<td>Bradycardias</td>
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<td>Sick sinus syndrome—Miniature Schnauzers</td>
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<td>Sinus standstill—English Springer Spaniels</td>
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being easy to breed; however, larger species, such as the dog and cat, have the advantage of a more heterogeneous genetic background, as well as a life span that allows assessment of long-term consequences of various therapeutic approaches (Haskins et al. 1979a,b, 1980a, 1980b, 1983a, 1983b, 1991; Wolfe et al. 1990; Ponder and Haskins 2007). Therefore, the large animal models of LSDs play a critical role in the evaluation of efficacy and safety of the various treatment options for these diseases. There are several excellent reviews regarding animal models of LSDs to which the interested reader is referred (Ellinwood et al. 2004; Haskins 2007, 2009; Patterson et al. 1982).

**NATURALLY OCCURRING MODELS OF CARDIOMYOPATHY**

**Dilated Cardiomyopathy**

Idiopathic dilated cardiomyopathy (DCM) is the most common cause of congestive heart failure in young humans and is characterized by increased myocardial mass with reduction in ventricular wall thickness (Hughes and McKenna 2005). The heart becomes globoid and dilated, and contractility is poor (Hughes and McKenna 2005). In humans, it is inherited in at least 20–40% of cases (Meurs et al. 2007b; Fatkin and Graham 2002) with variable patterns of inheritance (autosomal dominant, X-linked, autosomal recessive, or a mitochondrial pattern).

DCM of the dog was first described in 1970 (Van Vleet et al. 1981) and is one of the most common acquired heart diseases in the dog (Tidholm and Jonsson 1997; Tidholm et al. 2001). In general, the disease occurs more frequently in large-breed dogs and congestive heart failure is common with severe disease (Van Vleet et al. 1981); however, like in humans, there is usually a prolonged presymptomatic phase of the disease, which may extend over years (Dukes-McEwan et al. 2003). Males seem to be more commonly affected than females, and affected dogs have increased heart weight (Van Vleet et al. 1981). Pathologic cardiac changes include dilated chambers and endocardial fibrosis resulting in generalized heart enlargement (see Figure 3.1). Histologic changes include multifocal necrosis, fibrosis, and degeneration of myocytes with myocytolysis and mitochondrial alterations (Van Vleet et al. 1981), and there appear to be two distinct histopathological forms (Dukes-McEwan et al. 2003). The attenuated wavy fiber type of DCM has been described by several authors in various breeds (Dukes-McEwan et al. 2003; Tidholm et al. 1998, 2000). In this form of DCM, myocytes are thinner than normal with a wavy appearance and are separated by a clear

![Figure 3.1](image-url) Lateral radiograph from a dog with dilated cardiomyopathy (a) and a normal dog (b). Note the generalized heart enlargement in the dog with DCM.
space, indicative of edema fluid. This form has also been reported in humans (Dukes-McEwan et al. 2003). The fatty-infiltration-degenerative form was first described in Boxers, but has since been described also in Doberman Pinschers (Everett et al. 1999). In this form, myocardial lesions are associated with myocytolysis, myofiber degeneration, and atrophy with extensive fibrotic and fatty infiltration (Dukes-McEwan et al. 2003).

In cats, the disease is caused by dietary taurine deficiency, but with current feeding practices, it is now rarely observed in the pet cat population. In humans, DCM can occur secondary to viral, autoimmune, or toxic injury, but 30–50% of cases are thought to be inherited (Stephenson et al. 2012). Various large canine breeds are commonly affected with this disease, in particular Doberman Pinschers, English Cocker Spaniels, and Newfoundlands. In Irish Wolfhounds, Newfoundlands, Dobermans, Boxers, Great Danes, and Portuguese Water Dogs, the disease is either known, or suspected to be inherited, but the specific causative gene remains unclear in most breeds. DCM in some of these specific breeds will be discussed below.

**Doberman Pinschers**

DCM in Dobermans is a common, slowly progressive, primary myocardial disease, which has been described as having three distinct phases or stages (Wess et al. 2010). Stage 1 is defined by a morphologically and electrically normal heart without evidence of clinical disease. Stage 2 is termed occult and is characterized by evidence of anatomical or electrical abnormalities in the absence of clinically evident heart disease. Sudden death caused by ventricular tachycardia-fibrillation during the occult phase occurs in at least 25–50% of affected dogs (Wess et al. 2010). Stage 3 is characterized by the presence of clinical signs referable to the underlying heart disease and is also called the overt stage of DCM (Wess et al. 2010). Once dogs have developed pulmonary edema and congestive heart failure (CHF), relapsing CHF or sudden death often occurs within 6 months (Calvert et al. 1997). As suggested above, ventricular ectopy is present in a large subset of Dobermans affected with DCM; however, atrial fibrillation is also common, particularly as heart enlargement develops, and development of this arrhythmia has been associated with a shorter survival time in Dobermans (Calvert et al. 1997). In this breed, the median age of onset is 7.5 years (Meurs et al. 2007b).

Autosomal dominant is the most common inheritance pattern of DCM in humans and also in Doberman Pinschers (Meurs et al. 2007a, 2008). A recent report identifies a splice site deletion in the PDK4 gene that is associated with the development of familial DCM in the Doberman Pinscher (Meurs et al. 2012); however, it is likely that additional causative mutations will be identified.

**Boxers**

Three clinical categories of cardiomyopathy in Boxers have been described, the first two of which are characterized by recurrent ventricular arrhythmias without left ventricular structural changes. The difference between these two categories is the presence of clinical signs referable to ventricular ectopy. The third form is characterized by left ventricular dysfunction, often with concurrent ventricular or supraventricular arrhythmias (Baumwart et al. 2005). In contrast, normal Boxers appear to have less than 91 ventricular premature complexes (VPCs) on a 24-hour Holter monitor (Stern et al. 2010). The disease has traditionally been called Boxer cardiomyopathy, but because of the clinical and pathologic similarities to a disease in humans, it is now called arrhythmogenic right ventricular cardiomyopathy (ARVC) (Baumwart et al. 2005; Basso et al. 2004). ARVC in Boxer dogs is more comparable to the human disease than the current murine models because the phenotype of affected dogs and that of humans are more similar (Oxford et al. 2011). Findings from a study using magnetic resonance imaging suggest that arrhythmias and myocardial dysfunction precede the development of morphological abnormalities in dogs with ARVC (Baumwart et al. 2005).
2009). Signal-averaged electrocardiography may be a diagnostic test that stratifies clinical outcome for affected dogs (Spier and Meurs 2004).

The causative genes, which have been identified in humans, are generally those that encode the proteins of mechanical cell junctions (plakoglobin, plakophilin, desmoglein, desmocollin, desmplakin) (Thiene et al. 2007). Mutations in these lead to intercalated disc remodeling. Several inheritance patterns have been recognized in humans (autosomal dominant with variable penetrance and recessive inheritance patterns) (Thiene et al. 2007). The disease in Boxers is also associated with abnormal gap junction formation, which likely promotes ventricular arrhythmogenesis and disrupts mechanical interactions (Oxford et al. 2007). The cardiac ryanodine receptor (important in excitation-contraction coupling) message and protein are reduced in affected dogs, with a greater reduction in the right ventricle (Meurs et al. 2006); however, mutations in the desmosomal genes (plakophilin-2, plakoglobin, desmplakin, and desmoglein-2) associated with the development of ARVC in humans were not found in 10 affected Boxers (Meurs et al. 2007a). Rather, an 8 bp deletion in the striatin gene (striatin localizes with plakophilin-2, plakoglobin, and desmplakin to the intercalated disc region) was found to be causative in a group of Boxers (Meurs et al. 2010). Considering the number of mutations that cause the phenotype in humans, it is likely additional causative mutations will be recognized in years to come. ARVC has also been recognized in cats (Harvey et al. 2005; Fox et al. 2000), although cases have been sporadic and a possible inheritance pattern is therefore uncertain.

**Great Danes**

Similar to acquired DCM in other large-breed dogs, DCM in Great Danes is characterized by myocardial systolic dysfunction, development of cardiac arrhythmias, and congestive heart failure (Oyama et al. 2009). However, at least one study suggests that this breed may be more predisposed to developing atrial fibrillation than some of the other breeds (Meurs et al. 2001). Although the risk of atrial fibrillation may be partly due to the large size of Great Danes, the Great Dane prevalence in this study was higher than that reported for another giant breed of dogs with DCM (Newfoundlands) (Tidholm and Jonsson 1996). A more recent study found that ventricular arrhythmias were more commonly present in Great Danes affected with DCM, with 54% of affected dogs having ventricular ectopy (Stephenson et al. 2012). This study also found a higher prevalence of DCM in the breed than has been previously reported (35.9%); however, this finding may have been due in part to selection bias (Stephenson et al. 2012). Another contrast to the earlier study was the presumed pattern of inheritance, which was most consistent with autosomal dominant (Stephenson et al. 2012). Although a previous study also demonstrated a strong familial tendency, these results suggested a mode of inheritance most consistent with an X-linked inheritance pattern (Meurs et al. 2001). It is certainly likely that, as in humans, multiple mutations with variable inheritance patterns can result in DCM.

Results from one study suggest that being a Great Dane is a negative risk factor for survival (Martin et al. 2010); however, the retrospective nature of the study and the relatively small number of Great Danes in the study (n = 37) make it difficult to be certain if this result is accurate, particularly since earlier studies failed to demonstrate a breed effect (Tidholm and Jonsson 1997). The beta adrenergic nervous system is known to be dysregulated in humans with heart disease, and a group evaluating its activity in Great Danes with normal cardiac function and individuals with DCM (occult and overt) found that B-adrenoceptor downregulation occurs early in Great Danes with DCM (Borgarelli et al. 1999). Moreover, the pattern of dysfunction is similar to what is present in humans, with mean plasma catecholamine levels significantly higher in affected dogs than in normal dogs (Re et al. 1999). Microarray-based technology used to compare gene expression between a small group of DCM-affected dogs and a control group of other large-breed dogs found that affected Great Danes had two genes that were particularly abnormally regulated: calstabin2 and triadin (Oyama et al. 2009). Both of these genes are essential components of the ryanodine receptor, suggesting that calcium regulation may be an important aspect of the disease in this breed.
Portuguese Water Dogs

Juvenile DCM (JDCM) in Portuguese Water Dogs (PWDs) was first reported in a retrospective analysis of postmortem and biopsy case records from 12 related PWDs (Dambach et al. 1999). This was followed by a prospective study of 124 PWD puppies, 10 of which were affected with JDCM (Sleeper et al. 2002). The clinical course of JDCM ranges from sudden unexpected collapse and death, with no preceding clinical signs (most common), to the presence of clinical signs of depression and reduced appetite for up to 5 days before collapse and fulminant congestive heart failure (Sleeper et al. 2002). Affected puppies die between 2 and 32 weeks of age, and the trait is inherited in an autosomal recessive pattern. Echocardiographic changes consistent with reduced systolic function and chamber dilation begin 1–4 weeks before the onset of clinical signs, and progression into fulminant congestive heart failure is rapid. Extensive biochemical analysis did not reveal any significant differences between affected pups and normal age-matched controls (Sleeper et al. 2002). Morphological and histological changes in affected hearts have been described (Sleeper et al. 2002). A linkage study has localized the mutation to chromosome 8 (Werner et al., 2008), and a linked marker test is available to identify carrier and affected status in PWD dogs (Section of Medical Genetics, University of Pennsylvania Veterinary School).

Irish Wolfhounds

The Irish Wolfhound breed also commonly develops DCM, and similar to in other breeds, there are two principal manifestations: sudden cardiac death or congestive heart failure (Vollmar 2000). In this breed, atrial fibrillation appears to be particularly common, with a prevalence of 23–88% in dogs with DCM (Vollmar 2000). In this study, survival time was longer in Irish Wolfhounds affected with DCM than in Doberman Pinschers (Vollmar 2000). Segregation analysis showed that a mixed monogenic-polygenic model, including a sex-dependent allele effect, best explained the inheritance pattern (Distl et al. 2007).

Iatrogenic Models of DCM

Many transgenic murine models of heart failure have been developed and characterized for cardiac research. The advantage is that these models may mimic a specific alteration in a molecular or cellular pathway, allowing in-depth study of that pathway (Shen 2010). However, the ability to precisely measure cardiac function in mice is problematic because of the small size of the heart (Shen 2010). Rats have been used extensively to study heart failure because they are also less costly and easier to handle than large animals (similar to mice), but they are large enough to facilitate surgical and post-surgical procedures (Zaragoza et al. 2011). Myocardial damage in rat hearts is generally induced by one of three procedures: surgical (permanent or temporary coronary ligation), pharmacological (isoproterenol administration to induce myocardial necrosis), or electrical (cryoinjury) (Zaragoza et al. 2011). The availability of transgenic and knockout murine strains make mice an attractive model for heart failure research in spite of their small size, and the coronary artery occlusion model is widely used in this species (Zaragoza et al. 2011).

Coronary artery ligation, ameroid constriction, and microembolization techniques have been used to produce myocardial infarction models in rabbits, dogs, pigs, and sheep (Dixon and Spinale 2009). A common model in pigs uses balloon occlusion of the left anterior descending coronary artery (Zaragoza et al. 2011). When using the microembolization technique, up to seven embolization procedures are performed in closed-chest dogs, and after several months, clinical signs of heart failure develop (left ventricular dilation, decreased ejection fraction, and neurohormonal
activation) (Hasenfuss 1998). Disadvantages of the microembolization technique are that it is time-consuming, technically challenging, associated with a high mortality (Hasenfuss 1998), and a reproducible degree of chronic heart failure cannot be consistently obtained in different animals (Shen 2010). Also, there are important differences between canine and human coronary circulation (Hasenfuss 1998; Protas et al. 2005). In humans, the major coronary artery perfusing the left ventricle is the left anterior descending, whereas in the dog, the major perfusing artery is the left circumflex (Hamlin 2007), which is why some researchers use the pig or sheep model instead. The similar size and cardiac physiology of pigs and humans makes the porcine myocardial infarct model particularly attractive.

In addition to its use in rats, cryotherapy is a technique that has been used to produce a syndrome similar to DCM in dogs. Transmyocardial direct-current shocks are applied through an intracardiac catheter inserted in the left ventricle in anesthetized dogs. This method results in hypertrophy and dilation of the chamber with reduced systolic function (Hasenfuss 1998).

Chronic pacing of the heart at rates above 200 bpm in previously healthy dogs results in a syndrome of DCM and congestive heart failure within several weeks (Hasenfuss 1998). It is the most well-characterized large animal model of DCM (Dixon and Spinale 2009). A decrease in cardiac output, abnormal diastolic function, and increased peripheral vascular resistance develop, but myocardial hypertrophy does not occur with this model (Hasenfuss 1998). In addition, heart failure is reversible when pacing is stopped and the model does not manifest the complete spectrum of heart failure (Hasenfuss 1998; Dixon and Spinale 2009). The technique has also been used in rabbits, pigs, and sheep (Hasenfuss 1998; Lucas et al. 2002; Zaragosa et al. 2011). Swine and nonhuman primate heart failure models have been developed that use sequential coronary artery occlusion followed by rapid ventricular pacing, in which heart failure is not reversible once pacing is terminated (Shen 2010). Nonhuman primates have significant physiological, metabolic, biochemical, and genetic similarities to humans, yet they represent less than 0.3% of laboratory animals currently being used in medical research, in large part because there are few relevant models of cardiovascular disease in these species (Shen 2010).

Volume overload (produced by creating an arteriovenous fistula or damaging the mitral valve) leads to eccentric hypertrophy and ultimately, congestive heart failure. Most often, the mitral valve apparatus is damaged by using forceps to tear the chordae tendinae or the valve itself (Hasenfuss 1998). The resultant mitral valve regurgitation creates chronic volume overload, leading to left ventricular dilation and eventually, heart failure (Dixon and Spinale 2009).

**Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is a genetic disorder affecting 1:500 adult humans (Dixon and Spinale 2009). It is an autosomal dominant trait, which leads to asymmetric or symmetric left ventricular hypertrophy (Dixon and Spinale 2009). HCM is the most common heart disease of cats. In two breeds, the Maine coon and the ragdoll, the causative mutations have been identified in the cardiac myosin binding protein C gene (Meurs et al. 2005, 2007c). The disease is inherited in an autosomal dominant pattern in both breeds (Meurs et al. 2005, 2007c). However, the mutations are different, suggesting they occurred independently, rather than being passed on from a common founder (Meurs et al. 2007c). The primary physiologic abnormality with HCM is diastolic dysfunction related to the increased ventricular wall thickness (see Figure 3.2). Ages of affected cats range from 8 months to 16 years (Liu and Tilley 1980). Dyspnea is the most common clinical sign once congestive heart failure has developed, and a subset of affected cats have systolic murmurs (Liu and Tilley 1980); however, a large proportion of affected cats are asymptomatic and normal on physical examination (Paige et al. 2009). Electrocardiographic abnormalities occur and range from a left ventricular hypertrophy pattern to conduction abnormalities to various cardiac arrhythmias (Liu and Tilley 1980). Dynamic obstruction of the left ventricle associated with systolic anterior mitral
valve motion occurs in a subset of affected cats, similar to humans, and arterial thromboembolic disease is also possible (Fox et al. 1995). Sudden death is another feature common in both the human and feline forms of HCM (Kittleson et al. 1999). Typical feline histologic changes are similar to those seen in human HCM and include myofiber disarray and myocardial fibrosis (Fox et al. 1995). A breeding colony of Maine coon cats with HCM was established at the School of Veterinary Medicine, University of California, Davis (Kittleson et al. 1999).

IATROGENIC MODELS OF LEFT VENTRICULAR HYPERTROPHY

Left ventricular pressure overload causes a compensatory increase in left ventricular mass, leading to reduced left ventricular compliance and increased myocardial collagen formation (Dixon and Spinale 2009). Aortic banding and renal artery constriction have been used in canines to study left ventricular remodeling mechanisms (Dixon and Spinale 2009).

NATURALLY OCCURRING MODELS OF CARDIAC VALVULAR DISEASE

Cavalier King Charles Spaniel (CKSP)

The pathological changes seen in human mitral valve prolapse closely resemble those in canine degenerative valve disease (Han et al. 2010; Pedersen et al. 2002). Myxomatous degeneration of the mitral valve (and sometimes the tricuspid valve) is the most common acquired cardiac disease in dogs, occurring most frequently in middle-aged to old, small- to medium-sized dogs (Haggstrom et al. 1992, 1995; Buchanan 1977; Lord et al. 2011). In Cavalier King Charles Spaniels (CKSPs), the disease often occurs at a younger age, and the prevalence in dogs that are older than 10 years of age is 90% (Haggstrom et al. 1992, 1995; Darke 1987; Beardow and Buchanan 1993; Borgarelli and Haggstrom 2010). Other studies have demonstrated similar levels of prevalence. One study performed in the United Kingdom demonstrated that 59% of CKSPs older than 4 years of age had evidence of the disease (Darke 1987). Similar results were noted in a study performed in the United States, which demonstrated that 56% of CKSP dogs were affected.
at 4 years of age (Beardow and Buchanan 1993). The disease starts with the formation of small nodules followed by progressive thickening and contraction of the mitral valve cusps and leakage of the valve (see Figure 3.3) (Haggstrom et al. 1992). The disease is characterized by a long preclinical period (Borgarelli and Haggstrom 2010; Haggstrom et al. 2009). In humans, cytokines appear to be associated with the progression of congestive heart failure and the pathophysiology of myxomatous mitral valve disease; results from a study evaluating CKSPs suggest a similar role for cytokines in the canine disease (Zois et al. 2012). At present, it is not known how chronic valve degeneration is inherited, although a recent study identified two loci associated with the disease in CKSPs (Madsen et al. 2011).

**Labrador Retriever**

Tricuspid valve dysplasia (TVD) is characterized by malformation of the tricuspid valve apparatus and is present from birth. It can be an isolated defect or can be present with other congenital heart diseases (Famula et al. 2002). Mildly affected dogs may be asymptomatic. However, the valve deformity often results in tricuspid valve leakage (or rarely stenosis), which usually causes right heart enlargement and cardiac arrhythmias plus or minus congestive heart failure in more severely affected individuals (Famula et al. 2002). Evidence suggests that, similar to the disease in humans, TVD is an inherited disease in the Labrador Retriever (Famula et al. 2002). The inheritance pattern in one study that examined three Labrador Retriever kindreds (families) is consistent with a monogenic disease mapping to canine chromosome 9 (Andelfinger et al. 2003). Labrador Retrievers also appear to be overrepresented for the conduction abnormality ventricular preexcitation and supraventricular tachycardia (Wright et al. 1996; Atkins et al. 1995). Interestingly, Wolff-Parkinson-White syndrome, the most common form of ventricular preexcitation in humans, is more frequently associated with an Ebstein anomaly (a form of TVD) than with any other congenital heart disease (Delhaas et al. 2010).

**IATROGENIC VALVE DISEASE**

See section on chronic volume overload and mitral valve disruption.
**NATURALLY OCCURRING MODELS OF CARDIOVASCULAR ARRHYTHMIAS**

There are many iatrogenic animal models being utilized in studies to increase our understanding of the mechanisms behind various arrhythmias and to improve our understanding of antiarrhythmic agents. Commercial swine have been proposed as a good model for human cardiovascular physiology because of their similar heart weight/body weight ratio and coronary circulation compared to humans (Hamlin 2007). However, the swine Purkinje system is much more extensive than in humans, cats, or dogs, and the ventricular activation process actually differs markedly (Hamlin 2007). For an excellent review of the topic, in particular the iatrogenic models, the interested reader is referred to Hamlin's review article from 2007 (Hamlin 2007). The most common naturally occurring animal models of arrhythmias are discussed here and listed in Table 3.3.

**German Shepherd Model of Sudden Death**

In this inherited disorder, young affected German Shepherd dogs often succumb to arrhythmic death between 15 and 76 weeks of age, with the peak incidence of arrhythmia occurring between weeks 24 and 26 (Moise 1994, 1997a, 1997b). Affected dogs are asymptomatic until sudden cardiac death, usually caused by the degeneration of ventricular tachycardia (VT) into ventricular fibrillation (VF) (Moise 1999). The rapid, polymorphic VT is bradycardia dependent, and factors causing slowing of the heart rate (such as sleep) tend to induce the arrhythmia (Moise 1999). In particular, the greatest frequency of the arrhythmias appears to occur with rapid eye movement sleep (Moise 1999), and it is hypothesized that a particular balance of parasympathetic and sympathetic activity predisposes to early after-depolarizations (Hamlin 2007). Additionally, an increased responsiveness to adrenergic stimulation has been documented in these dogs (Moise 1999). Differences in the L-type Ca\(^{2+}\) current and regional reductions in repolarizing currents (K\(^+\)) have been described between affected and control animals and likely provide the substrate for the T-wave abnormalities and pause-dependent arrhythmias that have been characterized in the model (Protas et al. 2005; Obrestchikova et al. 2003). After 28 weeks of age, the frequency of arrhythmias decreases so that many dogs older than 100 weeks no longer have arrhythmias (Moise 1999). However, the most severely affected dogs may continue to have occasional ectopy (Moise 1999). A colony of these dogs has been developed at the Cornell University College of Veterinary Medicine.

**Boxers**

As described above, arrhythmogenic right ventricular cardiomyopathy is inherited in Boxer dogs as an autosomal dominant trait. Some dogs have coexisting myocardial failure, but most with VT have no clinical signs of congestive heart failure and the echocardiogram is normal (Moise 1999). Ectopic beats usually have QRS morphology consistent with a left bundle branch block pattern, and are presumed to originate from the right ventricle (Hamlin 2007; Spier et al. 2001). In fact, approximately 90% of Boxers have a VT that is positive in the inferior leads (II, III, aVF) and negative in aVR (Moise 1999). Some individuals have bradyarrhythmias as well (Moise 1999). Affected dogs may have episodes of syncope or sudden cardiac death due to degeneration of VT into ventricular fibrillation. Ventricular ectopy may be significantly reduced with antiarrhythmic therapy (sotalol, atenolol, or mexilitine), but arrhythmias usually worsen, and there is no evidence that therapy reduces the risk of sudden death (Hamlin 2007). Moreover, there appears to be no causal relationship between the frequency of ventricular ectopy and the risk of sudden death (Hamlin 2007).
Miniature Schnauzers

Miniature schnauzers appear frequently in retrospective studies focusing on canine bradycardia (Wess et al. 2006). Sick sinus syndrome in Miniature Schnauzers appears to have a familial occurrence, although the inheritance has not been studied (Moise 1999). Most commonly, female, middle-aged dogs present with syncope due to prolonged sinus pauses during which subsidiary pacemakers fail to escape (Moise 1999).

English Springer Spaniels

English Springer Spaniels (ESSs) are one of the most frequently presented breeds for pacemaker implantation in the United Kingdom, and they are significantly younger than other breeds at presentation for bradyarrhythmia (Fonfara et al. 2010). The inheritance of atrial standstill in English Springer Spaniels is unknown, but it has been recognized as familial (Moise 1999). Affected animals are usually identified as young adults (1 to 3 years of age) with clinical signs such as lethargy, syncope, or congestive heart failure. Bradycardia and sinus arrest are identified in affected animals, and various other abnormalities may also be present (facioscapulohumeral or temporal muscle atrophy, megaesophagus, atrial dilation). The disease is typically progressive and leads to congestive heart failure. This syndrome appears similar to inherited facioscapulohumeral muscular dystrophy or Emery-Dreifuss muscular dystrophy in humans (Moise 1999).

SUMMARY

Animal models of human diseases allow scientists to dissect the molecular and physiological consequences of disease as well as to investigate various therapeutic options. In addition to naturally occurring mouse models, transgenic mouse lines, and iatrogenic models of disease, there are now many naturally occurring orthologs of human genetic diseases recognized in large animal species. These animal models provide an opportunity to monitor therapeutic efficacy and the possible development of negative side effects in out-bred, long-lived animals (Haskins 2007).

REFERENCES


