

ECHOCARDIOGRAPHIC ASSESSMENT OF 537 DOGS WITH MITRAL VALVE PROLAPSE AND LEAFLET INVOLVEMENT

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In this work we investigated which mitral valve leaflet was most often involved in mitral valve prolapse with degenerative mitral valve disease and whether there was an association with breed, age, gender, or weight. Five hundred and thirty-seven dogs with mitral valve prolapse-degenerative mitral valve disease were assessed; the cross-breed dog was the most represented breed (248 dogs, 46.2%). Mitral valve prolapse was more common in male dogs, and the average age was 11.3 ± 2.8 years. Prolapse of the anterior leaflet was present in 48.4% of dogs, prolapse of the posterior leaflet in 7.1%, and bileaflet prolapse was present in 44.5%; this distribution is different than that typically found in humans. There was a significant correlation between severity of mitral regurgitation and severity of mitral valve prolapse or ISACHC class, and between severity of mitral valve prolapse and ISACHC class. There was no relationship between the particular affected leaflet(s) and severity of mitral regurgitation, severity of mitral valve prolapse, or ISACHC class. Our findings suggest that the susceptibility to the mitral valve prolapse-degenerative mitral valve disease is not confined to a specific breeds and that the specific leaflet prolapsing is different in dogs compared with humans. *Veterinary Radiology & Ultrasound*, Vol. 50, No. 4, 2009, pp 416–422.

Key words: degenerative mitral valve disease, dog, echocardiography, leaflet prolapse, mitral valve prolapse.

Introduction

NORMAL MITRAL VALVE leaflets appose in the left ventricle.^{1–3} With mitral valve prolapse there is displacement of the mitral valve leaflets during ventricular systole to the atrial side of the mitral annulus.^{2–7} Mitral valve prolapse may be part of degenerative mitral valve disease, defined as primary chronic progressive myxomatous degeneration in the valvular apparatus leading to thickening and nodular proliferation on the valvular leaflets and chordae tendineae that may cause valvular insufficiency.^{3,8–16} In this paper mitral valve prolapse associated with degenerative mitral valve disease is referred to as mitral valve prolapse-degenerative mitral valve disease.

Degenerative mitral valve disease is the most common acquired cardiac disease in dogs and is the third most common cause of death in this species.^{9,17,18} Advanced age and male gender are known risk factors.^{2,3,10,19} Degenerative mitral valve disease commonly affects small and deep-chested

breeds such as Miniature Poodles, Miniature Schnauzers, Chihuahuas, Dachshunds, and Small Terriers. Small breeds such as the Cavalier King Charles Spaniel and Dachshund are prone to develop mitral valve prolapse^{10–13,20–22} as part of degenerative mitral valve disease, and in these breeds it has also been reported in young animals.^{10–14,20,23,24} Mitral valve prolapse associated with degenerative mitral valve disease occurs in German Shepherds,²⁵ but the presence of this combination in cross-breed dogs has not been reported.

When mitral regurgitation develops in degenerative mitral valve disease it may lead to left atrioventricular volume overload, pulmonary edema, atrial dilation, and supraventricular arrhythmias. Occasionally, in advanced heart disease, myocardial failure, and pulmonary hypertension may result. In degenerative mitral valve disease, mitral valve prolapse may precede the development of mitral regurgitation, however, mitral regurgitation may be present without mitral valve prolapse.^{3,4,8,26,27}

In humans, mitral valve prolapse can be primary when it is part of a generalized connective tissue abnormality and pathologically shares similarities with degenerative mitral valve disease in dogs.^{8,9,11} In humans, primary mitral valve prolapse may involve the anterior, the posterior, or both leaflets,^{28,29} with the posterior leaflet more commonly involved whereas sole involvement of the anterior leaflet is rare.^{8,29,30} In dogs, the frequency of prolapse of the particular valve leaflets has not been investigated. In dogs mitral valve prolapse-degenerative mitral valve disease occurs

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more frequently in males,^{11,13,14,22} but there are no data regarding the influence of the neutering on its prevalence. There are no reported studies that deal with the relationship of mitral valve prolapse with other echocardiographic measurements or the effect of mitral valve prolapse on the clinical status of the patient.

The purpose of this study was to assess which mitral valve leaflet was most often involved in mitral valve prolapse-degenerative mitral valve disease, and to examine the influence of breed, age, gender, weight and clinical, and echocardiographic data on mitral valve prolapse-degenerative mitral valve disease.

Materials and Methods

Five hundred and thirty-seven dogs with mitral valve prolapse-degenerative mitral valve disease were assessed. Dogs were referred either to the University of Milan (286 dogs) or to the Centro Medico Veterinario Cellatica (251 dogs) between January 1, 2004, to December 30, 2006. The most common breeds were cross-breed dogs (248 dogs, 46.2%), Poodle (59 dogs, 11%), Yorkshire Terrier (34 dogs, 6.3%), Dachshund (31 dogs, 5.8%), and Shih Tzu (28 dogs, 5.2%). The criteria used for the selection of the 537 dogs were (1) diagnosis of mitral valve prolapse with valve thickening and/or nodular proliferations, (2) presence of a systolic mitral regurgitant jet, and (3) echocardiographic, clinical, radiographic, and electrocardiographic data recorded in the computerized database. Exclusion criteria were other congenital or acquired cardiac disease and echocardiographic evidence of Dirofilaria.

All dogs were examined with an AU3 Partner, Esaote Biomedica, or with a Pie Medical 300 S Pandion Vet Echocardiograph with 2.5–3.5, 3.5–5, 7.5–10 MHz mechanical phased array transducers or with Esaote Megas CVX and GPX (2.5–3.5, 3.5–5, 5–7.5 MHz phased array transducers) from multiple standard windows.^{31–33} The dogs were scanned through an aperture in the table. None of the dogs were sedated and when the patient was cooperative, continuous ECG monitoring was carried out. Mitral valve prolapse was assessed in the right parasternal long axis four–five chamber views.

When a clear image of the mitral valve was obtained, mitral valve prolapse was assessed at the end of the QRS complex of the ECG corresponding to protosystole.^{2,3,31,32} The clearest still-frame of protrusion of the leaflet margins across the mitral annulus was chosen.^{3,34,35} This method was selected because tracing the thickened leaflet tip was difficult.

In noncooperative patients, the protosystolic event was identified from the observation of mitral valve closure at the beginning of systole in the two-dimensional (2D) mode, which corresponded with the first frame in which mitral valve closure was evident. The hinge points of the two leaflets were used to define the position of the leaflets rel-

ative to the mitral annulus.^{2,3,31,32} The degree of mitral valve prolapse was classified as follows^{7,12,13}: line P was a line between the hinge points of the two leaflets illustrating the borderline between no prolapse and mild prolapse; line T was a line from the middle of the elliptical echogenic area at the lower part of the atrial septum to the atrioventricular junction, illustrating the borderline between mild and severe prolapse. Following these criteria, mild mitral valve prolapse was a leaflet protruding to the atrial side of line P, moderate mitral valve prolapse was a leaflet protruding between line P and line T, and severe mitral valve prolapse was a leaflet prolapsing over line T. The anatomic leaflet(s) that was prolapsing was noted (Fig. 1).

The classification of the regurgitant jet was according to the guidelines of the American Society of Echocardiography.³¹ When prolapse was assessed, the regurgitant jet was visualized with color Doppler and the initial jet direction was observed immediately behind the point of mitral leaflet coaptation. To determine the maximal regurgitant area in any view, the transducer was carefully panned to achieve the largest jet area. The regurgitant flow was aligned with the ultrasound beam and this was often achieved in the left apical four-chamber view. The grade of mitral regurgitation was assessed semi-quantitatively by studying color Doppler velocity and the jet direction, jet width, and area of the regurgitant jet. Doppler intensity and the shape of the regurgitant jet were obtained by continuous wave Doppler examination, and the mitral valve E wave velocity was measured using pulsed wave Doppler. When the operators considered all data, mitral regurgitation grade was classified as mild, moderate, or severe.

The intraobserver and interobserver variability were assessed. For all echocardiographic measurements in this study, in accordance with previous data,⁷ both the intraobserver and interobserver variability were < 10%.

Data were analyzed using an SPSS database (SPSS-10).^{*} All values are reported as the mean \pm SD, unless otherwise specified. One way analysis of variance and χ^2 tests were used to compare the qualitative echocardiographic grading of mitral regurgitation, leaflet involvement, and severity of mitral valve prolapse with signalment, clinical, and echocardiographic data. The Mann–Whitney *U* test was used to compare characteristics between different groups. To examine univariate associations between epidemiologic, clinical, and echocardiographic variables, Spearman correlation coefficient (ρ) was used. Statistical significance level was set $P < 0.05$.

Results

The percentage of intact male dogs with mitral valve prolapse-degenerative mitral valve disease (57.5%, $n = 309$)

^{*}SPSS 10: Statistical Package for the Social Sciences (Windows).

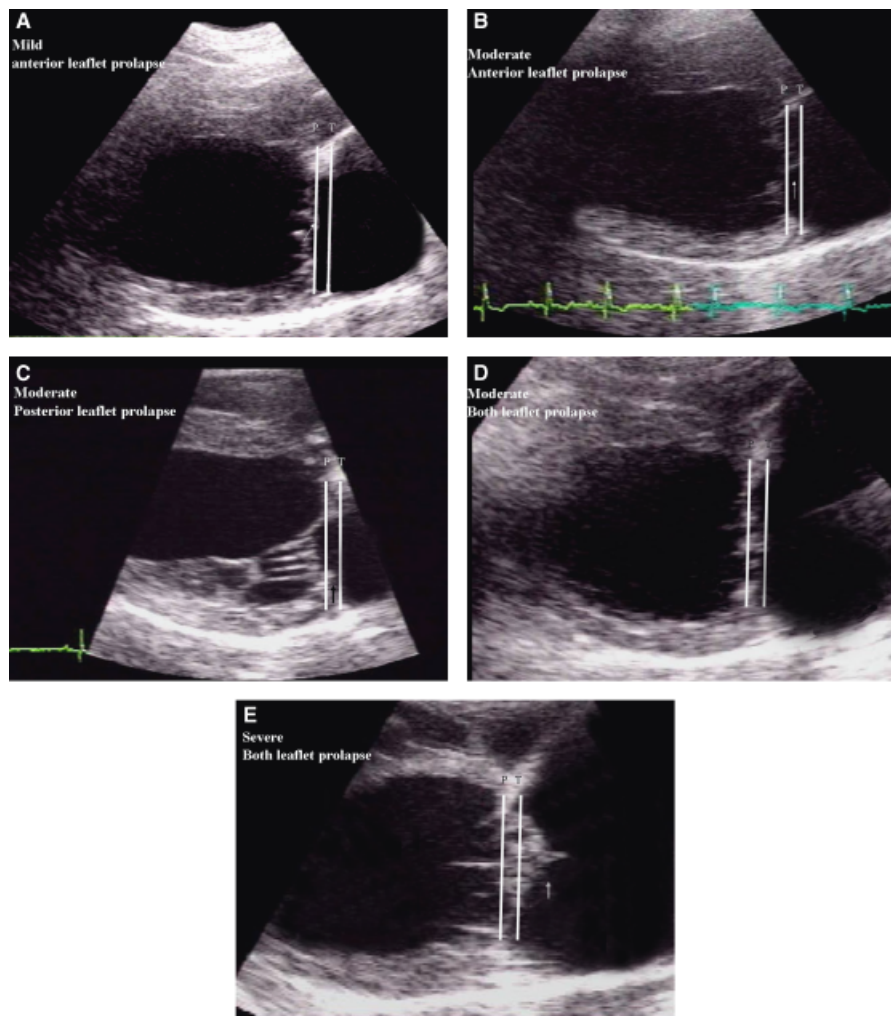


FIG. 1. (A, B, C, D, E) Right parasternal long axis four-chamber view: (A) Mild mitral valve prolapse was assessed by the protrusion of one of both leaflets to line P. (B, C, D) Moderate mitral valve prolapse was assessed by the protrusion of one or both leaflets between line P and line T; In D note also the thickening of cordae tendinae. (E) Severe mitral valve prolapse was assessed by the protrusion of one or both leaflets over line T. The arrows outline the severity of mitral valve prolapse and the affected leaflet.

was similar to the number of male dogs in the general population of dogs presented to the clinics (58%). However, the percentage of neutered females with mitral valve prolapse-degenerative mitral valve disease (25%, $n = 134$) was higher than the general population of neutered female dogs seen at both clinics (9%).

In 370 dogs (68.9%) degenerative changes were present only in the mitral valve apparatus while in the remaining 167 dogs (31.1%) with mitral valve prolapse-degenerative mitral valve disease concurrent degenerative changes were evident in the mitral and tricuspid valves (Table 1). There was a similar distribution of involvement of the anterior and both leaflets of the mitral valve among the five most represented breeds. Poodles had a relative frequency of prolapse of the anterior leaflet higher than the other breeds ($P = 0.038$) (Fig. 2).

The anterior leaflet of the mitral valve was involved in 259 dogs (48.2%), 167 of which were male dogs (31.1%), including 16 neutered males, and 92 females (17.1%), 67 of which were neutered. The posterior leaflet was involved in 40 dogs (7.5%), 26 male dogs (4.9%) including two that were neutered, and in 14 females (2.6%), including eight that were neutered. Both anterior and posterior leaflets were affected in 238 dogs (44.3%), 154 of which were male dogs (28.7%), including 20 that were neutered, and in 84 females (15.6%) including 59 that were neutered ($P = 0.924$) (Fig. 3). No statistically significant difference in age was noted among the groups ($P = 0.224$).

There was a moderate correlation between the severity of mitral regurgitation and the severity of mitral valve prolapse ($\rho = 0.608$, $P < 0.001$). A higher correlation was found between severity of mitral regurgitation and

TABLE 1. Clinical and Echocardiographic Data of the 537 Dogs Affected by Mitral Valve Prolapse–Degenerative Mitral Valve Disease

	Dogs Population
MVP–DMVD	537
MVP–DMVD (lesions only on the mitral valve)	370 (68.9%)
MVP–DMVD (lesions also on the tricuspid valve)	165 (31.1%)
ISACHC Class I	321 (59.8%)
ISACHC Class II	187 (34.8%)
ISACHC Class III	29 (5.4%)
Mitral regurgitation grade:	
Mild	133 (24.8%)
Moderate	199 (37.1%)
Severe	205 (38.1%)
Severity of mitral valve prolapse:	
Mild	153 (28.5%)
Moderate	236 (43.9%)
Severe	148 (27.6%)

ISACHC class ($\rho = 0.718, P < 0.0001$), but only a fair correlation between severity of mitral valve prolapse and ISACHC class ($\rho = 0.504, P < 0.001$). There was no significant correlation between the particular affected leaflet and mitral regurgitation grade or severity of prolapse. No significant correlation was found between the particular leaflet(s) affected and ISACHC class ($P > 0.4$).

Discussion

In this assessment, we found that the anterior leaflet was the most frequently affected by prolapse and sole involvement of the posterior leaflet was uncommon. Although

cross-breed dogs were not the highest represented breed in the general clinical population, the incidence of mitral valve prolapse-degenerative mitral valve disease in cross-breed dogs was higher than in the pure-breeds. Mitral valve prolapse-degenerative mitral valve disease was common in intact male dogs ($n = 309; 57.6\%$), but this was not surprising because intact males comprised approximately 58% of the general population of both clinics. Interestingly, there was also a high frequency of mitral valve prolapse-degenerative mitral valve disease among neutered females ($n = 134; 25\%$). This has not been reported. In the general population of both clinics, neutered females were not the predominant gender (9%) and there was a higher distribution of neutered females affected by mitral valve prolapse-degenerative mitral valve disease than entire females. Further studies are warranted to establish possible involvement of a hormonal influence in the development of mitral valve prolapse.

It is proposed but not proven that mitral valve prolapse may be the precursor of degenerative mitral valve disease.²⁷ However, an alternative proposal is that mitral valve prolapse and the associated degenerative mitral valve disease are unrelated familial lesions that may be present with greater prevalence in specific breeds.^{27,36} Chronic degenerative changes may be confined to the mitral valve or may also affect the tricuspid valve.^{3,9,27} In our study, 68.9% ($n = 370$) of dogs had only mitral valve prolapse-degenerative mitral valve disease lesions, and the remainder (31.1%, $n = 165$) had tricuspid valve thickening as well, either with or without tricuspid valve insufficiency.

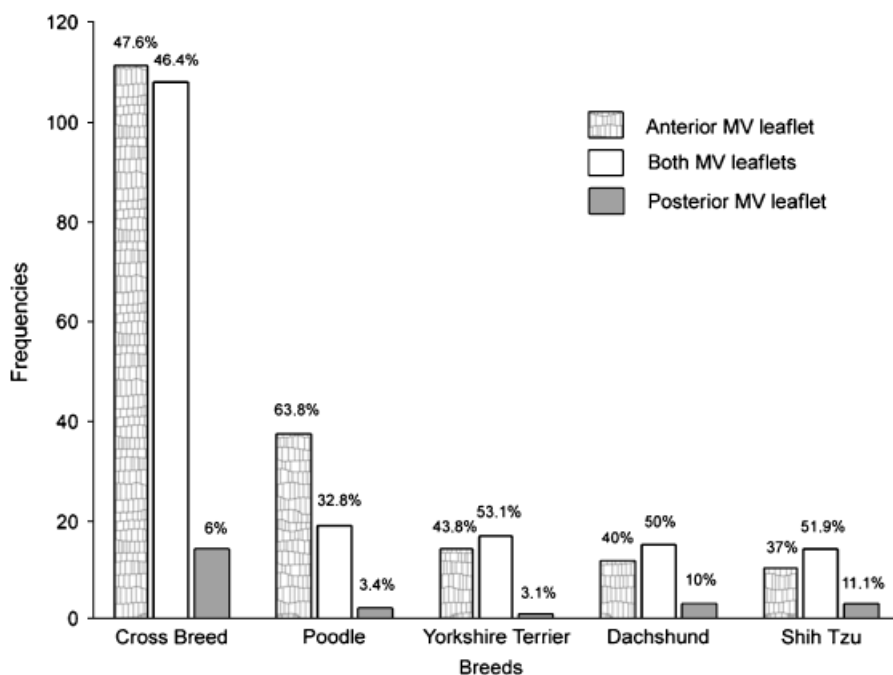


FIG. 2. Distribution of the affected mitral valve leaflet for the five most represented breeds.

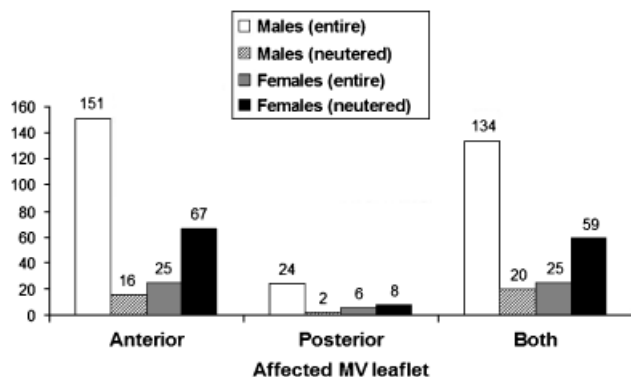


FIG. 3. Distribution of mitral valve leaflet involvement according to gender.

Two-dimensional echocardiography has been used routinely for many years for the diagnosis of mitral valve prolapse in both humans and dogs.^{2,3,7,13,34} For assessment of mitral valve prolapse in dogs, the right parasternal long axis four-chamber view is reasonably accurate, having a low day-to-day variability and good intra- and interobserver repeatability.^{2,3,7,12,13} In humans, mitral valve prolapse may be assessed in the long axis five-chamber view because the plane of the mitral annulus is defined mainly by a line extending from the base of the aortic valve to the atrioventricular junction and the long axis five-chamber view allows good visualization of the mitral and aortic valves.^{6,31} In both species, in the left parasternal apical view the valve leaflets may appear artifactually thick if the transducer is not properly aligned, and in humans this may lead to a misdiagnosis of mitral valve prolapse because of the saddle shape of the mitral valve annulus.^{6,8}

Short axis, cross sectional views of the valve are useful for identifying large lesions of the mitral valve, but can be misleading in identifying small lesions.^{2,3,37}

Although not the same disease, mitral valve prolapse-degenerative mitral valve disease in dogs and primary mitral valve prolapse in humans have similarities including an autosomal dominant polygenic mode of inheritance, a marked effect of age on prevalence and severity, higher incidence in low body weight and narrow chest individuals, slow progression to degenerative mitral valve disease, and no major gender differences, except that males have a higher risk than females of developing severe disease with old age.^{3,4,8,9,11,20,28,36,38} On the other hand, differences include a 10 times higher tendency for development of degenerative mitral valve disease in dogs than in humans, a greater tendency to develop endocarditis in humans than in dogs, and systolic clicks commonly found in humans but rarely in dogs. Finally, mild mitral regurgitation associated with degenerative mitral valve disease usually occurs in early systole in the dog, but in late systole in humans.^{11,27}

In humans primary mitral valve prolapse may be caused by mechanisms unrelated to degenerative mitral valve dis-

ease and then the condition would be referred to as secondary mitral valve prolapse. Secondary mitral valve prolapse may be due to rupture of papillary muscle due to myocardial infarction, rupture of tendinous chords due to bacterial endocarditis, abnormal wall motion in the setting of myocardial ischemia that may result in prolapse of a segment of valve leaflet in the dyskinetic area of the left ventricle. Also, a relatively high proportion of fit young individuals may have minor upward movement of a mitral valve leaflet and there is disagreement whether this should be called echo-prolapse or physiologic prolapse.⁸ In dogs, mitral valve prolapse has been mainly reported as part of degenerative mitral valve disease.^{3,9,12-15,20,24}

Findings typical of early degenerative mitral valve disease include elongated chordae tendineae and enlarged thickened mitral valve leaflets with areas of prolapse toward the atrial side; this may be present in dogs with or without mitral regurgitation,^{2,3,10,14,34} particularly in young Cavalier King Charles Spaniels.^{12,14} In our study the number of Cavalier King Charles Spaniels was small, precluding conclusions regarding this breed.

We found a fair correlation between the severity of mitral valve prolapse-degenerative mitral valve disease and grade of mitral regurgitation and this is in accordance with the findings of others.^{12,14} No correlation was found between the leaflet(s) prolapsing and the severity of mitral regurgitation. The relationship between the particular leaflet involved and the degree of prolapse has not been previously reported. In 2000 autopsies in humans, prolapse of the anterior leaflet was found in 10% of subjects, the posterior leaflet in 67% of subjects, and bileaflet prolapse in 23% of subjects.^{8,30} These findings contrast with ours in that there was prolapse of the anterior leaflet in 48.2% of dogs, posterior leaflet prolapse in only 7.5%, and bileaflet prolapse in 44.3% of the dogs. This difference in leaflet prolapse may be due to differences in the morphology of the mitral valve apparatus. In the dog, the annular attachment of the anterior leaflet circumscribes two-thirds of the annulus and is about twice that of the posterior leaflet, while in humans it is the converse.^{1,3,27,39} Also, the larger the leaflet, the greater the response to the jet impact. The progression of mitral valve lesions, may be due to repeated impact of the regurgitant jet on the leaflets and high shear forces on the endocardial surface, conditions that promote growth of fibrous tissue.^{2,3,9,11} Also, in humans, prolapse of the mitral valve occurs in association with a variety of connective tissue disorders, craniofacial skeletal deformities, and congenital thoracic deformities such as straight back and pectus excavatum.^{4,8,38} Little is known about such associations in dogs.⁹

Knowing which leaflet is affected by prolapse may have significant clinical implications. In humans with mitral valve prolapse-degenerative mitral valve disease, the repair of a prolapsed posterior leaflet is more durable and more

satisfactory than the repair of an anterior leaflet.²⁹ Although mitral valve repair in dogs is not routinely performed, valve replacement, insertion of a purse string suture to reduce the enlarged mitral orifice, or plication of the redundant leaflet may be useful.^{27,40}

Based on experimental studies in dogs, a certain severity of mitral regurgitation occurred when the prolapse of the anterior leaflet was more severe than prolapse of the posterior leaflet. Our results, however, suggest there is no significant correlation between a particular prolapsed leaflet and mitral regurgitation grade or severity of prolapse. Furthermore, there is no significant correlation between any specific prolapsed leaflet and ISACHC class.

Limitations of our work include the following. Our study was based on data from transthoracic echocardiograms. More accurate information regarding the mitral valve can be obtained from 2D or 3D transesophageal echocardiography.^{41,42} The number of dogs in four of the five most represented breeds in this study is relatively small and prevents definitive conclusions about the propensity of partic-

ular leaflet involvement. The right parasternal long axis four-chamber view may not be adequate for accurate assessment of mitral valve prolapse in dogs and one must keep in mind that the identification of lesions depends on gain and depth, which are transducer dependent.^{2,3,7,14,24,32} Although one could argue that in both dogs and humans even normal valves may billow to a certain extent into the left atrium, in our experience the standard techniques are reasonably accurate in the assessment of mild, moderate, and severe mitral valve prolapse.^{7,12,14} Finally, our findings were not confirmed with surgical or postmortem data.

In conclusion, our main finding was the difference in the leaflet predominantly affected by mitral valve prolapse-degenerative mitral valve disease in dogs compared with humans with primary mitral valve prolapse. We also found that cross-breed dogs were commonly affected with mitral valve prolapse-degenerative mitral valve disease, and this condition may not be confined to specific breeds such as King Charles Cavalier Spaniel, Dachshund, or German Shepherd.

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