Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration

Survival Characteristics and Prognostic Variables of Dogs with Preclinical Chronic Degenerative Mitral Valve Disease Attributable to Myxomatous Degeneration

Authors:

M. Borgarelli,
Department of Clinical Sciences, Kansas State University, Manhattan, KS
S. Crosara,
Department of Clinical Sciences, Kansas State University, Manhattan, KS
K. Lamb,
Dip. Patologia Animale, University of Torino, Torino, Italy
P. Savarino,
Department of Clinical Sciences, Kansas State University, Manhattan, KS
G. La Rosa,
Department of Clinical Sciences, Kansas State University, Manhattan, KS
A. Tarducci,
Department of Clinical Sciences, Kansas State University, Manhattan, KS
J. Haggstrom
Chronic Disease Research Group, Minneapolis, MN

Funding Information
This work was started at Dip Patologia Animale, University of Torino. Analysis of data has been performed at Kansas State University.

Corresponding author: Michele Borgarelli, A-106 Mosier Hall, Department of Clinical Sciences, Kansas State University, Manhattan, KS 66506; e-mail:, mborgarelli@gmail.com.

Abstract

Background: Preclinical myxomatous mitral valve degeneration (MMVD) includes a heterogeneous group of dogs. Therefore, identifying risk factors for progression of the disease is of clinical importance.

Objectives: To investigate survival time and risk factors for clinical and echocardiographic variables taken at initial examination for clinical progression in preclinical MMVD dogs.

Animals:A total of 256 dogs with stage B1 or B2 MMVD.

Materials and Methods: Medical records of 256 dogs with preclinical MMVD were reviewed retrospectively. Long-term outcome was assessed by telephone interview. Dogs alive at the time of phone interview were asked to return to the hospital for re-evaluation of their cardiac status.

Results: Seventy of 256 (27.3%) dogs died during the observation period. The median survival time, regardless of cause of death, was 588 (range 75–1,668) days. The presence of a murmur was associated with an increased risk of death (AHR 2.14; 95% CI 1.12, 4.11; $P = 0.022$). Thirty (12%) deaths were considered cardiac related. LA/Ao > 1.4 was the only negative predictor (AHR 2.64; 1.13, 6.13; $P = 0.024$) for cardiac-related deaths. Eighty-three dogs were re-examined, of which 34 progressed to a more advanced stage of MMVD. The presence of Emax > 1.2 (AHR 2.75; 95% CI 1.01, 7.48; $P = 0.047$) and cough (AHR 7.89; 95% CI 3.18, 20.07; $P < 0.001$) were significant in the multivariate analysis.

Conclusions and Clinical Importance: Preclinical MMVD represents a relatively benign condition in dogs. Clinicians might find stratification of this dog population according to risk factors based on clinical and echocardiographic findings helpful in determining treatment.

Abbreviation:

AHR
: adjusted hazard ratio

CI
: confidence interval

FS
: fractional shortening

HF
: heart failure

EDDn
: normalized end diastolic diameter

ESDn
: normalized end systolic diameter

EDV-I
: end diastolic volume index

Edt
: E wave deceleration time

E-max
: peak velocity of E-wave

E/A
: ratio between peak velocity of E and A waves

HR
: hazard ratio

LA/Ao

left atrium aortic root ratio

MMVD

myxomatous mitral valve degeneration

MVP

mitral valve prolapse

MR

mitral regurgitation

Chronic degenerative mitral valve disease as a result of myxomatous degeneration (MMVD) represents the most common acquired cardiovascular disease in the dog.[1] The prevalence of MMVD is associated with age and breed.[2-6] The disease is characterized by a long preclinical period. Many dogs die for other reasons and never progress to heart failure (HF).[7] However, dogs with preclinical MMVD are a very heterogeneous group of animals. Some of these animals are affected by relatively mild disease, whereas others have a more advanced stage of the disease and will likely develop clinical signs of HF. To properly provide preventative care to this heterogeneous group of animals, clinicians must be able to identify risk factors for HF and cardiac death. Few studies in veterinary medicine have aimed to identify possible risk factors associated with progression of the MMVD. In dogs affected by MMVD at different stages, the proposed prognostic indicators include age,[3, 5] sex,[8, 9] intensity of heart murmur,[10] degree of mitral valve regurgitation,[11] left atrial enlargement,[7] changes in radiographic or echocardiographic cardiac dimensions observed between 2 different time points,[12] and increased N-terminal fragment of proBrain Natriuretic Peptide (NT-proBNP).[13, 14]

The aims of the present study were to estimate the survival times in dogs with preclinical MMVD (stages B1 and B2 according to ACVIM consensus)[15] and to assess the prognostic value of clinical and echocardiographic variables on progression and survival.

Materials and Methods

Study Population

The medical records of dogs examined at the Veterinary Teaching Hospital, College of Veterinary Medicine of Torino, Italy, between January 2001 and December 2006 were reviewed. From these records, 256 cases diagnosed with preclinical MMVD were identified. All dogs presented for a cardiology consultation because of previous identification of a heart murmur, other clinical signs, or both, possibly indicating a cardiovascular disorder including cough, exercise intolerance or syncope, or both.

Inclusion Criteria

To be included in the study, dogs required a documented physical exam and echocardiogram. Each dog had to meet the following echocardiographic inclusion criteria: 2-D echocardiographic detection of mitral valve prolapse (MVP) and/or any degree of mitral valve leaflet thickening; color Doppler identification of any degree of mitral valve regurgitation; and M-mode left ventricular fractional shortening (FS) greater than 20%. Finally, the dog owners had to be available for a telephone interview and willing to bring their dog for a cardiovascular re-evaluation including a physical exam, x-ray, and echocardiogram.

Exclusion Criteria

Dogs were excluded if they had congenital heart disease or acquired cardiovascular disorders that directly or indirectly affected the mitral valve or its function, such as bacterial endocarditis or dilated cardiomyopathy. Dogs with mitral endocarditis were excluded based on clinical findings and the lack of obvious large vegetative lesions with heterogeneous appearance, as detected by echocardiography.[16] Dilated cardiomyopathy was excluded based on the presence of valve changes consistent with MMVD and MVP and the absence of echocardiographic criteria such as an FS less than 20%.[17] Finally, we excluded dogs with past or present documented HF and dogs with clinical signs, such as cough or syncope, that were considered related to MMVD.

Baseline Data

Data obtained from case records were breed, sex, age, body weight, presence of heart murmur, presence of cough, history of syncope, presence of arrhythmia, and baseline treatment. Echocardiographic data retrieved were normalized end diastolic (EDDn) and end systolic diameter (ESDn),[18] end-diastolic volume index (EDV-I)[19], description of mitral valve leaflet morphology (prolapse and/or thickening of cranial, caudal, or both), left atrial to aortic root ratio (LA/Ao) and trans-mitral flow data. The latter included peak E-wave (Emax) velocity (early filling), E-wave deceleration time (Edt) and the ratio between Emax and peak A-wave (late filling) velocity of transmitral flow (E/A ratio). In each dog, based on clinical signs, thoracic radiographs and echocardiographic findings, the stage of MMVD was classified according to the ACVIM consensus.[15] Dogs were classified as stage B1 if they had a normal or equivocal enlarged left atrium and/or left ventricle, defined as an LA/Ao ratio ≤ 1.4 and/or an EDDn > 1.73 and an EDV-I ≤ 100 mL/m2. Dogs were classified as stage B2 if the LA/Ao > 1.4 and/or the EDDn > 1.73 and EDV-I > 100 mL/m2.[15] All clinical datasets were reviewed by a single experienced investigator (MB).

Echocardiography

All dogs had previously undergone a complete echocardiographic examination, which included transthoracic 2-D, M-mode, spectral, and color flow Doppler. Transducer arrays of 5.0–7.5 and 2.5–3.5 MHz were used. The dogs were conscious and unsedated during the examinations. Right parasternal M-mode recordings were obtained from short-axis views with the dogs positioned in right lateral recumbency, and the 2-D echocardiograms were obtained in accordance with techniques described elsewhere.[20, 21]

The presence of MVP and mitral valve thickening was evaluated from the right parasternal long-axis, the right parasternal 4-chamber view, and the left apical 4-chamber view. MVP was defined as any systolic displacement of one or both mitral valve leaflets basal to the mitral annulus observed in at least

2 of these views.[3] The presence of mitral valve regurgitation (MR) was evaluated by color Doppler in the right parasternal long-axis and left apical views.

Echocardiographic Measurements

One of 3 investigators (MB, SC, PS) made all echocardiographic measurements. One experienced investigator (MB) reviewed the echocardiograms with videotape or digital recordings. M-mode measurements were obtained according to the leading-edge-to-leading-edge method. The LA/Ao was obtained from the 2-D short-axis view.[22] End diastolic volume was calculated according to the Teichholz M-mode formula,and the values were indexed to body surface area.[19] The EDV-I was used only for classification purposes and not analyzed as a variable in the statistical analysis. EDDn and ESDn were calculated according to Cornell's equations: EDDn = EDD/BW0.294 and ESDn = ESD/BW0.315.[18]

Clinical Progress and Survival

Trained senior veterinary students conducted telephone interviews with the dog owners to determine the clinical progress of each dog as previously described.[7] The interview results were recorded electronically. The questionnaire consisted of questions with a definite number of possible answers, most commonly yes/no. The interviewer was not blinded to the clinical status of the dog at the initial examination. The owner was asked if the dog was dead or alive. If the dog was dead, the owner was asked if the dog had been euthanized or died spontaneously, the reasons for euthanasia, and in case of spontaneous death, the possible causes, including cardiac-related sudden death, presence of syncope, or progression of HF. Cardiac-related death was defined as death occurring due to progression of the clinical signs of HF. Dogs euthanized because of refractory HF were categorized as having cardiac-related deaths. Separate survival analyses were performed for all causes of deaths, cardiac-related deaths alone, and on clinical progression.

Dogs alive at the time of phone interview were asked to return to the hospital for a cardiovascular re-evaluation including a physical exam, thoracic radiographs, and echocardiogram. When the original diagnosis occurred more than 1 year before the end of the observation period, dogs were asked to return for re-examination. At the end of re-examination, the dogs were considered “stable” if the severity of the MMVD stage did not change. The dogs were considered “progressed” if the severity of the MMVD advanced to the next stage of the disease.

Statistical Analysis

Normal distribution of data was assessed by way of visual assessment from a univariate procedure. Data were reported as the median and (range). Descriptive statistics were used for sex, age, body weight, the presence of heart murmur, syncope, class of HF, and all 2-D, M-mode, and Doppler-derived variables. Effects on survival of the following 13 clinical, echocardiographic, and Doppler variables at baseline were evaluated: age > 8 years, sex, weight > 20 kg, presence of cough, presence of syncope, presence of murmur, affected mitral valve leaflet, LA/Ao > 1.4, EDDn > 1.73, ESDn > 1.14, E max > 1.2, Edt > 80 ms, E/A ratio > 2. Continuous variables were redefined as categorical based on previous literature[18, 22] and clinical significance related to the disease.

Univariate analysis was carried out through Kaplan–Meier log-rank analysis. Survival time was calculated as the minimum date of death or end of follow-up (December 31, 2006) subtracted from the inclusion date. Time to progression was calculated as the time of re-examination subtracted from the inclusion date. Dogs were censored if they were still alive or the follow-up date was the end of the study. Unadjusted hazard ratios (HR) and the adjusted hazard ratio (AHR) were generated through Cox semiparametric regression analysis. AHRs were determined through Cox semiparametric regression analysis for death and cardiac death. Missing data were accounted as their own category within a variable (ie, sex: male, female, missing) as opposed to being omitted in the model in order to maximize the number of subjects available in the proportional hazards multivariate models but are not reported in the models. Multivariate model building was carried out by the enter approach. Variable selection was based upon significance from univariate analyses and clinical significance. Survival times are reported as median and range. All analyses were conducted with SAS1 and a type 1 error probability of .05 was considered statistically significant.

Results

Baseline Characteristics

Two-hundred-fifty-six dogs, 173 males (67%) and 83 females (33%), from 34 breeds were included in the analysis. The most represented breeds were mixed breed dogs (n = 97; 38%), followed by Yorkshire Terrier (n = 28; 11%), Miniature Poodles (n = 17; 7%) Dachshund (n = 13; 5%), and German Shepherd (n = 12; 5%). The majority of dogs included in the study weighed less than 20 kg (n = 194; 76%). The median weight was 8.3 kg (2–48.5 kg). The median age was 10 years (1–17). At baseline examination 136 dogs were in stage B1 (53%) and 120 (47%) were in stage B2 of MMVD, 53 (21%) dogs had cough, 24 (9%) had a case history of syncope. A systolic murmur was reported in 167 (65%) dogs, whereas 67 (26%) dogs had no detectable murmur at the time of diagnosis. The medical records for the remaining 22 dogs (9%) were missing information concerning murmur status. The median EDDn (n = 251) and ESDn (n = 251) were 1.66 (1.02–2.78) and 0.92 (0.42–1.91), respectively. The median LA/Ao (n = 250) was 1.5 (0.8–2.9). The median Emax (n = 78) was 0.85 (0.43–1.9) and the median Edt (n = 205) was 97 ms (6–177). Baseline characteristics for the general dog population and dogs with stages B1 and B2 are summarized in Table 1.

Table 1. Baseline characteristics at diagnosis of 256 dogs diagnosed with MMVD stages B1 and B2 according to ACVIM consensus.

	All Dogs	**Stage B1 (n = 139)**	**Stage B2 (n = 117)**
Age (years)	10 (1–17) (n = 256)	10 (1–17)	11 (4–16)
Sex	173 m; 83 f (n = 256)	92 m; 47 f	81 m; 36 f
Murmur	167 (n = 234)	79	84
Cough	53 (n = 230)	20	33
Syncope	24 (n = 256)	10	14
Affected MVL	AMVL 56; PMVL 7;	AMVL 36; PMVL 6;	AMVL 20; PMVL 1;

	BMVL 98 (n = 161)	BMVL 34	BMVL 64
LA/Ao > 1.4	122 (n = 250)	40	82
EDDn > 1.73	98 (n = 251)	8	90
ESDn > 1.14	37(n = 251)	7	30
Emax > 1.2 m/s	11(n = 78)	2	9
Edt > 80 ms	149 (n = 201)	77	72
E/A ratio > 2	69 (n = 78)	1	5

. MMVD, myxomatous mitral valve degeneration; MVL, mitral valve leaflet; AMVL, anterior mitral valve leaflet;

. PMVL, posterior mitral valve leaflet; BMVL, both mitral valve leaflet; LA/Ao left atrium aortic root ratio;

. EDDn, normalized end-diastolic diameter; ESDn, normalized end-systolic diameter;

. Emax, peak velocity of E wave of transmitral flow; Edt, deceleration time of E wave transmitral flow;

. E/A Ewave to A wave ratio of transmitral flow.

According to 2D-echocardiogram, all dogs presented with MVP, various degrees of mitral valve leaflet thickening and various degrees of MR. A description of the leaflet affected was available for 161 (63%) dogs. In this subgroup 98 animals (61%) had bilateral mitral valve leaflet involvement, 56 (35%) had only the anterior leaflet affected, and 7 dogs (4%) had only the posterior leaflet affected. At baseline, 93 (36%) dogs were receiving medical treatment. Of these dogs, 83 received an ACE-I alone or in combination with other drugs. Thirty-seven dogs received furosemide alone or in combination with other drugs. After the initial examination, all medical treatment except ACE-I was discontinued.

Overall Survival

During the observation period, 70 dogs (27.3%) died or were euthanized. Twenty-five dogs (9.7%) were euthanized, 9 because of refractory HF. The median observation time for the whole population was 833 (11–1,977 days), for dogs in stage B1 was 843 (12–1,977), and for dogs in stage B2 was 820 (11–1,942) days. The median survival time, regardless of the cause of death, was 588 (75–1,668) days. Overall survival and survival according to the stage of the disease are presented in Figure 1. Of the 13 variables used as predictors in the univariate analysis, only the presence of a murmur showed a negative prognostic effect on survival (HR 1.87; 95% CI 1.02, 3.43; $P = .043$). In the multivariate analysis the presence of murmur remained significant where the AHR negative effect persisted (AHR 2.14; 95% CI 1.12, 4.11; $P = .022$).

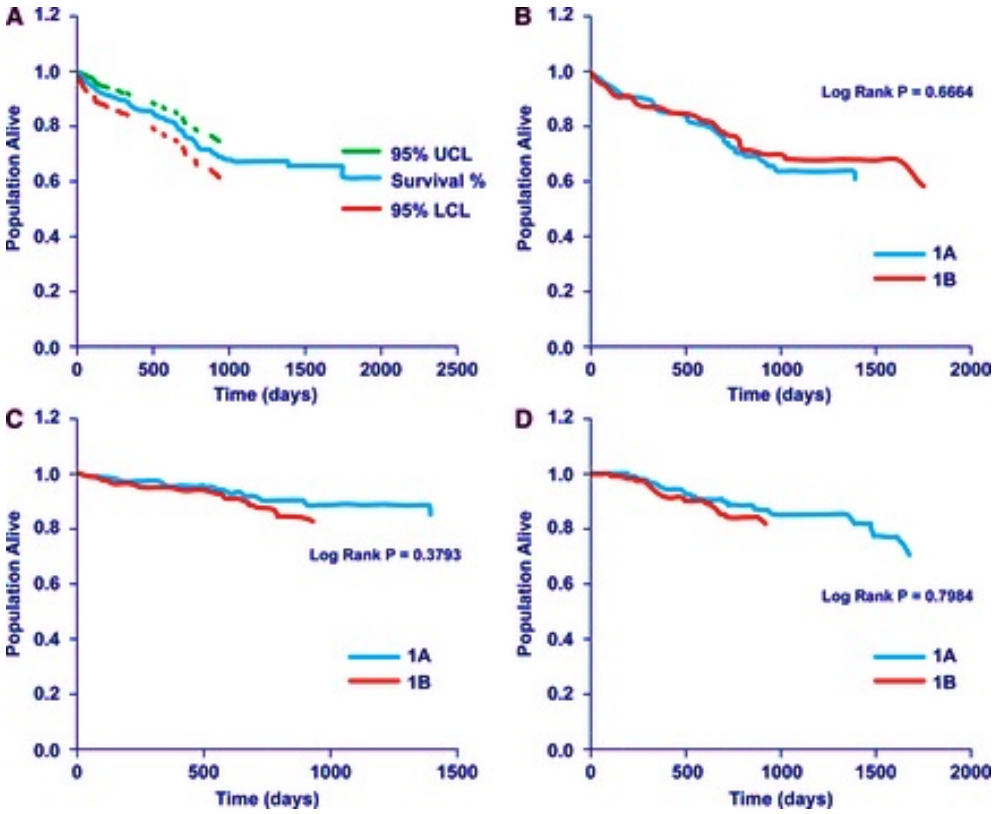

Figure 1.

Graphs depicting survival times and progression time as Kaplan–Meier curves for all 256 dogs with MMVD and dogs with stages B1 and B2 accordingly to ACVIM consensus. **(A)** All population. **(B)** Overall death for dogs with stages B1 and B2. **(C)** Cardiac death for dogs with stages B1 and B2. **(D)** Time to progression to a more advanced stage for dogs with stages B1 and B2.

Cardiac-Related Deaths

Thirty (12%) deaths were classified as cardiac-related. Nine of these thirty deaths were due to euthanasia for refractory HF. Figure 1C depicts Kaplan–Meier curves for cardiac death. Three variables were significant for death due to cardiac failure in the univariate model. A negative effect on survival was shown for EDDn > 1.73 (HR 2.08; 95% CI 1.01,4.29; $P = .047$), E/A ratio group >2 (HR 4.38; 95% CI 1.32, 14.56; $P = .016$) and LA/Ao greater than 1.4 (HR 2.96; 95% CI 1.31, 6.68; $P = .009$). The only variable that had a significant effect on survival time in the multivariate analysis was LA/Ao > 1.4 (AHR = 2.64; 95% CI 1.13, 6.13; $P = .024$).

Progression of Class of HF

Eighty-three dogs were available for re-examination. Of these, 32 animals progressed to a more advanced stage of MMVD. The median observation time was 756 days (11–1,977). Figure 1D depicts Kaplan–Meier curves for the progression of HF class from stages B1 and B2 into the worst stage. Eleven dogs (4%) advanced from stage B1 to stage B2, 5(2%) from stage B1 to C, 12 (5%) from B2 to

C, and 4 (2%) from stage B2 to D. All together, 21 (8%) dogs progressed to HF (stage C or D). Three variables were associated with progression to an advanced HF class in the univariate model. Similar to the results for cardiac-related deaths, LA/Ao was associated with an increased risk for progression (HR 2.42; 1.18, 4.96; $P = .0163$). Other significant variables were E-max > 1.2 (HR 2.73; 95% CI 1.17, 6.39; $P = .021$) and the presence of cough at the initial examination (HR 2.13; 95% CI 1.03, 4.38; $P = .041$). Only Emax > 1.2 (AHR 2.75; 95% CI 1.01, 7.48; $P = .047$) and cough at the initial examination (AHR 7.89; 95% CI 3.18, 20.072; $P < .001$) remained significant in the multivariate analysis.

Cardiac-Related Deaths and Progression of HF

When cardiac related deaths and progression of HF class were evaluated as a combined single end point, 5 variables were associated with a worse prognosis in the univariate analysis. These variables included the presence of a murmur (HR 1.90; 95% CI 0.98, 3.68; $P = .058$), syncope (HR 2.27; 95% CI 1.11, 4.61; $P = .024$), cough (HR 1.06; 95% CI 1.13, 3.41; $P = .017$), left atrial enlargement (HR 2.40; 95% CI 1.39, 4.15; $P = .024$), and E-max > 1.2 (HR 2.33; 95% CI 1.01, 5.38; $P = .048$). Only the presence of murmur at exam (AHR 2.19; 95% CI 1.15–4.17; $P = .031$) was significant in the multivariate analysis.

Discussion

Myxomatous mitral valve degeneration represents a common problem in the geriatric population of dogs. The most common clinical presentation for these animals is the presence of a cardiac murmur. Most of these animals lack clinical signs of HF. Although several studies have previously described clinical outcomes and epidemiology for dogs with MMVD, they focused on a specific breed, particularly Cavalier King Charles Spaniels, or included dogs with more advanced stage of HF.[3, 4, 7, 23-25] This study describes the natural history of pre-clinical MMVD in a large and varied population of dogs breeds, including large breed dogs.

This study demonstrates that dogs with stages B1 and B2 MMVD have a comparatively low morbidity and mortality. However, preclinical MMVD is not uniformly benign because affected dogs have a widely heterogeneous outcome, and a significant proportion of animals died during the observation period. A detectable heart murmur is associated with an increased risk of overall death. In addition, when cardiac death and the progression of HF class are considered as a single end point, heart murmur is a significant predictor of the worst prognosis. Mild left atrial enlargement is the strongest predictor of cardiac death, and the presence of cough and increased Emax are associated with an increased risk of the class of HF.

Overall Case Fatality

The median survival time for dogs included in this study was 588 days. These data are similar to the data reported in the VETPROOF trial, which was for dogs alive and free of signs of HF at the end of the observation period.[26] Similar to our previous study, 27% of the dogs in this trial died during the observation period.[7] These data are in agreement with the case fatality rate reported in a population of 100 primarily preclinical dogs at different stages of MMVD.[14] In the univariate analysis of our study, a detectable murmur was associated with an increased risk of death (all causes). This variable remained significant in the multivariate model. A murmur in dogs with MMVD is associated with the presence of MR. In humans, this association is a negative predictor for outcome.[27, 28] In dogs, the intensity of the murmur is associated with the severity of the disease.[10, 29] One possible explanation for the association between murmur and death could be related to the reaction of the owner to the knowledge of an existing cardiac disease. In some cases, the knowledge of a heart condition could influence the owner's decision to treat other diseases. For example, if treatment includes a surgical procedure, the owner could decide to euthanize the dog rather than treat the other disease. Interestingly, 18 of the 25 dogs in this study were euthanized for reasons unrelated to the cardiac disease. In our study, due to the retrospective nature of data collection from medical records, we were not able to evaluate the severity of the murmur. However, one can hypothesize that dogs with a murmur had a more severe degree of MR as compared to dogs without a murmur. Twenty-six percent of the dogs did not have a murmur on auscultation even though they met echocardiographic criteria for MMVD, including mild MR. This result is in agreement with a previous study and suggests that echocardiography is a more sensitive method of diagnosing dogs with very mild disease.[30] In addition, the population of dogs in the study included a large proportion of large breed dogs. We previously reported that large breed dogs affected by MMVD have less intense murmurs compared with affected small breed dogs.[31] In humans, studies have reported that murmur audibility is variable with mild MMVD, and the systolic murmur may not be constant. Presumably, auscultation after stress may enhance the chance of detecting occult murmur or midsystolic click.[30, 32]

Cardiac-Related Deaths and Progression of the Class of HF

Univariate analysis indicated that an increased E/A ratio of transmitral flow, left atrial enlargement, and left ventricular enlargement were predictors of cardiac death. However, only left atrial enlargement was a predictor of cardiac death in the multivariate analysis. Another study reported that left ventricular enlargement is a negative predictor of survival.[14] In our study left atrial enlargement, cough and increased Emax were also predictors of progression of MMVD, although only cough and Emax persisted in the multivariate model. In this study, the time to progression to a more advanced class of HF is similar to 2 other research groups' previous studies.[33, 34] We classified these dogs as stage B1 if they had an LA/Ao ratio > 1.4 and an EDV-I less than 100 mL/m2. Although these parameters are commonly accepted to identify dogs with moderate left atrial and left ventricular enlargement,[17, 19, 35] no firm consensus exists on what should be considered the echocardiographic cut off for identifying these animals. The ACVIM consensus on diagnosis and treatment of MMVD states that dogs with stage B1 are dogs with normal or equivocally enlarged left atrium and/or left ventricle and a normal vertebral heart score on radiographs. Although this study uses an LA/Ao ratio 2 standard deviations above the normal reported value, this ratio of 1.4 suggests very mild left atrial enlargement.[22]Accordingly, from this study, even mild left atrial enlargement represents a significant risk factor for cardiac death. In patients with chronic MR, left atrial size and left ventricular enlargement are related to the degree of MR and are associated with a poor outcome in both humans and dogs.[7, 14, 36, 37] A recent study showed that the rate of cardiac enlargement on radiographs predicted the onset of HF in dogs.[12] An increased E/A ratio and Emax are associated with a

restrictive physiology and poor prognosis in both people and dogs with several cardiac diseases.[38-41] However, in patients with volume overload and normal ventricular function, such as dogs with preclinical MMVD, a restrictive transmitral flow pattern is more likely to reflect the overfilling of the ventricles and is not necessarily associated with an increased left atrial pressure.[42] Therefore, in this study the negative effect increased Emax and E/A ratio have on survival and progression may simply be a reflection of the degree of volume overload rather than a result of increased left ventricular filling pressure. In this study, the presence of cough was associated with a significantly increased risk of progression to a more advanced stage of disease. We have recently reported that cough was not associated with the presence of HF in dogs with MMVD at different stages.[43] However, preliminary data from a larger group of dogs demonstrated that left atrial enlargement is associated with cough. Cough in dogs with MMVD has been related to the compression of left main stem bronchus by an enlarged left atrium,[44] and for this reason cough can simply reflect a more advanced stage of MMVD.

Limitations

This study has several limitations. First, this study includes a large number of mixed breed dogs. Although this population represents the general population of dogs seen in general practice, our results may not apply to a specific breed. Second, some of the dogs included in the study received medicinal cardiac treatment at the time of inclusion in the study. This treatment could have affected the classification of the dogs at the time of inclusion. Moreover, although all treatments but the ACE-I were discontinued after the initial examination, the treatment could have influenced their classification and survival. Two independent clinical trials failed to demonstrate any effect of ACE-I treatment in delaying the onset of clinical signs in dogs with preclinical MMVD.[33, 34] Accordingly, outcome is unlikely influenced by ACE-I treatment. Due to the lack of standard treatment in this study, we were not able to analyze the effect of treatment on survival. Third, despite the prospective nature of collecting data in the database, this study has a retrospective design. Retrospective studies increase the risk for uncontrolled systematic errors. Furthermore, because of the retrospective design, all variables were not available at the baseline. Fourth, we measured the LA/Ao ratio to evaluate left atrial enlargement. Although this technique is generally considered the gold standard enlargement is only detectable on 1 plane. The left atrium enlarges asymmetrically, and volumetric measurements might provide a more accurate measure of left atrium size.[45] However, no reference range for left atrial measurement exists in dogs. Fifth, although we accurately designed the questionnaire to discriminate between overall death and cardiac causes of death, some of the reported events may not be cardiac related. Finally, this study has a relatively low number of observed events for the number of variables investigated.

Clinical Relevance

This study demonstrated that preclinical MMVD represents a relatively benign condition in dogs, similar to reports in humans. However, this stage of the disease cannot be described as homogeneous, because the affected dogs present with heterogeneous outcomes. Thus, this population of preclinical

dogs may benefit from stratification according to the presence or absence of risk factors based on clinical and relatively simple echocardiographic findings.

Acknowledgments

The study was supported by a Regione Piemonte, Italy 2004 Research Grant.

We would like to thank Melissa A. Lamb of http://www.LambConsulting.com for her assistance in the editing of this manuscript.

References

1Haggstrom J, Kvart C, Pedersen HD. Acquired valvular heart disease. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine, 6th ed. St. Louis, MO: Elsevier Saunders; 2005:1022–1039.

2Haggstrom J. Chronic valvular disease in Cavalier King Charles Spaniels: Epidemiology, inheritance and pathophysiology. Department of Physiology, Uppsala: Swedish University of Agricultural Sciences; 1996.

3Haggstrom J, Hansson K, Kvart C, et al. Chronic valvular disease in the Cavalier King Charles Spaniels in Sweeden. *Vet Rec* 1992;**131**:549–553.

4Beardow AW, Buchanan JW. Chronic mitral valve disease in Cavalier King Charles Spaniels: 95 cases (1987-1991). *J Am Vet Med Assoc* 1993;**203**:1023–1029.

5Olsen LH, Fredholm M, Pedersen HD. Epidemiology and inheritance of mitral valve prolapse in Dachshunds. *J Vet Intern Med* 1999;**13**:448–456.

6Pedersen HD, Kristensen BO, Lorentzen KA, et al. Mitral valve prolapse in 3-year-old healthy Cavalier King Charles Spaniels. An echocardiographic study. *Can J Vet Res* 1995;**59**:294–298.

7Borgarelli M, Savarino P, Crosara S, et al. Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. *J Vet Intern Med* 2008;**22**:120–128.

8Olsen LH, Mow T, Koch J, et al. Heart rate variability in young, clinically healthy Dachshunds: Influence of sex, mitral valve prolapse status, sampling period and time of day. *J Vet Cardiol* 1999;**1**:7–16.

9Buchanan JW. Chronic valvular disease (endocardiosis) in dogs. *Adv Vet Sci Comp Med* 1977;**21**:75–106.

10Haggstrom J, Kvart C, Hansson K. Heart sounds and murmurs: Changes related to severity of chronic valvular disease in the Cavalier King Charles Spaniel. *J Vet Intern Med* 1995;**9**:75–85.

11Olsen LH, Martinussen T, Pedersen HD. Early echocardiographic predictors of myxomatous mitral valve disease in Dachshunds. *Vet Rec* 2003;**152**:293–297.

12Lord P, Hansson K, Kvart C, et al. Rate of change of heart size before congestive heart failure in dogs with mitral regurgitation. *J Small Anim Pract* 2010;**51**:210–218.

13Chetboul V, Serres F, Tissier R, et al. Association of plasma N-terminal pro-B-type natriuretic peptide concentration with mitral regurgitation severity and outcome in dogs with asymptomatic degenerative mitral valve disease. *J Vet Intern Med* 2009;**23**:984–994.

14Moonarmart W, Boswood A, Luis Fuentes V, et al. N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease. *J Small Anim Pract* 2010;**51**:84–96.

15Atkins C, Bonagura J, Ettinger S, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *J Vet Intern Med* 2009;**23**:1142–1150.

16Boon JA. Acquired Heard Disease. Baltimore, MD: Williams & Wilkins; 1998:261–382.

17Dukes-McEwan J, Borgarelli M, Tidholm A, et al. Proposed guidelines for the diagnosis of canine idiopathic dilated cardiomyopathy. *J Vet Cardiol* 2003;**5**:7–19.

18Cornell CC, Kittleson MD, Della Torre P, et al. Allometric scaling of M-mode cardiac measurements in normal adult dogs. *J Vet Intern Med* 2004;**18**:311–321.

19Borgarelli M, Tarducci A, Zanatta R, et al. Decreased systolic function and inadequate hypertrophy in large and small breed dogs with chronic mitral valve insufficiency. *J Vet Intern Med* 2007;**21**:61–67.

20Thomas WP, Gaber CE, Jacobs GJ, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine. *J Vet Intern Med* 1993;**7**:247–252.

21Bonagura JD. M-mode echocardiography. Basic principles. *Vet Clin North Am Small Anim Pract* 1983;**13**:299–319.

22Hansson K, Haggstrom J, Kvart C, et al. Left atrial to aortic root indices using two-dimensional and M-mode echocardiography in Cavalier King Charles Spaniels with and without left atrial enlargement. *Vet Radiol Ultrasound* 2002;**43**:568–575.

23Pedersen HD, Lorentzen KA, Kristensen BO. Echocardiographic mitral valve prolapse in Cavalier King Charles Spaniels: Epidemiology and prognostic significance for regurgitation. *Vet Rec* 1999;**144**:315–320.

24Serres F, Chetboul V, Tissier R, et al. Chordae tendineae rupture in dogs with degenerative mitral valve disease: Prevalence, survival, and prognostic factors (114 cases, 2001-2006). *J Vet Intern Med* 2007;**21**:258–264.

25Chetboul V, Tissier R, Villaret F, et al. Epidemiological, clinical, echo-Doppler characteristics of mitral valve endocardiosis in Cavalier King Charles in France: A retrospective study of 451 cases (1995 to 2003). *Can Vet J* 2004;**45**:1012–1015.

26Atkins CE, Brown WA, Coats JR, et al. Effects of long-term administration of enalapril on clinical indicators of renal function in dogs with compensated mitral regurgitation. *J Am Vet Med Assoc* 2002;**221**:654–658.

27Zuppiroli A, Mori F, Favilli S, et al. "Natural histories" of mitral valve prolapse. Influence of patient selection on cardiovascular event rates. *Ital Heart J* 2001;**2**:107–114.

28Freed LA, Benjamin EJ, Levy D, et al. Mitral valve prolapse in the general population: The benign nature of echocardiographic features in the Framingham Heart Study. *J Am Coll Cardiol* 2002;**40**:1298–1304.

29Ljungvall I, Ahlstrom C, Hoglund K, et al. Use of signal analysis of heart sounds and murmurs to assess severity of mitral valve regurgitation attributable to myxomatous mitral valve disease in dogs. *Am J Vet Res* 2009;**70**:604–613.

30Pedersen HD, Haggstrom J, Falk T, 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.

31Borgarelli M, Zini E, D'Agnolo G, et al. Comparison of primary mitral valve disease in German Sheperd dogs and in small breeds. *J Vet Cardiol* 2004;**6**:25–31.

32Hoglund K, Haggstrom J, Bussadori C, et al. A prospective study of systolic ejection murmurs and left ventricular outflow tract in Boxers. *J Small Anim Pract* 2011;**52**:11–17.

33Atkins CE, Keene BW, Brown WA, et al. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency. *J Am Vet Med Assoc* 2007;**231**:1061–1069.

34Kvart C, Haggstrom 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**:80–88.

35Boon JA. Evaluation of size, function and hemodynamics. In: Boon JA, ed. Manual of Veterinary Echocardiography. Baltimore, MD: Williams & Wilkins; 1998:151–260.

36Haggstrom J, Boswood A, O'Grady M, et al. Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: The QUEST study. *J Vet Intern Med* 2008;**22**:1124–1135.

37Zuppiroli A, Rinaldi M, Kramer-Fox R, et al. Natural history of mitral valve prolapse. *Am J Cardiol* 1995;**75**:1028–1032.

38Xie GY, Berk MR, Smith MD, et al. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. *J Am Coll Cardiol* 1994;**24**:132–139.

39Chen L, Benjamin EJ, Larson MG, et al. Doppler diastolic filling indexes in relation to disease states. *Am Heart J* 1996;**131**:519–524.

40Borgarelli M, Santilli RA, Chiavegato D, et al. Prognostic indicators for dogs with dilated cardiomyopathy. *J Vet Intern Med* 2006;**20**:104–110.

41O'Sullivan ML, O'Grady MR, Minors SL. Assessment of diastolic function by Doppler echocardiography in normal Doberman Pinschers and Doberman Pinschers with dilated cardiomyopathy. *J Vet Intern Med* 2007;**21**:81–91.

42Kihara Y, Sasayama S, Miyazaki S, et al. Role of the left atrium in adaptation of the heart to chronic mitral regurgitation in conscious dogs. *Circ Res* 1988;**62**:543–553.

43Borgarelli M, Haggstrom J. Canine degenerative myxomatous mitral valve disease: Natural history, clinical presentation and therapy. *Vet Clin North Am Small Anim Pract* 2010;**40**:651–663.

44Ettinger S, Kantrowitz B. Disease of the trachea. In: Ettinger S, Feldman EC, eds. Textbook of Veterinary Internal Medicine, 6th ed. St. Louis, MO: Elsevier Saunders; 2005:1217–1232.

45Tanabe K, Yamaguchi K, Tani T, et al. Left atrial volume: Predictor of atrial fibrillation in patients with degenerative mitral regurgitation. *J Heart Valve Dis* 2007;**16**:8–12.