

New insights into degenerative mitral valve disease in dogs

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Degenerative mitral valve disease (DMVD) is, by far, the most commonly encountered acquired cardiac disease in adult dogs, and the condition is caused by a progressive myxomatous degeneration (MD) of the atrioventricular (AV) valves. DMVD has been given many names in the veterinary literature, including endocardiosis and chronic valvular disease [1,2]. Similar changes of the mitral valve are also seen in human beings, horses, and pigs [3–5]. In people, the condition with similarities to DMVD in dogs is called mitral valve prolapse (MVP) syndrome [3,6]. Clinical signs of mitral regurgitation (MR) caused by myxomatous lesions have long been recognized in veterinary medicine [7], and because of the high prevalence of DMVD in the canine population, the disease is important for the veterinary small animal practitioner. Indeed, a recent estimation of the mortality caused by cardiac disease in the general canine population indicates that about 7% of all dogs die or are euthanized because of heart failure (HF) before 10 years of age (eg, the third most common cause of death in dogs in that age group) [8]. Because many dogs develop decompensated HF because of DMVD after 10 years of age, we can assume that this proportion is even greater in dogs of all ages. MR caused by DMVD has been reported to account for 75% of the cases of heart disease in dogs [9–12] and for a considerably higher proportion in

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affected breeds [1,8,13]. Many of the affected dogs eventually need therapy for decompensated HF and die or are euthanized in the end because of refractory cardiac failure. The presence of MR and ongoing medical treatment for HF may negatively interact with other drugs, decisions for surgical procedures, or anesthesia. Because DMVD is characterized by chronic progression, the owner and veterinarian often have no other alternative than to observe how the valvular lesions and MR progress slowly, with little possibility of affecting the course of the disease, a fact that many find frustrating. Finally, there is a need for breeding measures in certain breeds with an exceptionally high prevalence of DMVD. This article does not cover all possible aspects of DMVD, because this subject is simply far too extensive to fit into this presentation. This presentation focuses on new information about some specific aspects of DMVD that may be controversial and of importance for the practicing veterinarian.

Mitral valve morphology

Because dogs that undergo postmortem examination are most commonly those with severe DMVD and MR, it is common to describe the macroscopic appearance of diseased leaflets as thickened and contracted with varying frequency of ruptured chordae tendineae (Fig. 1) [10,14]. The macroscopic appearance of DMVD depends on at which stage of disease the valve is examined, however. This classic description is a manifestation of severe disease that has progressed over a long time, often several years. The



Fig. 1. Postmortem specimen from a dog showing classic severe degenerative mitral valve disease. The mitral valve leaflets are thickened and contracted, with nodules rolling in the free edges. Although changes are evident along the entire leaflet margin and its vicinity, they are unevenly distributed and seem to be most pronounced in sections in which chordae tendineae insert. Evidence of chordal involvement is present in the form of thickening, and some chordae are missing, presumably ruptured. This stage of degenerative mitral valve disease is to be regarded as end-stage disease. (Courtesy of Professor L. Jönsson, Uppsala, Sweden.)

macroscopic findings in cases of mild DMVD may not be apparent and may be overlooked, especially in dogs without clinical evidence of MR. Findings typical for early stages of DMVD include elongated chordae tendineae and enlarged thickened leaflets with areas showing bulging/ballooning/prolapse toward the atrial side [11,15,16], which may be identified on a two-dimensional (2D) echocardiogram in the living dog (Fig. 2). The changes begin in the area of apposition of the leaflets and are usually most pronounced in sections where chordae tendineae insert. The bulging of such areas toward the atrial side of the leaflets has been described as rolling of the edges. With progression, the bulging becomes worse, the free edge becomes thickened and irregular, and the lesions spread into other parts of the leaflets [15]. Within the same valve leaflet, one section may look relatively normal, whereas another neighboring section is moderately or severely diseased. In late stages, secondary fibrosis can cause marked thickening and contraction of leaflets and chordae tendineae. The chordae tendineae may rupture [16], leading to an unattached free edge. Microscopically, there is myxomatous proliferation of the valve, in which the spongiosa component of the valve is unusually prominent and the quantity of acid-staining glucosaminoglycans is increased [11,15,16]. The valvular interstitial cells in affected areas often have morphologic changes of the nucleus, a localized concentration of abnormally shaped mitochondria and rough endoplasmic reticulum, a disorganized cytoskeleton, and lack of secretory vesicles [17]. There is haphazard arrangement, disruption, and fragmentation of the collagen fibrils surrounding the interstitial cells [14,17]. The endothelial cells covering affected areas become polymorphic, and some areas completely lose the endothelium, exposing the underlying extracellular matrix [17]. Some large-breed dogs may present with massive MR but comparably minor mitral valve abnormalities on a 2D echocardiogram or at postmortem examination [18,19]. It is currently not known if the MR in some of these large-breed dogs is the manifestation of DMVD or another cardiac disease.

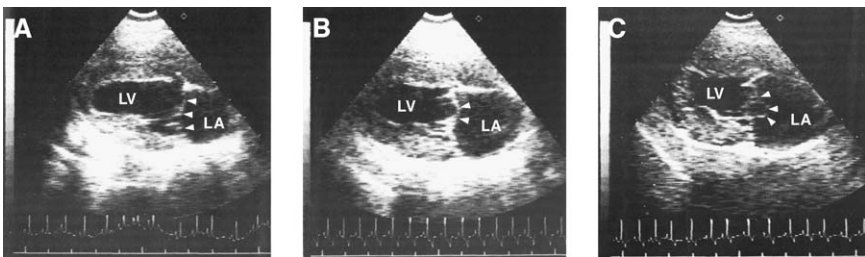


Fig. 2. Right parasternal long-axis four-chamber echocardiograms in which the mitral valve in systole is apparent. A normal mitral valve (A), mild mitral valve prolapse (B), and severe mitral valve prolapse (C). LV, left ventricle, LA, left atrium. The arrowheads indicate the mitral valve leaflets. (From Pedersen HD, Lorentzen KA, Kristensen B, et al. Observer variation in the two-dimensional echocardiographic evaluation of mitral valve prolapse in dogs. *Vet Radiol Ultrasound* 1996;37:65–70; with permission.)

Etiology and pathogenesis of degenerative mitral valve disease

Little is known with certainty about the underlying cause and pathogenesis of the progressive thickening and degeneration of the leaflets. An old theory is that the changes are a response to injury type lesions (ie, repeated impact to the leaflets [especially in the areas of apposition] results in slowly progressive changes) [20]. Because not all dogs develop DMVD, one or more primary inciting factors probably increases the risk of disease in predisposed animals. The nature of these primary initiating factors is not currently known, although certain abnormalities of collagen and other extracellular matrix components have been suggested to predispose to DMVD [1]. In people, MVP occurs in association with a variety of connective tissue disorders [21–25] and craniofacial skeletal deformities [26] as well as in a variety of congenital thoracic deformities, such as straight back, pectus excavatum, or shallow chest [27–29]. Little is known about such associations in dogs. Recently, a relation between MVP and a narrow chest in a population of Dachshunds was reported [30]. It was hypothesized in this report and in one on human patients [31] that a narrow chest may lead to entrapment of the heart within the thorax, which could predispose to MVP and DMVD.

Regardless of the exact nature of the primary inciting factor(s), it has been suggested that it leads to abnormal valve motion (ie, prolapse of the leaflets), which, in turn, increases the shear stress imposed on them directly through the abnormal leaflet apposition and indirectly through the increased regurgitant flow [32,33]. It is likely that the endothelial damage or loss plays an important role in the progression of the disease, because endothelial cells are known to communicate extensively with subendothelial cells (eg, valvular interstitial cells) [17,34]. Endothelial damage may lead to an imbalance in local concentrations of growth-promoting and growth-inhibiting substances produced by endothelial cells. Evidence for such imbalances in diseased canine mitral valves includes the reported associations between disease severity and the expression of endothelin receptors and nitric oxide synthase [35,36]. Furthermore, collagen and other matrix components become exposed to the blood in areas of diseased valves in which the endothelium seems to be missing, and this exposure is expected to promote thrombosis. Although thrombosis may develop as a complication of DMVD in dogs, thrombus formation on the mitral valve is uncommon. Its absence in the presence of endothelial damage in DMVD is not currently understood. Increased knowledge and understanding of the actions of these local mechanisms may be of great importance for future treatment of DMVD because they may suggest ways of treating the actual valve lesions rather than only treating the resulting circulatory disturbances.

Because the underlying cause of DMVD remains uncertain, several scientifically unsupported theories have been proposed. Examples of these theories especially prevalent among breeders are that the valvular lesions develop as a consequence of poor dental health, with hematogenic spread of

bacteria from the oral cavity to the valves, or that DMVD may develop as an unwanted side effect of vaccination. There is currently no scientific evidence that any of these theories are well founded. Inflammation is not an apparent part of DMVD [11,37], and although low-degree DMVD may macroscopically or echocardiographically not always be easy to differentiate from bacterial endocarditis, these two diseases have completely different histopathologic features. In dogs, endocarditis is rare, and when it does occur, it typically affects large-breed dogs rather than the small-breed dogs that typically have DMVD and MR [38]. With regard to species differences of pathologic findings between dogs and people, a major difference seems to be that human beings are more prone than dogs to develop endocarditis as a complication of MD. In people, endocarditis is found in approximately 10% of operatively excised and severely affected mitral valves [39,40].

Myxomatous degeneration and vascular changes

Myxomatous degeneration is not restricted to the mitral valve, and it may be detected in any of the four intracardiac valves. The incidence of valve involvement in dogs was reported as follows: 62% incidence of mitral valve alone, 32.5% incidence of mitral and tricuspid valves, and 1.3% incidence of tricuspid valve alone [11]. The pulmonary and aortic valves are less commonly affected. Interestingly, lesions similar to MD of the AV valves have been described in the main pulmonary artery in Cavalier King Charles Spaniels [41]. Other findings in dogs with advanced stages of DMVD include hyaline or fibromuscular intramural arteriosclerosis and multiple small myocardial infarcts [42–44]. Histologically, these vascular changes (which are common in old dogs) resemble the changes seen in myxomatous valves, and the two conditions often occur together [9,42]. Coexistence of these two abnormalities is to be expected in old dogs, however, because of the high prevalence of both conditions. Furthermore, intramural arteriosclerosis and multiple small myocardial infarcts should predispose to sudden death. Sudden death is rare in dogs with DMVD without decompensated HF, however, and it is interesting that a recent retrospective study of 65 dogs with histologically confirmed hyaline or fibromuscular arteriosclerosis of the intramural coronary arteries showed that 16 (25%) had died suddenly [44]. Therefore, a possible relation between DMVD and vascular changes in the intramural coronary arteries and sudden death needs to be investigated further.

Inheritance and breeding

Heredity has long been suspected to play a major role in the transmission of DMVD because of the strong association of this disease with certain small- to medium-sized breeds. Two studies of families of Cavalier King Charles spaniels and families of Dachshunds provide evidence that genetic

factors play a large role in the etiology (Fig. 3) [30,45]. The disease seems to have a polygenic inheritance; multiple genes influence the trait, and a certain threshold has to be reached before DMVD develops [30,45]. Male dogs have a lower threshold than female dogs, which means that male dogs develop the disease at younger age than female dogs within a family of dogs in which the offspring, on average, have the same genotype. The polygenic mode of inheritance means that a combination of a sire and a dam that both have early onset of DMVD results in offspring that have, on average, early onset of DMVD (and HF). A combination of dogs with late onset results in offspring that manifest the disease at old age or never. The major role played by genetic factors suggests that other factors (eg, level of exercise, degree of obesity, diet) play a comparably small role in the etiology. Probably because of this, little is known about the influence of such factors on the disease. Breeding measures aimed at reducing the prevalence of DMVD have been initiated in many countries in certain breeds, such as Cavalier King Charles Spaniels and Dachshunds. These breeding programs use auscultation to identify the presence of a heart murmur or echocardiography to detect and quantify MVP or regurgitation. Dogs that are younger than a specific age and have developed a heart murmur or echocardiographic findings consistent with DMVD are not allowed to breed. Likewise, offspring from parents that have developed a heart murmur or echocardiographic evidence of early DMVD younger than a certain age limit are excluded from breeding in some programs. These age limits are presumably different depending on whether auscultation or echocardiography is used as the method of diagnosing DMVD, because at a certain age, more dogs are likely to be diagnosed with DMVD when echocardiographic evidence of MVP is used as a diagnostic method than with auscultation [1,13,46]. Nevertheless, the age limits for potential breeding dogs and parents are important. Because the prevalence of DMVD is highly age dependent, the age limit should be set at an age at which dogs with early onset of DMVD are excluded from breeding but not at too high an age, because this may lead an unacceptable proportion of dogs being excluded, which may leave the breeding population at unacceptably low numbers [1]. It has been suggested that it is not advisable to exclude more than 30% of the dogs from breeding because of a single disease [1,47]. With improved DMVD status in the breed, the age limits may later be raised to push the development and manifestation of DMVD toward a higher age.

Diagnosis of early degenerative mitral valve disease

The diagnosis of MR caused by DMVD is often not complicated, because the clinical and echocardiographic findings are obvious and match. There are, however, situations in which the diagnosis of DMVD may be less obvious. Early stages of DMVD may be especially difficult. It may not be clinically important for managing the patient to diagnose these early stages correctly, because the effect of mild MR on the circulation is minimal and so

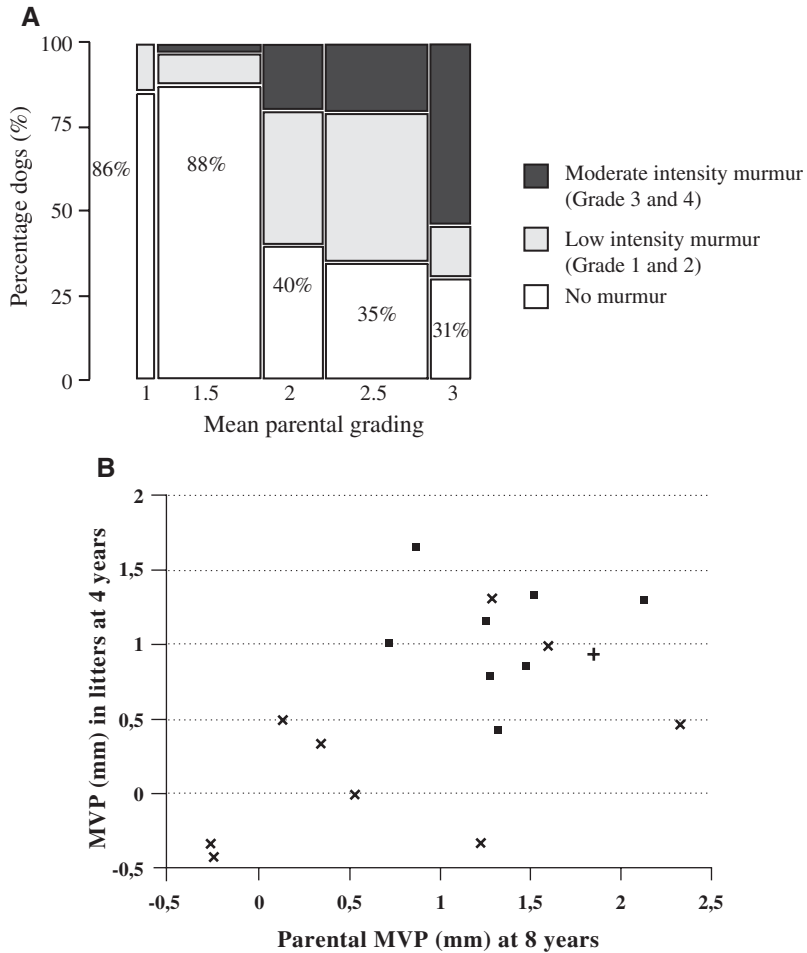


Fig. 3. Two studies have shown that genetic factors play a role in the etiology of degenerative mitral valve disease (DMVD). (A) Relation between mean parental cardiac status and the prevalence and intensity of cardiac murmur in offspring at 5 years of age in 30 different Cavalier King Charles Spaniel litters. The parental cardiac status was graded 1 (late or no development of DMVD) to 3 (DMVD present at a young age). Parents with a high mean cardiac status (ie, developed DMVD at a young age) produced more offspring with heart murmurs than parents with low mean parental grading (ie, late or no development of DMVD). Black, moderate-intensity murmurs in offspring; shaded, low-intensity murmurs in offspring; white, no murmur in offspring. (From Swenson L, Haggstrom J, Kwart C, Juneja RK. Relationship between parental cardiac status in Cavalier King Charles Spaniels and prevalence and severity of chronic valvular disease in offspring. *J Am Vet Med Assoc* 1996;208:2009–12; with permission.) (B) The average mitral valve prolapse (MVP) severity in 18 different Dachshund litters at 4 years of age shown as a function of mean MVP severity at 8 years of age. Parents with a high mean degree of MVP produced offspring with a greater mean degree of MVP than parents with a low degree of MVP. Boxes, family of long-haired Dachshunds; cross, family of short-haired Dachshunds. (From Olsen LH, Fredholm M, Pedersen HD. Epidemiology and inheritance of mitral valve prolapse in Dachshunds. *J Vet Intern Med* 1999;3:448–56; with permission.)

is the likelihood that the disease will cause clinical signs of disease in the near future [33,48]. Nevertheless, it is of great importance for breeding that these dogs are correctly diagnosed, because the currently used breeding programs are founded on the principle of excluding dogs with early onset of DMVD and promoting the use of dogs with late or no onset. Because the age limits in the breeding programs (especially in Cavalier King Charles Spaniels) are set at an age at which many dogs start to develop DMVD [13], a significant number of dogs with mild disease are screened. There is currently no “gold standard” for diagnosing cases of mild DMVD.

Auscultation

The early stages of DMVD are often characterized by the presence of a soft heart murmur with maximal intensity over the mitral area. This murmur may occur in every heartbeat, but it may also be intermittent [14,49–51]. A systolic click may be present in some dogs, and this click may be the only abnormal sound, but it may also be accompanied by an early, late, or holosystolic murmur or by no murmur at all [14, 49–51]. In the case of early systolic murmur, potential differential diagnoses, such as physiologic flow murmurs or low-degree aortic or pulmonic stenosis, should be ruled out. The presence of these low-intensity murmurs is influenced by the degree of stress of the dog at the time of examination. Stress or physical exercise may provoke murmurs in dogs free of a murmur at rest or increase the intensity of the murmur in dogs with a low-intensity murmur at rest [51]. Naturally, this variation may cause confusion if the dog is examined at different times by different auscultators and the results are in disagreement. Dogs with these auscultatory findings indicative of early DMVD are not normal, even if progression to more severe forms of DMVD does not occur in the near future. Echocardiography often reveals changes consistent with DMVD (see below) in the many of these dogs, but the findings may be inconclusive or normal in others, with the latter being especially common in dogs with only a systolic click. These early forms of DMVD may be classified as normal in some breeding programs to ensure that only diseased dogs are classified as diseased. This strategy has been chosen because the observer variation among auscultators has been shown to be considerable in dogs with no or mild DMVD but less in dogs with more progressive forms [51].

Echocardiography

Echocardiography is a valuable tool to evaluate dogs with early DMVD because it provides information about valve morphology and valve leakage and it helps to rule out differential diagnoses. The technique has disadvantages, however, because it is comparably time-consuming and expensive compared with auscultation and it requires trained operators, which makes it less convenient as a screening method of large populations. Ideally, diagnosis

of early DMVD should be founded on the findings of abnormal mitral valve morphology typical for DMVD and valve leakage. Abnormal mitral valve morphology may be present without leakage and vice versa, however [46,51,52]. Although DMVD is the most common cause for mitral valve leakage, the diagnosis of DMVD is less obvious in cases in which the only abnormal finding is the presence of a small regurgitant jet. When examining a mitral valve using 2D echocardiography, it is important to examine the entire valve, because the lesions are often quite unevenly distributed [14,17,37]. A systolic bulging of one or both leaflets to the atrial side of the mitral annulus is an early indication of affected valves, and it may be present in dogs with or without MR (and a murmur) (see Fig. 2) [32,46]. The presence and degree of protrusion of the leaflets may be measured or subjectively evaluated in the right parasternal long-axis view [2,46]. In dogs, the hinge points of the two leaflets (imaged in the right parasternal long-axis view, which consistently provides good images) have been used to define the position of the mitral annulus in all recent studies assessing the presence and severity of MVP [33,52,53]. In cases with insufficient valves, the degree of displacement is reported to relate well to the severity of MR [2,32,46]. With progression, the degenerative changes become more prominent and the leaflets often have an irregular “club-like” appearance with greatest thickening at the tip. The gross pathologic changes of the two leaflets (anterior and posterior) are often equally severe at postmortem examination, but the degenerative changes commonly appear more prominent on the anterior leaflet in the right parasternal long-axis view on the echocardiogram.

It is rare, even in severe cases of DMVD and MR, to detect incomplete closure of the leaflets as a means of confirming the presence of MR. Instead, the MR may be detected and quantified by spectral or color-flow Doppler ultrasonography [19,51,54–56]. Ideally, the regurgitant flow should be aligned with the ultrasound beam, and this is most often achieved in the left apical four-chamber view. Because the flow direction depends on the orientation of the regurgitant orifice, which, in turn depends on the leaflet morphology, other views may also give good alignment. Spectral Doppler mapping may be used to identify the regurgitant jet when color-Doppler mapping is not available. Furthermore, spectral Doppler mapping gives information about the velocity of the regurgitant jet, and velocity time tracings may help in estimating regurgitant volume (see below) [19]. Color-flow echocardiography confirms the presence of a regurgitant jet, and the size of the jet can be compared with the size of the left atrium. This measurement is semiquantitative. A small jet rules out moderate to severe MR, but it is difficult to discriminate between moderate and severe regurgitation from the jet size. Nevertheless, the method has been reported to correlate reasonably well with other echocardiographic measurements of regurgitant flow and volume [56]. In case a more exact quantitative measurement of regurgitant fraction is desired, the proximal isovelocity surface area (PISA) color-flow method or spectral Doppler subtraction of forward aortic and regurgitant

flows may be used [54–56]. Small jets in the vicinity of the mitral valve should not be overinterpreted in dogs without any other valve abnormality, because trivial regurgitation may often be detected in normal dogs [57].

Consequences of mitral regurgitation on left ventricular function

A low degree of MR caused by DMVD does not lead to an apparent change in any cardiac chamber or wall size or pump function. The forward stroke volume is maintained, and the small regurgitant volume is easily accepted by the left atrium. With progression of the valve lesions and increasing MR, however, the potential loss of forward stroke volume is compensated for by increased total stroke volume, increased force of contraction, remodeling of the left atrium and left ventricle with myocardial hypertrophy and dilatation, increased heart rate, and modulations of systemic vascular tonus and extracellular fluid volume. The exact sequence in which these compensatory mechanisms are recruited is currently not fully understood. The cardiac compensatory mechanisms are presumably recruited first, whereas the systemic mechanisms do not seem to be activated until the cardiac mechanisms fail to compensate the MR (ie, decompensated HF) [58]. To some extent, the MR is already compensated for by a slightly increased heart rate during compensated phases, but this increase is usually not obvious at a clinical examination because of the overall variability of heart rate in dogs [59,60]. The heart rate is usually significantly increased in advanced stages of MR, however, with evidence of decompensated HF [19,59,60]. MR creates unique hemodynamic stress by means of the development of a low-pressure form of volume overload as a result of ejection into the left atrium [61]. Myocardial systolic function is relatively well preserved, because the ejection into the left atrium at low pressure require little work by the left ventricle compared with other forms of heart disease [19,61,62]. Dogs may tolerate even severe MR for years. Nevertheless, because of chronic volume overload and the fact that the hypertrophy, although necessary, is a pathologic remodeling, myocardial contractility decreases slowly, even in clinically compensated dogs, but progressively and inevitably [12,19,59,63]. Clinical overt myocardial failure in MR is referred to as cardiomyopathy of volume overload, a condition that may also develop in other types of heart disease, such as large patent ductus arteriosus [19]. Reliable measurements of myocardial contractility are not readily obtained in MR, and it is currently not known at which stage the depressed myocardial contractility becomes of clinical significance. The reason for this is that the volume overload causes an increase in preload (increased end-diastolic filling), which, in turn, leads to an increased force of contraction according to the Frank-Starling law [64]. When the ventricles contract, the resistance to ventricular emptying is reduced in the first stages of ejection, because the regurgitant volume is ejected into the left atrium at low pressure, leading to exaggerated motion of the left ventricle (hyperkinesia) [14], which is readily

identified on the echocardiogram of a diseased dog. In moderate to severe MR, values of ejection phase indices obtained from the echocardiogram (eg, left ventricular fractional shortening, ejection fraction, mean velocity of circumferential shortening) are often greater than normal. Therefore, in the setting of moderate or severe MR, a normal fractional shortening represents a significant reduction of myocardial contractility. End-systolic volume indices (eg, left ventricular end-systolic short-axis dimension, end-systolic volume index) more accurately estimate myocardial contractility in MR [14,62]. When decompensated HF is present and the sympathetic nervous system is activated to increase apparent contractility, even these measurements overestimate intrinsic myocardial contractility [63]. Our longitudinal studies in Cavalier King Charles Spaniels indicate that although the end-systolic dimension of the left ventricle does increase gradually before the onset of signs of decompensated HF, the change is not great and may even be within the normal reference range [58,65]. This increase in end-systolic diameter usually becomes apparent after the onset of clinical signs of decompensated HF [58,65]. This finding is in agreement with previously published observations, but it does not provide information about overall cardiac pump function [12,19,62]. Because the cardiac output is determined by the forward stroke volume and the heart rate, evaluation of cardiac output must take into account both heart rate and stroke volume. We recently completed a study in which the pulmonary transit time (ie, the time it takes for a blood cell to travel from the pulmonary trunk to the left atrium) was studied using nuclear angiocardigraphy in dogs with varying severity of MR caused by DMVD [59]. When the transit time was normalized for the heart rate, we found that dogs with compensated MR but with evidence of cardiomegaly had increased transit times. Dogs with signs of decompensated HF had an even higher increase in transit times. Our interpretation of these findings is that dogs with MR have reduced overall pump function (forward stroke volume) even before signs of decompensated HF have developed. It is currently not known if this finding is an indication that inotropic support is indicated at this stage of the disease.

Diagnosis of mild decompensated heart failure

Dogs with DMVD attributable to DMVD usually develop clinical signs of left-sided HF (cough, dyspnea, lethargy, reduced mobility, and increased heart rate), although evidence of right-sided HF (ascites) may develop in advanced cases [14,19]. Diagnosing moderate to severe HF is usually not difficult, because the clinical signs of HF are usually obvious and match the findings on the radiographs (ie, pulmonary edema, congestion). Likewise, it is usually not difficult to diagnose the MR because it is invariably significant [14,19]. Mild decompensated HF may be difficult to diagnose, however, because of the presence of vague clinical signs and the fact that the signs may have gradually developed over a comparably long time. The stage when

a patient starts to show clinical signs of DMVD and MR (ie, development of decompensated HF) is the end of a process that started much earlier with the onset of valve leakage. Over time, the valvular leakage was compensated through a variety of mechanisms, a condition called “asymptomatic” or compensated MR [14,19]. As the valve leakage increased, the valves eventually became incapable of preventing pulmonary capillary pressures from exceeding the threshold for pulmonary edema or of maintaining forward cardiac output, a condition called “symptomatic” or decompensated MR [14,19]. The distinction between these two stages is not clear, however, and it is likely that minor signs of reduced activity and mobility are present even before overt signs of decompensated HF have developed. It is difficult to evaluate the presence of slight to moderately reduced exercise capacity in most dogs with DMVD and MR objectively; many affected animals are old and small companion dogs, which if obese, have little, if any, demand on their exercise capacity. Furthermore, other concurrent diseases in the locomotor system or elsewhere are common and restrict exercise. Likewise, the hallmark of left-sided HF, coughing and dyspnea, may be caused by several conditions, such as small airway disease, tracheal instability, pulmonary fibrosis, neoplasia, heartworm disease, and pneumonia [14,19]. An increased heart rate and loss of respiratory sinus arrhythmia may also be indicative of decompensated HF, but heart rate is variable and is increased by many factors, such as stress and concurrent disease [14,19,60]. Many of these differential diagnoses can be excluded by different clinical tests, particularly radiography. Pulmonary findings on the radiographs may also be inconclusive, because early radiographic changes of pulmonary interstitial edema and bronchial pattern resemble the radiographic appearance of chronic airway disease [14,19,60]. The tendency is to overdiagnose pulmonary edema of HF [66]. Therefore, the most effective means to separate dogs with early mild decompensated HF from those with other disease is presumably to make the diagnosis based on the combined findings from the clinical examination and the radiographs, an approach that has been used in large clinical trials [48]. It is also useful to have series of radiographs and to evaluate other evidence of left-sided HF that should be present by the time pulmonary edema has developed, such as pulmonary venous distention. If the findings are still inconclusive, re-examination within a week or a 48- to 72-hour trial of diuretic therapy with repeat radiographs may help to identify the underlying cause. In the near future, “bedside” assays of different endogenous markers of heart disease and HF, such as natriuretic peptides (atrial natriuretic peptide [ANP] and brain natriuretic peptide [BNP]), should be available to aid in diagnosing difficult cases.

When should therapy begin?

Ideally, DMVD therapy should halt the progression of the valvular degeneration or improve valvular function by surgical repair or valve

replacement. This therapy should preferably start before the onset of clinical signs of disease. No medical therapy has been shown to change the course of the disease by inhibiting or preventing the valvular degeneration, however, and surgery is usually not technically, economically, or ethically possible in dogs. Medical therapy of DMVD is therefore aimed at improving quality of life by ameliorating the clinical signs and at improving survival. Monotherapy with angiotensin-converting enzyme (ACE) inhibitors has frequently been prescribed for dogs with DMVD before the onset of decompensated HF, most commonly in dogs with evidence of left atrial and ventricular dilatation. Presumably, there are many reasons for this strategy. Clinical trials in dogs with decompensated HF caused by DMVD have shown that ACE inhibitor therapy improves quality of life and increases survival when administered as adjunct therapy to other ongoing HF therapy [67–69]. Furthermore, there is evidence from large clinical trials in people that monotherapy with ACE inhibitors improves quality of life and survival not only in asymptomatic patients with left ventricular dysfunction [70] but in those without heart disease but belonging to a risk group for developing it [71]. The local tissue renin-angiotensin-aldosterone system (RAAS) has been suggested to be important for myocardial remodeling in various animal models of HF [72,73]. An increased concentration of plasma renin and aldosterone was reported in some asymptomatic dogs with DMVD, indicating an early activation of the RAAS [74]. It is therefore plausible that suppression of the RAAS could also be beneficial in asymptomatic dogs with MR by counteracting systemic neuroendocrine activation and left ventricular remodeling. Two large, placebo-controlled, multicenter trials, the Scandinavian Veterinary Enalapril Prevention (SVEP) and the VetProof trials [48,75], were undertaken to study the effect of ACE inhibitor monotherapy on the progression of clinical signs in asymptomatic DMVD and MR in dogs. Both failed to show a significant difference between the placebo and treatment groups in time from onset of therapy to confirmed decompensated HF (Fig. 4) [48,75] in dogs with or without cardiomegaly. The two trials differed in the following features: the SVEP trial included only dogs of one breed (Cavalier King Charles Spaniels), whereas the VetProof trial included a variety of breeds; the dogs in the VetProof trial more frequently had advanced DMVD than the dogs in the SVEP trial; and the SVEP trial comprised more dogs than the VetProof trial (229 versus 139 dogs). There are studies that may shed light on the results of these two trials. The increased plasma concentration of renin and aldosterone found in some asymptomatic dogs with MVD [74] was later found to be associated with the presence of MVP rather than with the degree of MR per se [76]. Furthermore, a longitudinal study involving Cavalier King Charles Spaniels with moderate to severe MR attributable to DMVD showed no signs of increased circulating RAAS activity during the progression from compensated (ie, asymptomatic) to decompensated (ie, symptomatic) HF [58]. This finding has recently been corroborated in a study involving other

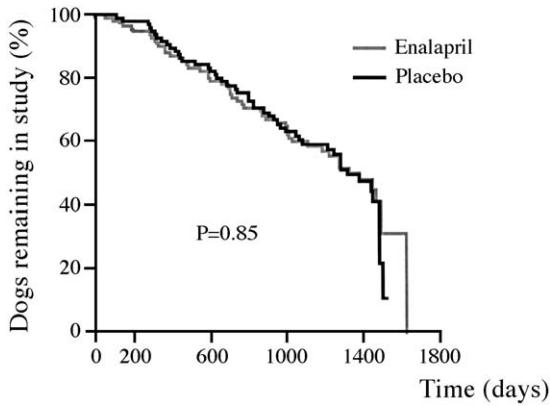


Fig. 4. The SVEP study investigated the effect of enalapril on preventing decompensated heart failure in dogs with asymptomatic DMVD. The graph shows the percentage of dogs included in the enalapril and placebo groups, respectively, versus time. The difference in the number of days in the study between placebo- and enalapril-treated dogs was not significant. (From Kwart C, Häggström J, Pedersen HD, et al. Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation. *J Vet Intern Med* 2002;16:80–8; with permission.)

breeds by Oyama and Sisson [77]. On the local tissue level, autoradiographic studies indicate that in canine mitral valves, as opposed to rat valves, angiotensin II receptors and ACE are scant [78]. This finding is at odds with the theory that local RAAS systems in the valves contribute to progressive valvular degeneration. In contrast, the canine myocardium has a comparably high concentration of angiotensin II receptors and ACE [79]. Nevertheless, experimental studies in dogs with MR showed no effect of an ACE inhibitor on myocardial remodeling and progressive ventricular dilatation [79]. Because angiotensin II production may be mediated through enzymes other than ACE, in particular through chymase in dogs and people [80], the same authors investigated whether blocking of angiotensin II receptors could prevent myocardial remodeling but found no effect [81]. Thus, it seems that the remodeling process in MR may be more complicated than previously thought; it has recently been suggested that this process is an example of tissue activation that is difficult to stop or slow by current pharmacologic means without changing the fundamental pathophysiology (ie, increased heart rate and loading conditions) [82]. Finally, the large clinical trials in asymptomatic heart disease in people have most commonly involved patients with left ventricular dysfunction. Published clinical trials in primary mitral valve disease and MR in people have been surprisingly few and have reported conflicting results [82]. In conclusion, there is no evidence that any therapy instituted before the onset of clinical signs of decompensated HF prevents or delays the progression of DMVD.

References

- [1] Häggström J. Chronic valvular disease in Cavalier King Charles Spaniels—epidemiology, inheritance and pathophysiology [thesis]. Uppsala: Swedish University of Agricultural Sciences; 1996.
- [2] Pedersen H. Mitral valve prolapse in the dog—pathogenesis, pathophysiology, diagnosis and comparative aspects of early myxomatous mitral valve disease [thesis]. Copenhagen: Royal Veterinary and Agricultural University; 2000.
- [3] Pedersen H, Häggström J. Mitral valve prolapse in the dog: a model of mitral valve prolapse in man. *J Cardiovasc Res* 2000;47:234–43.
- [4] Reef V, Bain F, Spencer P. Severe mitral regurgitation in horses: clinical, echocardiographic and pathological findings. *Equine Vet J* 1998;30:18–27.
- [5] Gagna C, Meier D, Ru G, Pospischil A, Guarda F. Pathology of mitral valve in regularly slaughtered pigs: an abattoir survey on the occurrence of myxoid degeneration (endocardiosis), fibrosis and valvulitis. *J Vet Med Ser A* 1998;45:383–95.
- [6] Playford D, Weyman A. Mitral valve prolapse: time for a fresh look. *Rev Cardiovasc Med* 2001;2:73–81.
- [7] Ackerknecht E. Kreislauforgane (herz). In: Joest EE, editor. *Spezielle pathologische Anatomie der Haustiere*. Berlin: Richard Schoetz; 1925. p. 317–586.
- [8] Bonnett B, Egenvall A, Olson P, Hedhammar A. Mortality in insured Swedish dogs: rates and causes of death in various breeds. *Vet Rec* 1997;141:40–4.
- [9] Detweiler DK, Patterson DF. The prevalence and types of cardiovascular disease in dogs. *Ann NY Acad Sci* 1965;127:481–516.
- [10] Das KM, Tashjian RJ. Chronic mitral valve disease in the dog. *Vet Med Small Anim Clin* 1965;60:1209–15.
- [11] Buchanan JW. Chronic valvular disease (endocardiosis) in dogs. *Adv Vet Sci* 1977;21:57–106.
- [12] Sisson D, Kvart C, Darke P. Acquired valvular heart disease in dogs and cats. In: Fox P, Sisson D, Moise N, editors. *Textbook of canine and feline cardiology*. 2nd edition. Philadelphia: WB Saunders; 1999. p. 536–65.
- [13] Häggström J, Hansson K, Kvart C, Swenson L. Chronic valvular disease in the Cavalier King Charles spaniel in Sweden. *Vet Rec* 1992;131:549–53.
- [14] Kvart C, Häggström J. Acquired valvular heart disease. In: Ettinger S, Feldman E, editors. *Textbook of veterinary internal medicine. Diseases of dogs and cats*. 5th edition. Philadelphia: WB Saunders; 2000. p. 787–800.
- [15] Whitney JC. Observation on the effect of age on the severity of heart valve lesions in the dog. *J Small Anim Pract* 1974;15:511–22.
- [16] Kogure K. Pathology of chronic mitral valve disease in the dog. *Jpn Vet Sci* 1980;42:323–35.
- [17] Corcoran B, Black A, Anderson H, Dukes McEvan J, French A. Investigation of mitral valve morphology in dogs with mitral valve endocardiosis using scanning electron microscopy. In: *Proceedings of the 12th European College of Veterinary Internal Medicine/European Society of Veterinary Internal Medicine Congress*. Munich, Germany; September 19–21, 2002, p. 178.
- [18] Borgarelli M, Zini E, D’Agnolo G, Tarducci A, Santilli RA, Chiavegato D, et al. Comparison of primary mitral valve disease in German Shepherd dogs and dogs of small-sized breeds. *J Vet Cardiol* 2004;6, in press.
- [19] Kittleson M. Myxomatous atrioventricular valvular degeneration. In: Kittleson M, Kienle R. *Small animal cardiovascular medicine*. St. Louis: Mosby; 1998. p. 297–318.
- [20] Pommerance A. Pathogenesis of “senile” nodular sclerosis of atrioventricular valves. *Br Heart J* 1966;28:815–23.
- [21] Sanyal SK, Johnson WW, Dische MR, Pitner SE, Beard C. Dystrophic degeneration of papillary muscle and ventricular myocardium. A basis for mitral valve prolapse in Duchenne’s muscular dystrophy. *Circulation* 1980;62:430–8.

- [22] Lebowohl M, Distefano D, Prioleau P. Pseudoxanthoma, elasticum and mitral valve prolapse. *N Engl J Med* 1982;307:228–31.
- [23] Cabeen WR, Reza MJ, Kovick RB, Stern MS. Mitral valve prolapse and conduction defects in Ehlers-Danlos syndrome. *Arch Intern Med* 1977;137:1227–31.
- [24] Wood S, Thomas J, Braimbridge M. Mitral valve disease and open heart surgery in osteogenesis imperfecta tarda. *Br Heart J* 1973;35:103–6.
- [25] Beardsley TL, Foulks GN. An association of keratoconus and mitral valve prolapse. *Ophthalmology* 1982;89:35–7.
- [26] Waite P, McCallum CA. Mitral valve prolapse in craniofacial skeletal deformities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1986;61:15–8.
- [27] Chan FL, Chen WW, Wong PH, Chow JS. Skeletal abnormalities in mitral valve prolapse. *Clin Radiol* 1983;34:207–13.
- [28] Chen WW, Chan FL, Wong PH, Chow JS. Familial occurrence of mitral valve prolapse: is this related to the straight back syndrome? *Br Heart J* 1983;50:97–100.
- [29] Hirschfeld SS, Rudner C, Nash CL Jr, Nussbaum E, Brower EM. Incidence of mitral valve prolapse in adolescent scoliosis and thoracic hypokyphosis. *Pediatrics* 1982;70:451–4.
- [30] Olsen L, Fredholm M, Pedersen H. Epidemiology and inheritance of mitral valve prolapse in Dachshunds. *J Vet Intern Med* 1999;13:448–56.
- [31] Raggi P, Callister T, Lippolis N, Russo D. Is mitral valve prolapse due to cardiac entrapment in the chest cavity? A CT view. *Chest* 2000;117:636–42.
- [32] Pedersen H, Lorentzen K, Kristensen B. Echocardiographic mitral valve prolapse in Cavalier King Charles spaniels: epidemiology and prognostic significance for regurgitation. *Vet Rec* 1999;144:315–20.
- [33] Olsen L, Martinussen T, Pedersen H. Early echocardiographic predictors of myxomatous mitral valve disease in dachshunds. *Vet Rec* 2003;152:293–7.
- [34] Stein P, Wang C, Riddle J, Sabbah H, Magilligan D, Hawkins E. Scanning electron microscopy of operatively excised severely regurgitant floppy mitral valves. *Am J Cardiol* 1989;64:392–4.
- [35] Mow T, Pedersen H. Increased endothelin-receptor density in myxomatous canine mitral valve leaflets. *J Cardiovasc Pharmacol* 1999;34:254–60.
- [36] Olsen L, Mortensen K, Martinussen T, Larsson L, Baandrup U, Pedersen H. Increased NADPH-diaphorase activity in canine myxomatous mitral valve leaflets. *J Comp Pathol* 2003;129:120–30.
- [37] Whitney JC. Cardiovascular pathology. *J Small Anim Pract* 1967;8:459–65.
- [38] Calvert CA. Valvular bacterial endocarditis in the dog. *J Am Vet Med Assoc* 1982;180:1080–4.
- [39] Davies M, Moore B, Braimbridge M. The floppy mitral valve—study of incidence, pathology, and complications in surgical, necropsy, and forensic material. *Br Heart J* 1978;40:468–81.
- [40] Agozzino L, Falco A, de Vivo F, de Vincentiis C, de Luca L, Esposito S, et al. Surgical pathology of the mitral valve: gross and histological study of 1288 surgically excised valves. *Int J Cardiol* 1992;37:79–89.
- [41] Karlstam E, Haggstrom J, Kvarn C, Jonsson L, Michaelsson M. Pulmonary artery lesions in Cavalier King Charles spaniels. *Vet Rec* 2000;147:166–7.
- [42] Jonsson L. Coronary arterial lesions and myocardial infarcts in the dog. A pathologic and microangiographic study. *Acta Vet Scand* 1972;38:1–80.
- [43] Tidholm A, Häggström J, Jönsson L. Prevalence of attenuated wavy fibers in myocardium of dogs with dilated cardiomyopathy. *J Am Vet Med Assoc* 1998;212:1732–4.
- [44] Falk T, Jönsson L. Ischaemic heart disease in the dog: a review of 65 cases. *J Small Anim Pract* 2000;41:97–103.
- [45] Swenson L, Häggström J, Kvarn J, Juneja K. Relationship between parental cardiac status in Cavalier King Charles Spaniels and prevalence and severity of chronic valvular disease in offspring. *J Am Vet Med Assoc* 1996;208:2009–12.

- [46] Pedersen HD. Mitral valve prolapse in 3-year old healthy Cavalier King Charles Spaniels. An echocardiographic study. *Can J Vet Res* 1995;59:294–8.
- [47] Lacy R. Loss of genetic diversity from managed populations: interacting effects on drift, mutation, immigration, selection and population subdivision. *Conserv Biol* 1987;1:143–58.
- [48] Kwart C, Häggström J, Pedersen HD, Hansson K, Eriksson A, Jarvinen AK, et al. Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation. *J Vet Intern Med* 2002;16:80–8.
- [49] Kwart C, Häggström J. Cardiac auscultation and phonocardiography in dogs, horses and cats. Uppsala: Clarence Kwart Selbstverlag; 2002. p. 61–4.
- [50] Häggström J, Hansson K, Kwart C. Heart sounds and murmurs: changes related to severity of mitral regurgitation in Cavalier King Charles Spaniels. *J Vet Intern Med* 1995;9:75–85.
- [51] Pedersen HD, Häggström J, Falk T, Mow T, Olsen LH, Iversen L, et al. Auscultation in mild mitral regurgitation in dogs: observer variation, effects of physical maneuvers, and agreement with color Doppler echocardiography and phonocardiography. *J Vet Intern Med* 1999;13:56–64.
- [52] Pedersen HD, Kristensen B, Norby B, Lorentzen KA. Echocardiographic study of mitral valve prolapse in dachshunds. *Zentralbl Veterinarmed A* 1996;43:103–10.
- [53] Pedersen HD, Lorentzen K, Kristensen B. Observer variation in the two-dimensional echocardiographic evaluation of mitral valve prolapse in dogs. *Vet Radiol Ultrasound* 1996;37:367–72.
- [54] Doiguchi O, Takahashi T. Examination of quantitative analysis and measurement of the regurgitation rate in mitral valve regurgitation by the “proximal isovelocity surface area” method. *J Vet Med Sci* 2000;62:109–12.
- [55] Kittleson M, Brown W. Regurgitant fraction measured by using the proximal isovelocity surface area in dogs with chronic myxomatous mitral valve disease. *J Vet Intern Med* 2003; 17:84–8.
- [56] al Muzzi R, de Araujo R, al Muzzi L, Pena JLB, Silva EF, et al. Regurgitant jet area by Doppler color flow mapping: quantitative assessment of mitral regurgitation severity in dogs. *J Vet Cardiol* 2003;5:33–8.
- [57] Nakayama T, Wakao Y, Takiguchi S, Uechi M, Tanaka K, Takahashi M. Prevalence of valvular regurgitation in normal Beagle dogs detected by color Doppler echocardiography. *J Vet Med Sci* 1994;56:973–5.
- [58] Häggström J, Hansson K, Kwart C, Karlberg B, Voulteenaho O, Olsson K. Effects of naturally acquired decompensated mitral valve regurgitation on the renin-angiotensin-aldosterone system and atrial natriuretic peptide concentration in dogs. *Am J Vet Res* 1997;58:77–82.
- [59] Lord P, Eriksson A, Häggström J, et al. Increased pulmonary transit times in asymptomatic dogs with mitral regurgitation. *J Vet Intern Med* 2003;17:824–9.
- [60] Häggström J, Hamlin RL, Hansson K, Kwart C. Heart-rate variability in relation to severity of mitral regurgitation in the Cavalier King Charles Spaniel. *J Small Anim Pract* 1996;37:69–75.
- [61] Lord PF. Left ventricular volumes of diseased canine heart: congestive cardiomyopathy and volume overload (patent ductus arteriosus and primary mitral insufficiency). *Am J Vet Res* 1973;35:493–501.
- [62] Kittleson MD, Eyster GE, Knowlen GG, Bari Olivier N, Anderson LK. Myocardial function in small dogs with chronic mitral regurgitation and severe congestive heart failure. *J Am Vet Med Assoc* 1984;184:455–9.
- [63] Urabe Y, Mann DL, Kent RL, Nakano K, Tomanek RJ, Carabello BA, et al. Cellular and ventricular contractile dysfunction in experimental canine mitral regurgitation. *Circ Res* 1992;70:131–47.
- [64] Komamura K, Shannon RP, Ihara T, Shen YT, Mirsky I, Bishop SP, et al. Exhaustion of Frank-Starling mechanism in conscious dogs with heart failure. *Am J Physiol* 1993;265: H1119–31.

- [65] Häggström J, Hansson K, Kvart C, Vuolteenaho O, Olsson K. Secretion patterns of the natriuretic peptides in naturally acquired mitral regurgitation attributable to chronic valvular disease in dogs. *J Vet Cardiol* 2000;2:7–16.
- [66] Hansson K. Diagnostic imaging of cardiopulmonary structures in normal dogs and dogs with mitral regurgitation [thesis]. Uppsala: Swedish University of Agricultural Sciences; 2004.
- [67] The COVE Study Group. Controlled clinical evaluation of enalapril in dogs with heart failure: results of the Cooperative Veterinary Enalapril Study Group. *J Vet Intern Med* 1995;9:243–52.
- [68] Ettinger SJ, Benitz AM, Ericsson GF, Cifelli S, Jernigan AD, Longhofer SL, et al. Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril (LIVE) Study Group. *J Am Vet Med Assoc* 1998;213:1573–7.
- [69] The BENCH Study Group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. *J Vet Cardiol* 1999;1:7–18.
- [70] The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:725–7.
- [71] Arnold J, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, et al. Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 2003;107:1234–6.
- [72] Brilla C, Maisch B. Regulation of the structural remodelling of the myocardium: from hypertrophy to heart failure. *Eur Heart J* 1994;15:45–52.
- [73] Lee M, Bohm M, Paul M, Ganten D, et al. Tissue renin-angiotensin systems: their role in cardiovascular disease? *Circulation* 1993;87(5 Suppl):IV7–13.
- [74] Pedersen HD, Koch J, Poulsen K, Jensen AL, Flagstad A. Activation of the renin-angiotensin system in dogs with asymptomatic and mildly symptomatic mitral valvular insufficiency. *J Vet Intern Med* 1995;9:328–31.
- [75] Atkins CE. Enalapril monotherapy in asymptomatic mitral regurgitation: results of the VetProof trial. In: Proceedings of the 20th Annual American College of Veterinary Internal Medicine Forum. Dallas, TX, May 29–June 1, 2002. p. 75–6.
- [76] Pedersen H, Olsen LH, Mow T, Christensen N. Neuroendocrine changes in Dachshunds with mitral valve prolapse examined under different study conditions. *Res Vet Sci* 1999;66: 11–7.
- [77] Oyama M, Sisson D. Blood based detection of occult heart disease. In: Proceedings of the 21st Annual American College of Veterinary Internal Medicine Forum. Charlotte, NC, June 4–8, 2003. p. 88–9.
- [78] Mow T, Pedersen H. No expression of angiotensin II receptors and angiotensin-converting enzyme in myxomatous canine mitral valve leaflets. An autoradiographic study. *J Vet Med A* 1999;46:465–72.
- [79] Dell’Italia LJ, Balcells E, Meng QC, Su X, Schultz D, Bishop SP, et al. Volume-overload cardiac hypertrophy is unaffected by ACE inhibitor treatment in dogs. *Am J Physiol* 1997; 273:H961–70.
- [80] Stewart JA Jr, Wei CC, Brower GL, Rynders PE, Hanks GH, Dillon AR, et al. Cardiac mast cell- and chymase-mediated matrix metalloproteinase activity and left ventricular remodeling in mitral regurgitation in the dog. *J Mol Cell Cardiol* 2003;35:311–9.
- [81] Perry GJ, Wei CC, Hanks GH, Dillon SR, Rynders P, Mukherjee R, et al. Angiotensin II receptor blockade does not improve left ventricular function and remodeling in subacute mitral regurgitation in the dog. *J Am Coll Cardiol* 2002;39:1374–9.
- [82] Dell’Italia L. The renin-angiotensin system in mitral regurgitation: a typical example of tissue activation. *Curr Cardiol Rep* 2002;4:97–103.