Review

Mitral valve prolapse in the dog: a model of mitral valve prolapse in man

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1. Introduction

Mitral valve prolapse (MVP), i.e. abnormal systolic protrusion of mitral valve leaflets into the left atrium, is a common cause of severe mitral regurgitation (MR) requiring operation in people living in industrialized nations [1,2]. MVP has been reported to have many causes but in the majority of cases it is a primary condition (called primary MVP in this paper) characterized by a progressive myxomatous degeneration of the mitral valve leaflets and chordae tendineae [1–3]. The disease typically emerges in adolescence but complications such as severe MR usually do not occur until middleage or senescence [1–3]. An animal model with a shorter course of disease could be useful in several ways, for instance, by making it feasible to evaluate the effects of different drugs on disease progression. Despite this, no animal model of primary MVP has been described so far.

From pathological studies, it has long been known that most dogs develop myxomatous mitral valve disease with age and that this disease is very similar macroscopically as well as microscopically to primary MVP in humans [4,5]. Traditionally, however, the canine disease has been given names other than MVP, including endocardiosis and chronic valvular disease. Recently, a number of studies, including many based on well-defined echocardiographic criteria for the diagnosis of MVP, have increased our understanding of this disease in the dog. The purpose of this article is to compare the knowledge which has been accumulated about myxomatous mitral valve disease/MVP in the dog with knowledge of primary MVP in humans.

2. Pathology

Pathologically, primary MVP in humans is very similar to canine myxomatous mitral valve disease [4,5]. In both species, the principal macroscopic findings are enlarged, thickened leaflets, interchordal hooding and elongated chordae tendineae (Fig. 1A, B) [4–9]. In addition, affected individuals from both species often display similar, albeit minor, changes in the tricuspid valve and, in late stages, secondary fibrosis of the leaflets, ruptured chordae tendineae, jet lesions and dilation of the left ventricle, left atrium and mitral annulus [4–9]. Light microscopy of the leaflets shows deposition of glycosaminoglycans and disruption of collagen as the primary findings in both species (Fig. 1C, D) [5–7,9]. Electron microscopy reveals areas with sparse, disorganized collagen fibrils which often have a spiraling appearance, in dogs as well as in humans (Fig. 1E, F) [10].

Humans with primary MVP seem to have an increased, albeit small risk of sudden death and in such cases, a marked nonatherogenic dysplasia of the intramural coronary arteries is often found [11,12]. In dogs, sudden death is also rare and it is therefore suggestive that a recent retrospective study of 65 dogs with histologically confirmed nonatherogenic dysplasia of the intramural coronary arteries showed that 16 (25%) had died suddenly [13]. Furthermore, it has been noted that the above-mentioned vessel changes (which are common in old dogs) histologically resemble the changes seen in myxomatous valves and that the two conditions often occur together [14,15]. Coexistence, however, is to be expected in old dogs because of the high prevalence of both conditions. The relationship between myxomatous valvular disease, dysplasia of the intramural coronary arteries and sudden death needs to be further elucidated in both species.

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Fig. 1. Myxomatous mitral valve disease/mitral valve prolapse in the dog (A, C and E) and in man (B, D and F). The photographs on the top (A and B) show post-mortem specimens from a dog and a human, respectively. The mitral valve leaflets are enlarged, thickened and display interchordal hooding (arrows). The jet lesion present on the atrial wall of the dog (arrowheads) result from impact of regurgitant jets of blood. The photographs in the center (C and D) show histology sections of the posterior mitral valve leaflet from a dog and a human, respectively. The sections are stained with PAS–Alcian blue–hematoxylin. In both valves, severe deposition of glycosaminoglycans (blue) and disrupted, disorganized collagen (pink) is seen. Scale bars: 1 mm. The electron micrographs on the bottom (E and F) are from a myxomatous mitral valve leaflet from a dog and a human, respectively. Collagen fibres are fragmented and show spiraling appearance in longitudinal sections (arrows). Cellular debris is seen in between the collagen bundles. Original magnification ×3500 (E) and ×27,000 (F). (B: courtesy of Ulrik Baandrup, MD, PhD; C: courtesy of Tomas Mow, DVM, PhD; D: courtesy of Lisbeth H. Olsen, DVM; F: reprinted from Ref. [10] with permission.)

With regard to pathological findings in the two species, the only major difference appears to be that humans are more prone than dogs to develop endocarditis as a sequela. In humans, endocarditis is found in approximately 10% of operatively excised, severely affected mitral valves [7,8]. In dogs, endocarditis is rare and when it does occur, it typically affects large breed dogs — not the small breed dogs which typically have MR [16].

3. Etiology and pathogenesis

In man, as well as in the dog, myxomatous mitral valve disease appears to be inherited. It has long been known that MVP in humans often displays familial transmission [17] and that MR due to myxomatous valvular disease is much more common in some dog breeds than in others [6,18]. Furthermore, it is known from two recent studies,
Fig. 1. (continued)
which each included dogs from only one breed, that parental MR status correlates strongly with offspring MR status [19] and that parental MVP status (degree of leaflet protrusion) correlates significantly with offspring MVP status [20]. With regard to the mode of inheritance, some reports state that primary MVP in humans is an autosomal dominant condition with age- and gender-dependent expression [17] whereas others argue in favor of a polygenic mode of inheritance [21]. Possibly several subtypes of the disease exist with different genetic background [22]. In dogs, the disease seems to have a polygenic mode of inheritance irrespective of whether it is assessed from the occurrence of MR or MVP [19,20].

In humans, primary MVP has often been speculated to be part of a generalized connective tissue abnormality [1–3,23]. Analogous with that, dog breeds predisposed to connective tissue disorders, such as intervertebral disc disease, collapsing trachea and ruptured cruciate ligaments, seem to be affected more frequently by myxomatous valvular disease than the general population [6,24]. And although segregation analyses performed in humans have excluded the involvement of the genes encoding collagen type I, III and V, the major types of collagen found in mitral valves [25,26], there are many other possible candidate genes encoding extracellular matrix proteins.

With regard to the pathogenesis of the progressive myxomatous degeneration, an often advanced theory is that it is a response to repeated impact to the leaflets. In support of that, the myxomatous changes begin along the line of apposition of the leaflets and progress in severity with advancing age. A recent echocardiographic screening of 190 clinically healthy Dachshunds (a breed in which 50% typically develops a regurgitant murmur before 10 years of age) disclosed a continuum of valvular changes, the degree of which correlated positively with age [20]. This was true irrespective of whether the disease severity was assessed by measuring leaflet thickness, degree of leaflet protrusion or regurgitant jet size. In further support of the response-to-injury hypothesis, humans with MVP and holosystolic murmurs (holosystolic regurgitant flow and with it, valvular shear stress) are known to have a higher risk of developing complications within a 5- to 10-year period than patients with murmurs of shorter duration who in turn have a higher risk than patients without murmurs [27–29].

Little is known about the vasoactive substances that mediate the subendothelial changes. By using autoradiography, it was recently found that angiotensin-converting enzyme and angiotensin II receptors — both present in rat mitral valve leaflets — were absent in both normal human, normal canine and diseased canine leaflets [30,31]. In contrast, a strong correlation was found between the endothelin-receptor density and the degree of disease in canine mitral valve leaflets, suggesting that endothelin plays a major pathogenic role [32]. Endothelin is known to play a major role in the pathogenesis of restenosis associated with percutaneous transluminal coronary angioplasty (PTCA), another condition in which endothelial damage leads to (comparable) subendothelial changes [33–35]. Further studies are needed to evaluate whether myxomatous human valve leaflets also display endothelin receptors and whether endothelin-receptor blockers, as in restenosis following PTCA [35,36], have protective effects.

### 4. Epidemiology and natural history

Age has a marked effect on the prevalence and severity of myxomatous mitral valve disease in the dog (Fig. 2A) [37]. The same is clearly the case in humans (Fig. 2B) [7], although this aspect has often been ignored. In many studies of MVP in man, allowance has not been made for the effects of age and the disease has not been graded.

![Fig. 2. Prevalence at post-mortem of different grades of myxomatous mitral valve disease shown as a function of age in unselected series of contrast, a strong correlation was found between the dogs (A) and humans (B). The graphs are based on data published by Whitney [37] and by Davies et al. [7]. Please note that different classifications were used in the two studies, although the valves were graded from 0 to 4 in both. The valvular changes were generally graded highest in the canine study.](https://academic.oup.com/cardiovascres/article-abstract/47/2/234/363875/72234308675?by=guest)
When allowance is made for this, it appears that myxomatous mitral valve disease is approximately ten times more common in dogs than in humans. Thus, marked changes are found at post-mortem in approximately 5–7% of old people and more than 50% of old dogs [6,7,9,37]. In some dog breeds, practically all dogs are affected. For instance, 50% of Cavalier King Charles (CKC) spaniels have a murmur due to MR by the age of 5–6 years and at 10 years of age, the prevalence of murmurs approaches 100% [38–40]. Echocardiographically, the majority of CKC spaniels have MVP [40,41].

In humans, as well as in the dog, myxomatous mitral valve disease is a slowly progressing disease which in most cases has a benign course. In the cases which develop into severe disease, this usually does not happen until old age. From studies in which humans with MVP have been followed for a mean period of 6–13 years, it appears that 5–10% develop severe MR requiring surgery [27,29,42,43]. However, a higher percentage would probably have been found in these studies had the patients been followed for a longer period and had only patients above a certain age, say 50 years, been included. Based on having followed 250 patients for an average period of 40 years, Chapman [44] estimated that ‘after the age of 50 about one fourth will undergo some form of surgical therapy’. In dogs, similar figures seem to apply: it has been estimated that 15–20% of CKC spaniels develop, before they are 10 years of age, MR severe enough to lead to spontaneous death or disease so intractable and severe that owners request euthanasia for the dog [24].

In the human, as well as the canine species, males have approximately twice the risk of females of developing severe disease with old age [7,8,15,19]. With regard to younger people, some studies show that both genders are equally affected whereas other studies document a female preponderance [45]. In that connection, it should be mentioned that leanness apparently can result in an otherwise normal valve displaying excessive leaflet protrusion. A high prevalence of such leaflet protrusion (usually without auscultatory evidence of MR) is found among ballet dancers [46] and patients with anorexia nervosa [47], in the latter seemingly because a reduced blood volume leads to decreased left ventricular volume and thereby ventriculo-valvular disproportion; the excessive leaflet protrusion disappears once the body weight and the left ventricular volume normalizes [47]. It has been found that lean men are just as likely to have excessive leaflet protrusion as lean women but that leanness is more common among women than men [48]. In young dogs, there appears to be no gender differences regarding the occurrence of either regurgitant murmurs or echocardiographic evidence of MVP [20,38–40]. With regard to influence of body weight, it has long been known that small dog breeds are affected more than large ones by myxomatous valvular disease [6,18] and, recently, an inverse relationship has been demonstrated between degree of MVP and body weight in a series of dogs coming from only one breed [40].

Several studies have documented that MVP in man is associated with a low anteroposterior chest diameter [49–51]. Recent findings show that there is also a relationship between MVP and a narrow chest in the dog. Thus, an echocardiographic screening of 190 Dachshunds disclosed a negative correlation between thorax circumference and degree of leaflet protrusion [20]. In addition to a repetition of this finding, thorax width was found to correlate inversely with regurgitant jet size and murmur intensity in a subgroup of the 190 Dachshunds (a progeny group of 92 dogs) [20].

### 5. Auscultatory findings

The auscultatory findings are highly dependent on the stage of the disease. In early stages, in which there is no or only mild MR, a clear midsystolic click is often found in humans [52–54]. A recent phonocardiographic study documented that midsystolic clicks also are common in CKC spaniels with early stages of the disease (Fig. 3) [55]. By auscultation, however, even highly experienced observers found only a few of these clicks, suggesting that midsystolic clicks in the dog generally have a low intensity [55]. Analogous with the situation in man, the few clicks that are found in the dog seem to be intermittent [55].

In humans as well as in dogs with MVP, a positive correlation has been documented between the degree of MR and murmur intensity [20,40,55–58]. In agreement with that, the likelihood of finding a systolic murmur increases with increasing degree of MR [55,56]. In addition to the degree of MR, it has been shown in both species, that the likelihood of detecting a systolic murmur is also highly dependent on the degree of observer experience and whether or not dynamic auscultation is performed [3,55,59]. With regard to the latter, it appears in humans and dog alike, that the ability of physical maneuvers to increase the murmur intensity depends on the provoked increase in heart rate [3,55].

The degree of MR relates not only to the intensity but also to the timing of the murmurs. In humans as well as in dogs, severe MR is associated with a holosystolic murmur whereas mild MR typically causes murmurs of shorter duration [52,54,55]. In humans with MVP and mild MR, such short murmurs are usually late systolic [52–54], the mechanism being that the ventriculo-valvular disproportion at some point in systole becomes severe enough to cause MR [3]. However, contrary to the impression given in most reviews and textbooks which only mention the late systolic murmur, 20–30% of humans with MVP and short regurgitant murmurs actually have early systolic murmurs [52–54]. In dogs with mild MR, the murmurs are typically early systolic; only a few dogs have a late systolic murmur and in those cases, it usually alternates with a holosystolic...
6. Two-dimensional echocardiography

Echocardiographically, it is possible to assess several different manifestations of myxomatous mitral valve disease, including leaflet thickness, degree of leaflet protrusion and degree of MR. By combining several quantitative or semiquantitative measurements, rather than mainly focussing on whether or not abnormal leaflet protrusion is present, a better assessment of valve status will likely be obtained. The risk of overdiagnosing mild protrusion of otherwise normal leaflets (e.g. in lean people) should be reduced as should the risk of underdiagnosing severely diseased, insufficient valves which only display mild protrusion, for instance because of secondary valvular fibrosis together with dilation and changed shape of the left ventricle and mitral annulus. That an incomplete picture is given by the simple assessment as to whether MVP is present or not when diagnosing myxomatous mitral valve disease in man, is illustrated by the fact that echocardiographic screenings, which utilize this type of assessment, typically show that the prevalence of MVP peaks shortly after adolescence and thereafter remains unaltered or decreases slightly with increasing age [61,62]. This impression is at odds with the fact that myxomatous degeneration increases markedly in prevalence and severity with increasing age (Fig. 2B).

In dogs, the hinge points of the two leaflets (imaged in Fig. 3. Simultaneous recording of electrocardiogram lead II (top), phonocardiogram with a nominal frequency of 50 Hz (middle), and phonocardiogram with a nominal frequency of 400 Hz (bottom) from a Cavalier King Charles spaniel with mild mitral regurgitation and mitral valve prolapse caused by myxomatous mitral valve disease. A midsystolic click (arrow) follows an early systolic murmur (M), S₁ = the first heart sound; S₂ = the second heart sound; paper speed = 50 mm/s. Reprinted from Ref. [55] with permission from the editor.

murmur [55]. In agreement with these auscultatory observations, it is unusual to find echocardiographic evidence of a midsystolic increase in the degree of leaflet protrusion in dogs. Species differences in the pattern of contraction of the left ventricle and mitral annulus could be one explanation why mild MVP typically is early systolic in the canine and late systolic in man, but further studies are needed to clarify this.

The ratio between the intensity of the first (S₁) and second (S₂) heart sound is higher in humans with early systolic prolapse than in both control subjects and humans with late systolic prolapse [60]. Analogous with this observation in humans, a positive correlation has been found between the presence and degree of MR (and thereby likely MVP, seeing that the presence and degree of MR correlates well with MVP severity [20]) and the S₁/S₂ ratio in clinically healthy CKC spaniels [58]. In humans with MVP, it has been speculated that those who have early systolic prolapse ... may have an accentuated first heart sound — a combination of normal components of S₁ with a superimposed click — as the valve is reaching its limit of prolapse coincident with S₁ [3].

7. Possible associations with other conditions

7.1. Changes in the circulating renin–angiotensin system

Humans and dogs with MVP appear to have a normal plasma renin activity (PRA), both in the supine position and after 10–15 min upright posture [63,71,72]. After
prolonged upright posture, however, young men with MVP syndrome (i.e. no significant MR but nevertheless symptoms such as chest pain, palpitations, dizziness and fatigue) were found to have a higher PRA than young men without MVP, possibly because of an increased sympathetic tone [71]. In dogs, sampled after a variable period of upright posture and other more indefinable stress, MVP also seems to be associated with a high PRA. Thus, CKC spaniels without murmurs (but practically always with MVP) generally have a higher PRA than less predisposed dogs [73]. And in clinically healthy Dachshunds, a positive correlation has been found between PRA and degree of MVP — not between PRA and degree of MR (allowing statistically for the effects of MVP) [63]. Thus, differences in the degree of MVP probably explains why CKC spaniels with mild, subclinical MR previously have been found to have higher PRAs than CKC spaniels without murmurs [74,75].

Humans with MVP syndrome have a normal plasma aldosterone concentration (PAC) in the supine position but in response to prolonged orthostatic stress or volume depletion with furosemide they exhibit a subnormal increase in aldosterone [71,72]. The reasons for this are unresolved but the observations agree with findings made in dogs. Thus, CKC spaniels without murmurs have a lower mean PAC than dogs from most other breeds [73]. Furthermore, a negative correlation was found recently between PAC and degree of MVP (allowing statistically for the degree of MR) in CKC spaniels with early stages of the disease [64]. In the same series of dogs, the degree of MR per se showed a positive correlation with PAC, indicating that the degree of MVP and the degree of MR have opposite effects on the PAC in dogs with subclinical myxomatous valvar disease. Whether this observation applies to humans with primary MVP remains to be investigated.

An inverse relationship has been found between the serum angiotensin-converting enzyme (ACE) activity and
the degree of MR in dogs with subclinical myxomatous valvular disease [64,75]. It remains to be clarified why there is such a relationship and whether it exists in humans with primary MVP.

7.2. Respiratory sinus arrhythmia

Humans with MVP have been found to have a higher degree of respiratory sinus arrhythmia than control subjects [68–70], a finding which is usually taken to reflect a relationship between MVP and autonomic dysfunction. Dogs generally have more pronounced sinus arrhythmia than humans and in dogs from predisposed breeds, it seems that the occurrence of severe sinus arrhythmia relates to the presence and severity of MVP [41,65].

7.3. Hypomagnesemia

A low magnesium status has been reported to be a common finding in humans with MVP syndrome [76–78]. Analogous with that, 50% of clinically healthy CKC spaniels with various degrees of MVP have been found to have hypomagnesemia [64]. It seems that the low magnesium status is not primarily due to a dietary deficiency since long-term oral magnesium supplementation does not fully correct the imbalance in either humans or CKC spaniels [64,76]. Interestingly, Dachshunds with MVP (which develop severe MVP/MR more slowly/rarely than CKC spaniels with MVP [39]) have been found to have a markedly lower prevalence of hypomagnesemia [63]. It remains to be clarified whether or not there is a relationship between magnesium status and prognosis and whether the above-mentioned breed-difference is a difference in magnesium status or only in the (small) plasma pool of magnesium [78].

Table 1
Comparison of human and canine myxomatous mitral valve disease

<table>
<thead>
<tr>
<th>Similarities</th>
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<tbody>
<tr>
<td>Pathology (macroscopic and microscopic)</td>
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<tr>
<td>Mitral valve prolapse is a common manifestation</td>
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<td>Strong genetic background (autosomal dominant or</td>
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<td>polygenic mode of inheritance)</td>
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<tr>
<td>Marked effect of age on prevalence and severity</td>
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<td>Associated with a low body weight and a narrow chest</td>
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<td>Slow progression; usually benign course</td>
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<tr>
<td>No major gender differences (except that males have higher risk than females of developing severe disease with old age)</td>
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<td>Auscultatory findings are highly dependent on physical maneuvers</td>
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<td>Often associated with a high renin/low aldosterone profile, pronounced respiratory sinus arrhythmia, hypomagnesemia and platelet abnormalities</td>
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<td>Differences</td>
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<td>Approximately ten times more prevalent in dogs than in humans</td>
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<td>Humans are more prone than dogs to develop endocarditis as a sequela</td>
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<td>Systolic clicks are difficult to perceive in the dog</td>
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<tr>
<td>Mild regurgitation is usually early systolic in the dog, late systolic in man</td>
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7.4. Platelet activation

Platelets have been found to be activated and to have a shortened life-span in humans with MVP [79,80], a finding which apparently relates to MR rather than to MVP per se [81,82]. The finding that clinically healthy CKC spaniels often have thrombocytopenia and enlarged platelets (suggesting increased platelet consumption and thrombopoiesis) indicates that platelet abnormalities may also be a feature of the disease in dogs [83,84]. In future studies on this topic in humans as well as in dogs, attention should be paid also to magnesium status — hypomagnesemia is known to cause platelet activation [85,86].

8. Concluding remarks

As summarized in Table 1, canine myxomatous mitral valve disease has a strong resemblance to primary MVP in man. Knowledge about the canine disease may help to increase the understanding of the disease in humans. The shorter life-expectancy of dogs, for instance, makes it much easier to realize the important influence that age has on the disease. Also, the occurrence in specific dog breeds makes it easier to perceive and investigate the existence of different subtypes of the disease. Finally, specific findings, e.g. that a strong correlation exists between the endothelin-receptor density and the degree of valvular changes, could lead to an increased understanding of the disease in man.

The dog could also prove to be a valuable model with regard to finding better ways of treating myxomatous mitral valve disease in humans. Since it takes a few years rather than a few decades before a significant proportion of mildly affected individuals develop severe disease, it would be feasible to perform clinical trials aimed at evaluating the effect of different drugs on disease progression. It would also be possible to test new surgical techniques on diseased valves. Seeing that the disease has a strong genetic component, it should be practicable to establish lines of highly diseased dogs.

Finally, while this paper has highlighted the potential usefulness of the canine disease as a model of disease in man, there are situations where the presence of MVP in dogs will be undesirable. Thus, the possibility that dogs purpose-bred for research may have myxomatous valvular disease should be borne in mind. Both authors have observed that MVP, on a rough estimate, affects 10–20% of purpose-bred Beagle dogs.

References


