Received: 26 November 2018 | Accepted: 6 February 2019

DOI: 10.1111/jvim.15461

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

STANDARD ARTICLE

Echocardiographic indices and severity of mitral regurgitation in dogs with preclinical degenerative mitral valve disease

Éva Larouche-Lebel[1†] | Kerry A. Loughran[1†] | Mark A. Oyama[1,2]

[1]Department of Clinical Sciences and Advanced Medicine, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[2]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Correspondence
Mark A. Oyama, 3900 Delancey St, Philadelphia, PA 19104.
Email: maoyama@upenn.edu

Abstract

Background: Describing severity of mitral regurgitation (MR) in dogs with degenerative mitral valve disease (DMVD) is challenging.

Hypothesis/Objectives: Mitral regurgitant fraction (RF), effective regurgitant orifice area (EROA), and the ratio of mitral regurgitant to aortic flow (Q_{MR}:Q_{Ao}) can be calculated from routine echocardiographic measurements and provide additional information regarding MR severity.

Animals: Fifty-seven dogs with preclinical DMVD including 36 without and 21 with cardiomegaly.

Methods: Prospective observational study. The expected relationships among RF, EROA, and Q_{MR}:Q_{Ao} and 1-dimensional measurements including left atrium to aortic root diameter ratio (LA:Ao) and normalized left ventricular internal dimension at end-diastole (LVIDdN) were mathematically derived and calculated using echocardiographic data from the study population. Nonlinear goodness of fit was determined by calculation of the root mean standard error. The correlations between 1-dimensional and multidimensional indices were analyzed using receiver operating characteristic curves.

Results: The relationships among RF, EROA, Q_{MR}:Q_{Ao}, and both LA:Ao and LVIDdN were curvilinear, and the multidimensional indices differentiated MR of variable severity. By contrast, 1-dimensional measurements were insensitive to MR severity until RF equaled or exceeded 50%. Regurgitant fraction ≥50%, EROA to body surface area ≥0.347 and Q_{MR}:Q_{Ao} ≥0.79 were strongly associated with LA:Ao ≥1.6 and LVIDdN ≥1.7.

Conclusions and Clinical Importance: Regurgitant fraction, EROA, and Q_{MR}:Q_{Ao} quantify MR severity in dogs with preclinical DMVD in a manner that 1-dimensional measurements do not.

KEYWORDS

degenerative mitral valve disease, heart disease, myxomatous degeneration, regurgitant fraction

Abbreviations: Amax, peak left ventricular late filling velocity; AoD, aortic diameter; AoDN, normalized diameter of the aorta; AUC, area under the curve; BSA, body surface area; BW, body weight; CHF, congestive heart failure; CSA, cross-sectional area; $D_{Ao\text{-}STJ}$, diameter of the aorta at the level the sinotubular junction; DMVD, degenerative mitral valve disease; E:A, ratio of the peak early to late left ventricular filling velocity; Emax, peak left ventricular early filling velocity; EROA, effective regurgitant orifice area; FS, fractional shortening; FSV, forward stroke volume; ICC, intraclass correlation coefficient; IVSdN, normalized thickness of the interventricular septum at end-diastole; LA:Ao, left atrium to aortic root diameter ratio; LAD, left atrial diameter; LADN, normalized diameter of the left atrium; LV, left ventricular; LVET, left ventricular ejection time; LVIDdN, normalized left ventricular internal diameter at end-diastole; LVIDsN, normalized left ventricular internal diameter at end-systole; LVPWdN, normalized thickness of the left ventricular posterior wall at end-diastole; LVVd, left ventricular volume at end-diastole; LVVs, left ventricular volume at end-systole; MR VOL, mitral regurgitation volume; MR, mitral regurgitation; OR, odds ratio; PISA, proximal isovelocity surface area; Q_{Ao}, aortic flow rate; Q_{MR}, mitral regurgitation flow rate; Q_{MR}:Q_{Ao}, ratio of mitral regurgitation to aortic flow rate; RF, regurgitant fraction; RMSE, root mean standard error; ROC, receiver-operating characteristic; SBP, systolic blood pressure; TOT SV, total stroke volume; $VTI_{Ao\text{-}STJ}$, velocity time integral of aortic flow signal at the level of the sinotubular junction; VTI_{MI}, velocity time integral of the mitral inflow signal; VTI_{MR}, velocity time integral of the continuous wave Doppler mitral regurgitation jet.

†Éva Larouche-Lebel and Kerry A. Loughran contributed equally to this study.

1 | INTRODUCTION

Degenerative mitral valve disease (DMVD) in the dog is characterized by age-related morphological and structural changes in the valve that lead to mitral regurgitation (MR).[1] The MR caused by DMVD has been called "unrelentingly although variably progressive"[2] and as such, stratification of MR severity in both humans and dogs with DMVD is a subject of considerable clinical interest.[3] Specifically, determination of which dogs with preclinical or asymptomatic MR will develop cardiomegaly is an important clinical question, particularly in light of the fact that treatment in this cohort improves outcome.[4] A substantial proportion of both dogs[5–8] and humans[9,10] remain in the preclinical stage of DMVD for extended periods of time whereas others experience progressive disease and clinical development of congestive heart failure (CHF). To date, little data examining risk of cardiomegaly in dogs with early preclinical DMVD exist.

In humans with DMVD, echocardiography is widely used to assess severity of MR,[11] however, in contrast to common practice in veterinary species, relatively little weight is given to 1-dimensional chamber sizes such as left atrial or left ventricular (LV) diameter. Rather, severity of MR is routinely assessed by multidimensional indices such as the mitral effective regurgitant orifice area (EROA) and regurgitant fraction (RF) that take into account not only diastolic heart size, but importantly forward and mitral flow and systolic function.[11–13] Mitral EROA corresponds to the cross-sectional area (CSA) of the narrowest region (ie, the vena contracta) of MR flow (Q_{MR}) as it moves from left ventricle to atrium during LV systole, whereas mitral RF is the percentage of total LV stroke volume (TOT SV) that regurgitates back through the mitral valve. In humans with DMVD, EROA ≥0.40 cm^2, regurgitant volume ≥60 mL, and RF ≥50% are established criteria for severe preclinical disease and increased risk for future clinical signs.[12]

We hypothesized that EROA, RF, and ratio of mitral regurgitant to aortic flow (Q_{MR}:Q_{Ao}) would provide more information regarding MR severity than 1-dimensional measures in dogs with preclinical DMVD. Previous studies have examined mitral EROA and RF in dogs,[14–19] however, adoption into routine clinical practice is hindered by the complexity of the echocardiographic procedures used to perform the necessary measurements and calculations. Thus, we specifically sought to evaluate relatively simple echocardiographic methods to derive EROA, RF, and Q_{MR}:Q_{Ao} and to describe their relationships with indices of left heart enlargement.

2 | MATERIALS AND METHODS

The study was a single-site prospective observational cohort study. The study utilized a convenience sample and all dogs recruited into the study were already scheduled to undergo 2D, M-mode, and Doppler echocardiography and indirect blood pressure measurement as part of their visit to the Veterinary Hospital of the University of Pennsylvania. Eligible dogs included those with a left apical systolic murmur and color flow Doppler evidence of MR in association with thickened or prolapsing mitral leaflets. Dogs with mild to moderate concurrent tricuspid regurgitation were eligible for the study. Exclusion criteria included current or previous episodes of CHF, receipt of diuretics, angiotensin-converting enzyme inhibitors, positive inotropes, or vasodilators, administration of parenteral fluids within the past 72 hours, evidence of significant heart disease other than DMVD, such as moderate or severe pulmonary hypertension or aortic insufficiency, or presence of significant extracardiac disease that might influence fluid balance or hemodynamics (ie, hyperadrenocorticism, diabetes mellitus, chronic kidney disease, etc.). Body surface area (BSA) in m^2 was calculated using the following formula: BSA = (body weight (kg)$^{0.67}$ × 10.1)/100.[20] Indirect systolic blood pressure (SBP) was measured using the Doppler method (Doppler Flow Detector Model 811-B, Parks Medical Electronics, Inc., Aloha, Oregon).

Echocardiograms (iE33, Philips Healthcare, Cambridge, Massachusetts) were performed by a board-certified cardiologist or a resident in training. Normalized LV internal dimension at end-diastole (LVIDdN) and at end-systole (LVIDsN) as well as interventricular septal (IVSdN) and LV posterior wall thickness (LVPWdN) at end-diastole were calculated from LV M-mode or 2-D images obtained from the right short or long axis views.[21] The specific imaging plane used for measurement was based on what the examiner regarded as the most accurate and representative view of the LV. Left atrial diameter (LAD), aortic root dimension (AoD), and their ratio (LA:Ao) were measured from the 2D right short axis view.[22] Normalized values for LAD (LADN) and AoD (AoDN) were calculated using previously reported formulae.[21] Peak early (Emax) and late (Amax) mitral inflow velocity were measured at the tips of the mitral valve leaflets from the left apical view and their ratio (E:A) was calculated. The velocity-time integral of aortic flow at the level of the sinotubular junction ($VTI_{Ao\text{-}STJ}$) and the LV ejection time (LVET) was measured from the pulsed wave Doppler tracing obtained from the left apical view. The diameter of the aortic sinotubular junction ($D_{Ao\text{-}STJ}$) was measured using the 2D image of the aorta obtained from either the left cranial or right parasternal long axis view and measured from inner edge to inner edge (ie, at the blood-tissue interface). The velocity time integral of the MR flow (VTI_{MR}) and duration of MR flow were measured from the continuous wave Doppler tracing obtained from the left apical view.

Left ventricular volume at end diastole (LVVd) and end-systole (LVVs) were calculated using the formula for the volume of a prolate ellipse with a length that is twice as long as the diameter (ie, volume = diameter^3), which has been previously validated primarily in the normal dog.[23–25] Specifically, LVVd was calculated as $LVIDd^3$ and LVVs was calculated as $LVIDs^3$. Both volume measurements were subsequently indexed to body weight. The TOT SV was calculated as LVVd-LVVs. Forward stroke volume (FSV) was derived by multiplying $VTI_{Ao\text{-}STJ}$ by the CSA of the sinotubular junction (CSA = $\pi \times (D_{Ao\text{-}STJ}/2)^2$). Mitral regurgitant volume (MR VOL) was calculated as TOT SV-FSV. Values for Q_{MR} and aortic flow (Q_{Ao}) in mL/sec were calculated as MR VOL divided by MR flow duration and FSV divided by LVET, respectively. Volume and flow parameters were indexed to body weight. A unitless ratio of MR to aortic flow was calculated as Q_{MR}:Q_{Ao}. Mitral RF was calculated as MR VOL divided by TOT SV and then multiplied by 100. Mitral EROA in cm^2 was calculated by dividing MR VOL by VTI_{MR}[11] and then indexed to BSA (EROA:BSA). Representative echocardiographic measurements as well as a spreadsheet to enter and calculate mitral RF are presented as Supplemental Materials. In order to validate findings based on the prolate ellipse method, the indices of interest were calculated a second time using an alternate echocardiographic technique that did not rely on LV

dimensions. Specifically, the product of the mitral inflow velocity time integral (VTI_{MI}) and the CSA of the mitral annulus measured at the tips of the mitral valve leaflets in early diastole as recorded from the left apical view (CSA = $\pi \times$ length between tips of the mitral leaflets/2)^2) was used to derive a value for TOT SV based on the mitral inflow technique (TOT SV_{MI}).[11] The TOT SV_{MI} was then used to calculate alternate MR VOL, RF, EROA, and Q_{MR}:Q_{Ao} values specific to the mitral inflow technique. All echocardiographic and blood pressure measurements were the result of averaging 3 separate beats or readings.

Dogs were classified into 2 groups based on specific LV and atrial sizes that have been previously identified as important in the clinical evolution of DMVD.[4] Dogs in Group 1 included dogs that failed to meet either or both of the following criteria: LVIDdN ≥1.7 or LA:Ao ≥1.6. Group 2 included dogs that met both of the criteria: LVIDdN ≥1.7 and LA:Ao ≥1.6. Data were tested for normality using the D'Agostino & Pearson normality test. Differences between groups were evaluated using *t* tests, Mann-Whitney *U* tests, or chi-square test. Plots of left heart size as the dependent variable and indices of MR severity as the independent variable were constructed. Using simplifying assumptions, equations were derived that related 1-dimensional variables such as LVIDdN and LA:Ao to multidimensional variables such as RF, EROA, and Q_{MR}:Q_{Ao}. Specifically, LVIDdN and LA:Ao were predicted to vary proportionally to RF raised to the −1/3 power (ie, $Y = X^{-1/3}$ or $Y = 1/X^{1/3}$) and for EROA and Q_{MR}:Q_{Ao}, LVIDdN and LA:Ao were predicted to vary proportionally to the cube root of EROA or Q_{MR}:Q_{Ao} (ie, $Y = X^{1/3}$). Goodness of the predicted model fit to the actual data was assessed by calculation of root mean standard error (RMSE) values.

Interobserver variability of the RF measurement was examined in a subset of 10 dogs by having 2 individuals (Eva Larouche-Lebel and Mark A. Oyama) acquire separate echocardiograms on the same dog during a single outpatient hospital visit. Interobserver variability was determined by calculating the intraclass correlation coefficient (ICC) and by calculating the mean difference among observers.[26] The strength of agreement was described as none, slight, fair, moderate, and substantial for ICC values of 0-0.10, 0.11-0.40, 0.41-0.60, 0.61-0.81, and 0.81-1.0, respectively.[27]

The utility of indices of MR severity to predict presence of clinically relevant heart enlargement (ie, inclusion in Group 2) was evaluated by construction of receiver-operating characteristic (ROC) curves and calculation of various diagnostic metrics as follows. First, the overall ability of each variable to predict patient group was assessed by the area under the curve (AUC). The AUC represents the probability that a randomly selected subject with the condition of interest has a test result indicating greater suspicion of disease than a randomly selected individual without the condition.[28] We defined AUC values >0.85 as indicative of a clinically useful test,[29] whereas an AUC value of 0.5 indicates the test is no better than chance. Second, sensitivity, specificity, positive likelihood ratio (ie, ratio of a positive test in the affected vs ratio of positive test in the unaffected) and negative likelihood ratio (ie, ratio of a negative test in the affected vs the ratio of a negative test in the unaffected) for various variable values were calculated. The diagnostic odds ratio (OR), which is the ratio of the odds of a positive test in the affected over the odds of the positive test in the unaffected, was calculated for various variable values.[30] The probabilistic method was used to calculate OR in instances where any cell contained a zero value.[31] Finally, the AUC values related to RF, EROA, and Q_{MR}:Q_{Ao} that were derived from the prolate ellipse method were compared to AUC values that were derived from the mitral inflow method.[32]

Significance was defined as $P < .05$. Data are reported as mean (SD) or median (interquartile range). Correction for multiple comparisons was not performed. Statistical analyses and graphing were performed using commercial software (STATA 14.0, Stata Corp, College Station, Texas; Prism 7.0, GraphPad, La Jolla, California; Solver plug in for Microsoft Excel 14.7.2, Microsoft Corp, Redmond, Washington).

The majority of the study protocol was deemed exempt from IACUC oversight and without need for informed owner consent based on the fact that the study (1) involved a convenience sample of dogs that were scheduled to receive an echocardiographic exam and blood pressure measurement as part of their regularly scheduled hospital visit, (2) the technical performance of the echocardiographic exam did not deviate from what is standard practice at our hospital, and (3) any analysis of echocardiographic data for purposes of the current study was done offline. IACUC approval and owner consent was obtained for the 10 dogs that received 2 separate echocardiograms as part of the effort to define interobserver variability.

3 | RESULTS

Echocardiography and blood pressure measurement were performed on 59 dogs. In 1 dog, satisfactory Doppler signals of the aortic outflow could not be obtained. Another dog, a Bull terrier, had an unusually small aortic diameter (AoDN = 0.61) that was below the 2.5% value of the reference range. Both of these dogs were excluded from further analysis. Thus, the analysis set included 57 dogs, including 36 dogs in Group 1 and 21 dogs in Group 2. Table 1 displays the signalment, physical examination findings, blood pressure, and echocardiographic data of the study groups. Dogs in Group 2 had significantly greater LVIDdN, LVIDsN, LADN, LA:Ao, Emax, Amax, and VTI_{MI} values than dogs in Group 1. Dogs in Group 2 had significantly lesser $VTI_{Ao\text{-}STJ}$ and LVET values compared to Dogs in Group 1. There were no significant differences in age, sex, body weight, BSA, heart rate, SBP, IVSdN, LVPWdN, fractional shortening (FS), AoDN, E:A, $D_{Ao\text{-}STJ}$, MR duration, or VTI_{MR} between groups. Table 2 displays mean or median echocardiographic indices of MR severity by group calculated using the prolate ellipse method. The LVVd, TOT SV, EROA, MR VOL, Q_{MR}, and Q_{MR}:Q_{Ao} were significantly greater in Group 2 vs Group 1. Indices of forward flow, including Q_{Ao}, FSV, and cardiac index were significantly lower in Group 2 vs Group 1. Severity of MR as measured by RF was significantly higher in Group 2 (69% [10];) vs Group 1 (33% [18]; $P < .0001$). Agreement among observers regarding measurement of RF using the prolate ellipse method was substantial with an ICC of 0.96. The mean difference in RF values was −1% (95% CI, −6 to 4%) and this value was not significantly different than a value of 0 ($P = .56$).

The relationships between LA:Ao and LVIDdN and RF, EROA: BSA, and Q_{MR}:Q_{Ao} were nonlinear and well described by the predicted regression formulae (Figure 1). As RF, EROA:BSA, and Q_{MR}:Q_{Ao} increased, LA:Ao and LVIDdN increased in a nonlinear fashion. Of note, the relationship between RF and LVIDdN and LA:Ao was

relatively flat in dogs with small RF values and became increasingly steep as RF increased. Thus, despite the fact that there were minimal to no increases in the 1-dimensional measures of heart size of dogs in Group 1, multidimensional echocardiographic data could be used to detect a wide range of MR severity.

In order to identify echocardiographic and physical exam variables that would help predict greatest risk of having increased LA:Ao and LVIDdN (ie, belonging to Group 2), ROC curves were constructed. Three variables had AUC values >0.85 indicating high discriminatory ability, including RF (AUC, 0.956; 95% CI, 0.911-1.00), EROA:BSA (AUC, 0.947; 95% CI, 0.894-1.00), and Q_{MR}:Q_{Ao} (AUC, 0.958; 95% CI, 0.911-1.00) (Figure 2 A-C). There was no significant difference among the AUC values of these 3 parameters (RF vs EROA:BSA, P = .51; RF vs Q_{MR}:Q_{Ao}, P = .88; EROA:BSA vs Q_{MR}:Q_{Ao}, P = .48). The sensitivity, specificity, and positive and negative likelihood ratios for various cut points of each parameter are shown in Table 3. The remaining variables, including Emax, FS, HR, and E:A, had low AUC values of 0.743 (95% CI, 0.613-0.872), 0.596 (95% CI, 0.445-0.747), 0.605 (95% CI, 0.452-0.757), and 0.591 (95% CI, 0.427-0.756), respectively (Figure 2 D-G), and no further analysis of individual cut points for these variables was performed. Based on the ROC results, the OR for each of the 3 indices of MR severity associated with having LA:Ao ≥1.6 and LVIDdN ≥1.7 were as follows: for RF ≥50%, odds were 108.5 (95% CI, 6.0-1959.7, P = .002) times higher vs RF < 50%; for EROA:BSA ≥0.347, odds were 100.0 (95% CI, 11.2-894.7, P < .0001) times higher vs EROA:BSA < 0.347; for Q_{MR}:Q_{Ao} was ≥0.79, odds were 33.3 (95% CI, 6.4-174.1, P < .0001) times higher vs Q_{MR}:Q_{Ao} < 0.79. There was good agreement between results using the prolate ellipse method as compared to the mitral inflow method (see Supplemental Materials).

TABLE 1 Signalment, physical examination, and echocardiographic characteristics of 57 dogs with preclinical degenerative mitral valve disease

Variable	Group 1 (n = 36)	Group 2 (N = 21)	P
Age (yrs)	10 (9-11)	9 (8-12)	.33
Sex (M/F)	23/13	12/9	.61
Body weight (kg)	8.1 (6.3-11.1)	7.4 (5.4-10.3)	.47
BSA (m^2)	0.409 (0.345-0.505)	0.386 (0.313-0.482)	.47
Heart rate (bpm)	120 (100-134)	124 (117-140)	.19
SBP (mmHg)	143 (18)	142 (26)	.92
IVSdN	0.47 (0.06)	0.45 (0.07)	.50
LVIDdN	1.60 (1.50-1.69)	1.83 (1.76-2.01)	<.0001
LVIDsN	0.85 (0.74-0.99)	0.94 (0.85-1.06)	.04
LVPWdN	0.46 (0.05)	0.44 (0.06)	.14
FS (%)	43.4 (8.2)	46.0 (8.8)	.28
LADN	1.09 (0.14)	1.34 (0.14)	<.0001
AoDN	0.76 (0.09)	0.73 (0.08)	.14
LA:Ao	1.45 (0.20)	1.89 (0.22)	<.0001
Emax (m/s)	0.82 (0.21)	1.02 (0.21)	.001
Amax (m/s)	0.77 (0.58-0.84); n, 35	0.89 (0.72-1.02); n, 20	.03
E:A	1.13 (0.27); n, 35	1.22 (0.32); n, 20	.24
$VTI_{Ao\text{-}STJ}$ (cm)	11.9 (2.7)	10.0 (2.7)	.01
LVET (sec)	0.17 (0.02)	0.16 (0.02)	.03
$D_{Ao\text{-}STJ}$ (cm)	1.2 (1.1-1.3)	1.1 (1.0-1.3)	.41
MR duration (sec)	0.228 (0.034)	0.222 (0.031)	.54
VTI_{MR} (cm)	97.6 (13.7)	92.6 (12.9)	.19
VTI_{MI} (cm)	12.9 (2.9)	14.9 (2.0)	.008

Abbreviations: Amax, peak left ventricular late filling velocity; AoDN, normalized diameter of the aorta; BSA, body surface area; $D_{Ao\text{-}STJ}$, diameter of the aorta at the level the sinotubular junction; E:A, ratio of the peak early to late left ventricular filling velocity; Emax, peak left ventricular early filling velocity; FS, fractional shortening; IVSdN, normalized thickness of the interventricular septum at end-diastole, LA:Ao, left atrium to aortic root diameter ratio; LADN, normalized diameter of the left atrium; LVET, left ventricular ejection time; LVIDdN, normalized left ventricular internal diameter at end-diastole; LVIDsN, normalized left ventricular internal diameter at end-systole; LVPWdN, normalized thickness of the left ventricular posterior wall at end-diastole; MR, mitral regurgitation; SBP, systolic blood pressure; $VTI_{Ao\text{-}STJ}$, velocity time integral of aortic flow signal at the level of the sinotubular junction; VTI_{MI}, velocity time integral of the pulsed wave mitral inflow signal; VTI_{MR}, velocity time integral of the continuous wave Doppler mitral regurgitation jet.

TABLE 2 Echocardiographically derived measures in 57 dogs with preclinical degenerative mitral valve disease

Variable	Group 1 (n = 36)	Group 2 (n = 21)	P
LVVd:BW (mLs/kg)	3.18 (2.55-3.68)	4.99 (4.26-6.44)	<.0001
LVVs:BW (mLs/kg)	0.55 (0.36-0.88)	0.74 (0.58-1.08)	.03
TOT SV:BW (mLs/kg)	2.44 (2.09-3.12)	4.07 (3.60-5.55)	<.0001
FSV:BW (mLs/kg)	1.65 (0.43)	1.31 (0.28)	.0007
Cardiac index ($L/min/m^2$)	3.88 (1.03)	3.23 (0.90)	.02
MR VOL:BW (mLs/kg)	0.78 (0.34-1.41)	2.86 (2.11-4.22)	<.0001
Q_{MR}:BW (mLs/min/kg)	3.08 (1.47-6.52)	14.17 (9.60-18.57)	<.0001
Q_{Ao}:BW (mLs/min/kg)	9.54 (2.41)	8.24 (1.75)	.04
Q_{MR}:Q_{Ao}	0.34 (0.17-0.74)	1.76 (1.16-2.43)	<.0001
EROA (cm^2)	0.084 (0.027-0.142)	0.244 (0.185-0.377)	<.0001
EROA:BSA (cm^2/m^2)	0.138 (0.062-0.292)	0.612 (0.500-0.759)	<.0001
RF (%)	33 (18)	69 (10)	<.0001

Abbreviations: BSA, body surface area; BW, body weight; EROA, effective regurgitant orifice area; FSV, forward stroke volume; LVVd, left ventricular volume at end-diastole; LVVs, left ventricular volume at end-systole; MR VOL, mitral regurgitation volume; Q_{Ao} aortic flow rate; Q_{MR}, mitral regurgitation flow rate; Q_{MR}:Q_{Ao}, ratio of mitral regurgitation to aortic flow rate; RF, regurgitant fraction; TOT SV, total stroke volume.

4 | DISCUSSION

The results of this study demonstrate that multidimensional echocardiographic indices, namely RF, EROA, and Q_{MR}:Q_{Ao}, vary in an expected mathematical manner with 1-dimensional measurements of left heart size, and that these indices differentiate severity of MR in dogs with preclinical DMVD in a way that 1-dimensional measurements do not. These findings make sense for a variety of reasons. First, the mathematical relationship between volume and length is based on the cube of the length, and the expected curvilinear function contributes to the relationships found in Figure 1. With respect to the expected relationship between mitral RF and 1-dimensional heart size, the specific presence of the independent variable (ie, RF) in the denominator creates an initial "flat" portion of the curve, wherein LA:Ao and LVIDdN show relatively little change as MR severity increases, followed by a more steep

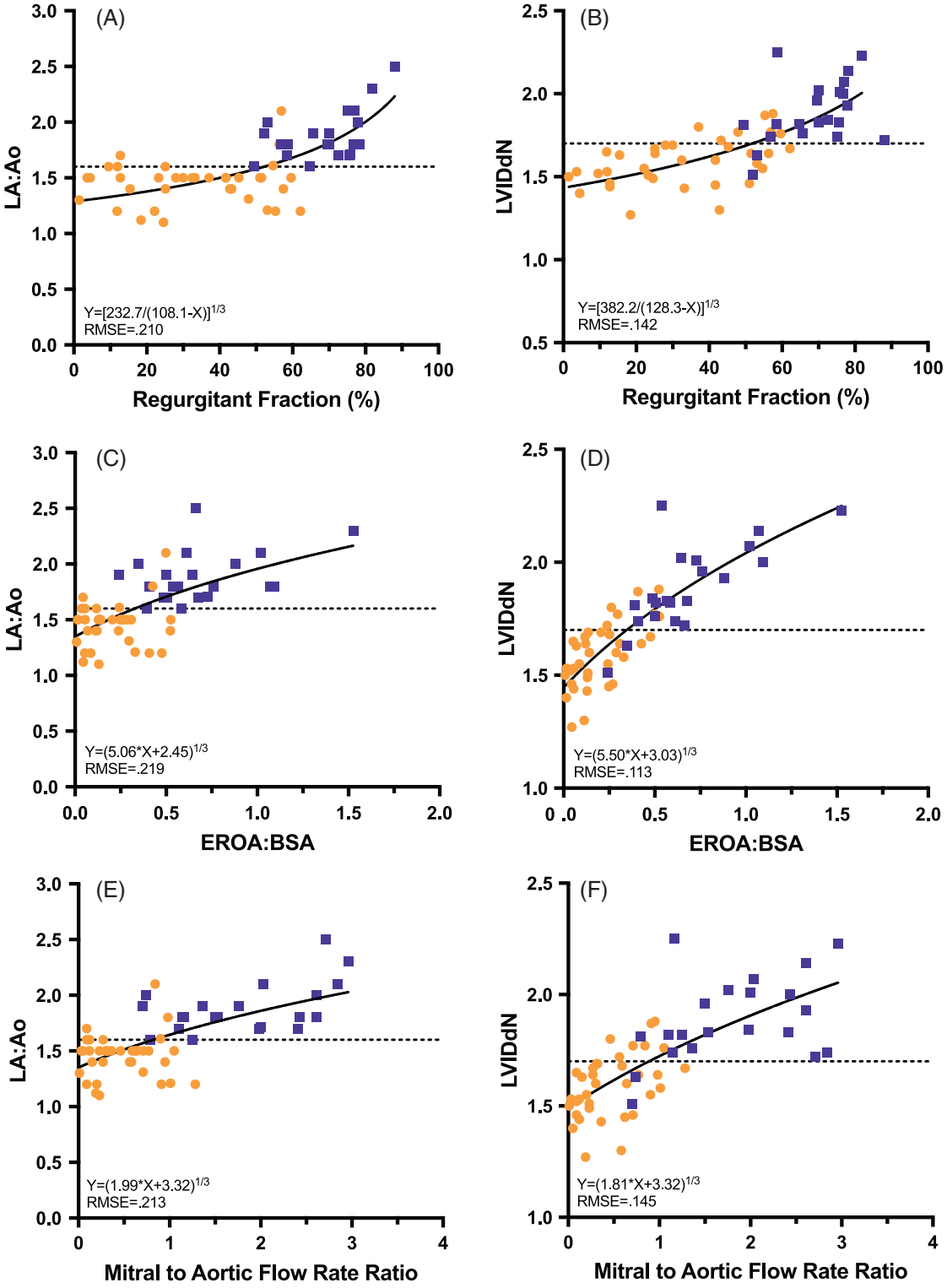

FIGURE 1 Relationship of echocardiographically derived indices of severity of mitral regurgitation and measures of left atrial and ventricular size in 57 dogs with degenerative mitral valve disease. Dogs with normalized left ventricular end-diastolic diameter (LVIDdN) <1.7 or left atrial to aortic root diameter ratio (LA:Ao) <1.6 (ie, Group 1) are displayed as orange circles and dogs with LVIDdN ≥1.7 and LA:Ao ≥1.6 (ie, Group 2) are displayed as purple squares. (A, B) Relationship of mitral regurgitant fraction (RF) to LA:Ao and LVIDdN. Both functions are well described by a curvilinear relationship in which the first portion of the curve is relatively flat so that dogs with RF values up to approximately 50% are in Group 1. Beyond this, the rate at which LA:Ao and LVIDdN increase becomes greater so that most dogs with RF values of ≥50% are those with heart enlargement and in Group 2. (C, D) Relationship of mitral valve effective regurgitant orifice area indexed to body surface area (EROA:BSA) to LA:Ao and LVIDdN are both well described by a curvilinear relationship in which dogs in Group 1 display a range of EROA:BSA values up to approximately 0.35 cm^2/m^2, after which most dogs have heart enlargement. (E, F) Relationship of Q_{MR}:Q_{Ao} to LA:Ao and LVIDdN are both well described by a curvilinear relationship in which dogs in Group 1 display a range of Q_{MR}:Q_{Ao} values up to approximately 0.8, after which dogs have heart enlargement

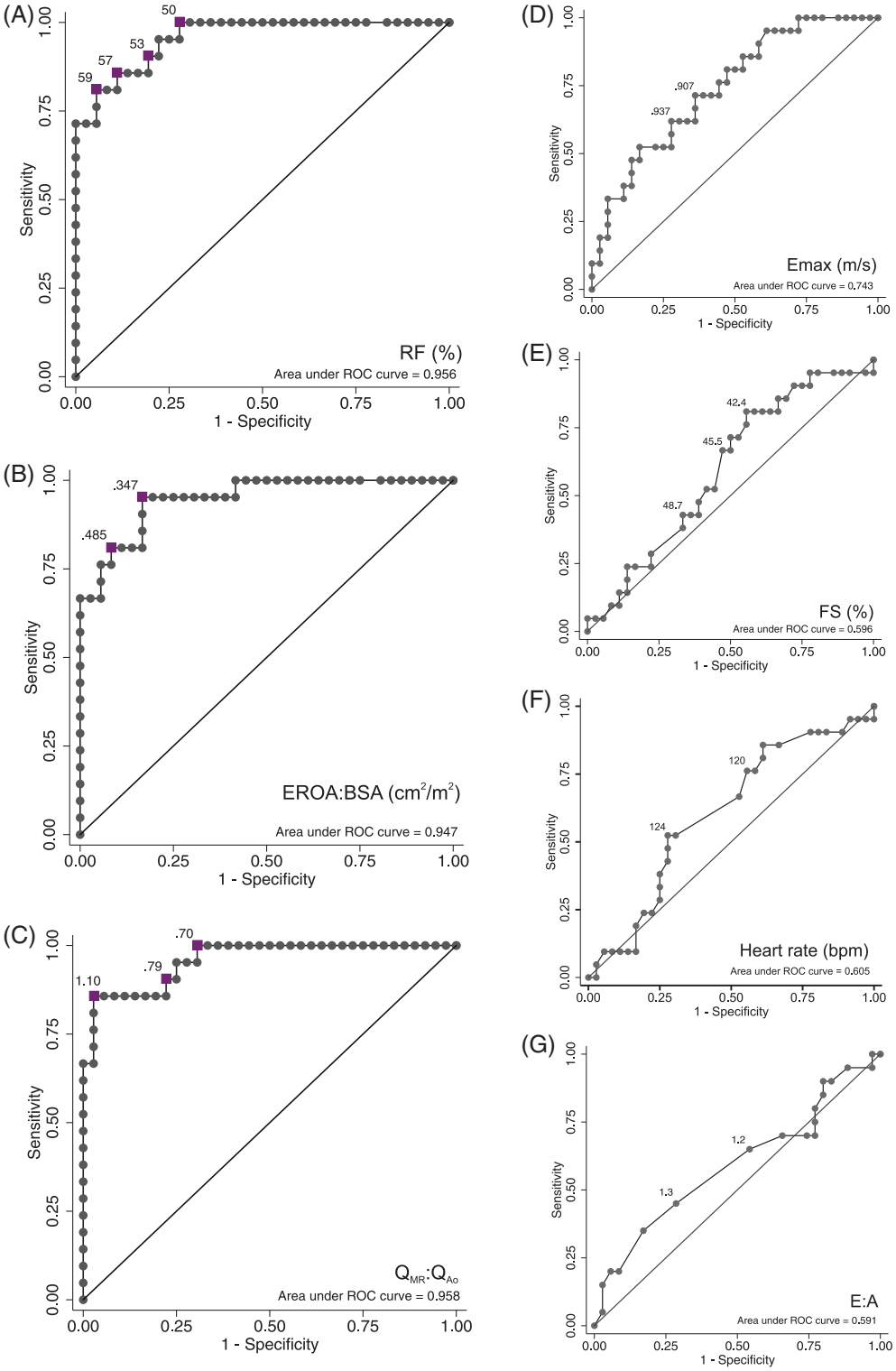

FIGURE 2 Receiver-operating characteristic (ROC) curves of echocardiographic parameters of mitral regurgitation (MR) severity in dogs with preclinical degenerative mitral valve disease. Three parameters, including (A) mitral regurgitant fraction (RF, %), (B) mitral effective regurgitant orifice area indexed to body surface area (EROA:BSA, cm^2/m^2), and (C) ratio of MR flow to aortic flow (Q_{MR}:Q_{Ao}) are associated with areas under the curve (AUC) of >0.85. Four additional parameters, including (D) maximum mitral E wave velocity (Emax, m/s), (E) fractional shortening (FS, %), (F) heart rate (bpm), and (G) the ratio of maximum E wave to A wave velocity (E:A) all have relatively low AUC values. Specific values on the ROC curves are noted

portion of the curve where LA:Ao and LVIDdN change increasingly fast in response to increases in RF. By transforming echocardiographic data via calculation of RF, seemingly subtle differences in 1-dimensional echocardiographic measurements of pre-cardiomegaly dogs are magnified to reveal differences in MR severity. Thus, an important finding of the current study is that calculation of RF enhances characterization of MR severity in the population of dogs with relatively normal left heart diameters in a way 1-dimensional measurements cannot. Second, multidimensional indices are more closely related to the pathophysiology of disease and expected to more holistically reflect MR severity than

TABLE 3 Sensitivity, specificity, and positive and negative likelihood ratios (95% confidence interval) for various values of mitral regurgitant fraction (RF), effective regurgitation orifice area indexed to body surface area (EROA:BSA) and the ratio of mitral regurgitant flow to aortic flow (Q_{MR}:Q_{Ao}) to determine whether or not a dog was classified into Group 2 (ie, having a left ventricular end-diastolic normalized diameter ≥1.7 and left atrium to aortic root diameter ratio ≥1.6)

Variable	Sensitivity	Specificity	+LR	−LR
RF (%)				
≥50	100.0	72.2	3.6	0
	(83.9-100.0)	(54.8-85.8)	(2.13-6.10)	NA
≥53	90.5	80.6	4.65	0.118
	(69.6-98.8)	(64.0-91.8)	(2.36-9.18)	(0.031-0.446)
≥57	85.7	88.9	7.71	0.161
	(63.7-97.0)	(73.9-96.9)	(3.01-19.8)	(0.056-0.461)
≥59	81.0	94.4	14.6	0.202
	(58.1-94.6)	(81.3-99.3)	(3.73-56.9)	(0.083-0.489)
EROA:BSA (cm^2/m^2)				
≥0.347	95.2	83.3	5.71	0.057
	(76.2-99.9)	(67.2-93.6)	(2.74-11.9)	(0.008-0.389)
≥0.485	81.1	91.7	9.71	0.208
	(58.1-94.6)	(77.5-98.2)	(3.22-29.3)	(0.087-0.505)
Q_{MR}:Q_{Ao}				
≥0.79	90.5	77.8	4.07	0.122
	(69.6-98.8)	(60.8-89.9)	(2.18-7.62)	(0.032-0.463)
≥1.10	85.7	97.2	30.9	0.147
	(63.7-97.0)	(85.5-99.9)	(4.43-215.0)	(0.052-0.420)

chamber diameter. The pathophysiology of DMVD is directly related to *volume* (ie, VOL MR) and volume per unit time (ie, *flow* or Q_{MR}:Q_{Ao}) as opposed to 1-dimensional cardiac chamber dimensions. For example, increased Q_{MR}:Q_{Ao} results in reduced renal blood and is a potent stimulus for renin secretion, activation of neurohormonal systems, and resultant chamber enlargement.[33,34] Finally, simple 1-dimensional measures, such as LV diastolic diameter, fail to account for systolic function, LVVs, or FSV, all of which affect MR VOL. Thus, 1-dimensional measurements of cardiac chamber diameter are a crude estimation of MR severity that lie far removed from the principal determinants of MR VOL as opposed to multidimensional indices such as RF, EROA, or Q_{MR}:Q_{Ao}.

Our findings have a high degree of clinical relevance. A consensus-based staging system[35] stratifies dogs with preclinical DMVD solely on the basis of unidimensional heart size. Stage B1 includes dogs with normal chamber dimensions whereas stage B2 describes dogs with radiographic or echocardiographic evidence of enlargement. Under the current system, further differentiation of dogs in Stage B1 is not possible, yet results of the current study clearly demonstrate that RF is able to differentiate a wide range MR severity. Our study reveals the odds of having LA:Ao ≥1.6 and LVEDdN ≥1.7 were 108 times higher for dogs with RF ≥50% vs those with RF <50%. The implication of our results is that RF might help determine which dogs are at highest risk for future left heart enlargement, and a longitudinal study to test this hypothesis is warranted. It is tempting to speculate that as RF increases toward 50% in dogs with stage B1 disease, the risk for cardiomegaly substantially increases. This is of particular interest because of the high variability associated with rate of progression.[5] Our data indicate that a simple method for deriving RF in dogs with preclinical DMVD helps discriminate MR severity. These findings are consistent with studies of asymptomatic MR in human patients wherein RF represents an important benchmarking tool with respect to disease severity and prognosis.[36] Guidelines developed by the American Heart Association and American College of Cardiology for management of valvular heart disease in asymptomatic MR patients specifically consider RF ≥50% as a major risk factor for development of clinical signs or need for valve surgery, especially when accompanied by declining myocardial function.[12]

Another marker of MR severity is EROA. In the current study, the odds of having LA:Ao ≥1.6 and LVEDdN ≥1.7 were 100 times higher for dogs with EROA:BSA ≥0.347 vs dogs with EROA:BSA <0.347. Failure of the valve leaflets to adequately close during ventricular systole results in a mitral valve regurgitant orifice through which MR flows. The anatomic regurgitant orifice area can be measured using 2D or 3D planimetry or approximated by derivation of EROA, which corresponds to the CSA of the narrowest region of MR flow (ie, the vena contracta) as it moves from LV to atrium. In humans with primary MR, EROA <0.20, 0.20-0.39, and ≥0.40 cm^2 are considered as indicative of mild, moderate, and severe MR, respectively.[37] In a longitudinal study of humans with asymptomatic primary MR, EROA was the strongest predictor of future morbidity and mortality.[37] Patients with EROA ≥0.40 cm^2 experienced substantially higher risk for major adverse cardiac events (relative risk, 5.66 [95% CI, 3.07-10.56]) and cardiac-related death (relative risk, 5.21 [95% CI, 1.98-14.40]) than patients with lesser values.[37] Direct comparison of nonindexed values of EROA between humans and dogs is difficult because of differences in body size. Assuming average human BSA for an adult male and female of 1.6 and 1.9 m^2, respectively, severe MR would be defined as EROA:BSA >0.21 cm/m^2 in males and >0.25 cm/m^2 in females.

The results of the current study agree with and expand upon previous studies examining RF and EROA in dogs with DMVD. There is a relationship between RF and clinical severity of DMVD. In a study of 67 dogs,[14] RF was significantly higher in dogs with moderate and severe CHF (RF, 58 and 73%, respectively) vs those with asymptomatic MR (RF, 41%). In 2 other studies,[15,38] dogs with early or moderate CHF had RF values of 56 and 57% vs RF value of 33% in dogs with mild disease. Relatively few studies[17,19] have examined EROA in relation to clinical severity of DMVD. One study[38] reported absolute (ie, nonindexed) EROA values of 0.07, 0.19, and 0.37 cm^2 in dogs with asymptomatic MR, mild CHF, and severe CHF, respectively. These values are roughly comparable with median EROA values in Groups 1 (0.084 cm^2) and 2 (0.244 cm^2) in the current study. At least 2 previous studies have examined the relationship between echocardiographic RF and left atrial size. In 1 study of 17 dogs,[15] the relationship between RF and LA:Ao was described as curvilinear. In a second study of 67 dogs,[14] the plot of RF to LA:Ao was fitted to a straight line with modest correlation (R^2 = 0.348). Visual inspection of that plot reveals a high degree of similarity to Figure 1A in the current study, and it is tempting to speculate that the previously published plot might have been better fit using a nonlinear function.

The results of the current study offer clues as to why a RF of 50% is an important threshold. The 3 main indices of MR investigated by

the current study are closely related. The EROA, when small, is associated with relatively high resistance and thus, limits Q_{MR}. Conversely, larger EROA permits greater Q_{MR} and by extension, greater MR VOL. As such, MR remains mild until the EROA is sufficiently large to the point that Q_{MR} equals or surpasses Q_{Ao} resulting in Q_{MR}:Q_{Ao} ≥1.[39] At a point when Q_{MR}:Q_{Ao} = 1, MR VOL will necessarily exceed FSV because of the fact that LVET is shorter than MR flow time (ie, the aortic valve closes at a time point earlier than the mitral valve opens), and by extension, RF will exceed 50%. The importance of RF values ≥50% to the pathophysiology of DMVD is supported by the fact that dogs in Group 2 exhibited decreased Q_{Ao}, FSV, and cardiac index and a mean Q_{MR}:Q_{Ao} ≥1 as compared to dogs in Group 1. Decreased forward output is a powerful stimulus for neurohormonal activation, fluid retention, and cardiac enlargement.[40] Once cardiomegaly ensues, it is well accepted that "MR begets MR" by causing ever increasing amounts of annular dilation, stress on the valve apparatus, and worsening of existing MR.[12] Thus, the importance of RF ≥50% is likely related to the start of this vicious cycle resulting in an increase in the rate of heart enlargement and disease severity.

Our study used a simple volumetric method to calculate indices of MR severity. The limitations of such methods include risk of underestimating or overestimating the true LV volume if foreshortened or oblique LV images are used, as well as compounding of errors when the systolic volume is subtracted from the diastolic volume.[11] The assumption inherent in the prolate ellipsoid method, that is, LV length is twice the diameter, becomes less accurate as the ventricle enlarges and takes on a more spherical shape. Correction factors, such as the Teichholz index, have been employed in humans to adjust for such changes, but are not specifically suited for use in the dog. The strengths of volumetric methods are their relative ease of use, lack of reliance on color flow Doppler, and applicability in cases of multiple or eccentric MR jets,[11] which are common in dogs with DMVD. Despite the simplicity of the current method, RF showed good discrimination of the study cohort. The validity of the prolate ellipsoid method is supported by acquisition of similar results using the mitral inflow method, which does not rely on measurement of the LV. There are a host of echocardiographic methods for quantification of LV volume and MR severity in dogs, including method of discs,[41] area-length,[42] anatomic or EROA by 3D echo,[17,43] regurgitant jet area,[38] vena contracta width,[18,44] and proximal isovelocity surface area (PISA),[14,15,19] respectively. The PISA method, in particular, has been extensively evaluated in humans with MR and its strengths and limitations are reviewed elsewhere.[11,45,46] In the authors' experience, and similar to others,[47] the PISA method is difficult to utilize routinely in dogs with MR, as it is difficult to measure, is invalidated in cases of multiple or highly eccentric MR jets, and requires a level of color flow image quality, frame rate, orientation, machine settings, and degree of offline analysis that is not always practical in a routine clinical setting. In humans, there are similar challenges related to use of PISA.[48] For example, 1 study reported that in 109 patients with asymptomatic MR that underwent comparative evaluation by cardiac magnetic resonance imaging (MRI) and echocardiography, only 53/109 (49%) had PISA studies deemed suitable for analysis.[36] Direct measurement of the anatomic or EROA is another quantitative method and can be performed using 2D, 3D, or color flow Doppler echocardiography, but is limited by high interobserver and intraobserver variability.[43]

There are several important potential limitations to this study. The study was observational in nature and longitudinal studies are needed to relate RF with the timeline of disease progression. Longitudinal studies are difficult and heavily resource-consuming, and in humans, much of the natural history of asymptomatic MR is derived from observational data,[3] however, the full value of the proposed indices will only be known from such studies. For instance, it is tempting to speculate that multidimensional indices of MR severity in dogs with preclinical DMVD will predict risk of future cardiac enlargement, onset of clinical signs, and prognosis in a way that current 1-dimensional measurements are unable to. In humans with DMVD, no single index best quantifies MR severity, and at least 6 different anatomic and qualitative and quantitative echocardiographic findings are integrated to best assess MR severity.[11,49,50] Future studies in dogs might investigate which combination of measures provides the greatest information. As previously mentioned, the volumetric method used in this study was based on assumptions of LV shape that are not necessary using more sophisticated techniques such as the planimetric method of disks (ie, modified Simpson's method) or 3-dimensional imaging. Furthermore, we used a combination of both M-mode and 2D-based methods to measure the diameter of the LV and this might have introduced additional variability of results. In the current study, we specifically aimed for a balance between the value of additional analysis and ease of daily clinical usage. Future studies that examine the incremental value of more sophisticated (and labor intensive) multidimensional methods for the assessment of MR severity are of interest. The methods used in this study specifically measured VTI_{Ao}, and $D_{Ao\text{-}STJ}$ at the aortic sinotubular junction. As such, the diameter of the aortic sinus of Valsalva, which is commonly measured as part of the 2-dimensional LA:Ao measurement, should not be used as a substitute. Future studies might explore the precision of VTI_{Ao} and corresponding measures of diameter at various different locations, such as the left ventricular outflow tract, sinus of Valsalva, or base of the aortic valves. The relationship among echocardiographic indices of MR severity and LV and left atrial size was tested against a predicted regression model, and it is possible that an unexplored model would provide better fit. Previous studies have shown correlation between cardiac MRI and measurement of RF using the PISA method, as well as between MRI and the echocardiographic vena contracta width and mitral Emax in dogs with DMVD.[18] In the current study, comparison of RF, EROA, and Q_{MR}:Q_{Ao} to a gold standard was not performed, however, the proposed utility of these parameters (ie, as repeated measures in an individual) is less reliant on validation against an external reference standard and more reliant on internal consistency. Our study involved a single referral center and results should be confirmed in a larger and more geographically diverse population; however, our study cohort included a typical older and small-breed population of dogs with DMVD. The patient sample size was relatively small and confidence intervals around OR values were wide, however, the magnitude of effect was substantial and clinically relevant across the range of estimates. Finally, measurement of MR VOL by the technique used in the current study is invalid or difficult to perform in dogs with substantial aortic insufficiency or arrhythmias, such as atrial fibrillation.

In conclusion, measurement of RF, EROA, and Q_{MR}:Q_{Ao} in dogs with preclinical DMVD is supported by the mathematical and pathophysiological aspects of their relationship with MR and differentiates severity of DMVD in a manner that 1-dimensional measurements of chamber diameter do not.

ACKNOWLEDGMENT

We thank Lila Sierra, Rory Loughran, and Drs. Megan Poad and Alex Crooks for assistance.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

University of Pennsylvania IACUC approval #806547.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Mark A. Oyama https://orcid.org/0000-0002-5218-9226

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SUPPORTING INFORMATION

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How to cite this article: Larouche-Lebel É, Loughran KA, Oyama MA. Echocardiographic indices and severity of mitral regurgitation in dogs with preclinical degenerative mitral valve disease. *J Vet Intern Med*. 2019;33:489–498. https://doi.org/10.1111/jvim.15461