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Echocardiographic estimation of left ventricular-arterial coupling in dogs with myxomatous mitral valve disease

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Abstract

Background: The effective arterial elastance (Ea) to left ventricular (LV) end-systolic elastance (Ees) ratio (Ea/Ees) is an index of the interaction between LV and systemic arterial systems, left ventricular-arterial coupling (VAC). The Ea is an index of total arterial load of the LV, whereas Ees is an index of LV systolic function. In humans, inappropriate VAC based on increased Ea/Ees estimated using echocardiography is associated with more advanced heart disease severity.

Hypothesis: Left ventricular-arterial coupling assessed by echocardiographic estimation of Ea/Ees is associated with disease severity in dogs with myxomatous mitral valve disease (MMVD).

Animals: Ninety MMVD dogs and 61 healthy dogs.

Methods: Prospective cross-sectional study. The MMVD dogs were classified into stages B1, B2, or C according to American College of Veterinary Internal Medicine guidelines. Effective arterial elastance was echocardiographically estimated using the formula: mean blood pressure/(forward stroke volume/body weight). End-systolic elastance was echocardiographically estimated using the formula: mean blood pressure/(LV end-systolic volume/body weight). The ratio Ea/Ees was calculated.

Results: The ratio Ea/Ees was higher in stage B2 dogs than in healthy dogs and dogs stage B1 (both $P < .0001$), and higher in stage C dogs than in healthy dogs and dogs in the other 2 stages (healthy vs C and B1 vs C, $P < .0001$; B2 vs C, $P = .0005$). Multivariable logistic regression analysis showed that Ea/Ees and the peak velocity of early diastolic transmitral flow to isovolumic relaxation time ratio were independent predictors of stage C among echocardiographic indices in MMVD dogs.

Abbreviations: A′, peak velocity of the late diastolic wave of myocardial velocity; A, peak velocity of the late diastolic wave of transmitral flow; ACVIM, American College of Veterinary Internal Medicine; CV, coefficient of variation; E′, peak velocity of the early diastolic wave of myocardial velocity; E, peak velocity of the early diastolic wave of transmitral flow; Ea, effective arterial elastance; Ees, left ventricular end-systolic elastance; ESV, left ventricular end-systolic volume; FSV, forward stroke volume; IVRT, isovolumic relaxation time; LA/Ao, left atrial to aortic ratio; LVIDDN, left ventricular end-diastolic internal diameter normalized for body weight; LVIDSN left ventricular end-systolic internal diameter normalized for body weight; MBP, mean blood pressure; MMVD, myxomatous mitral valve disease; PI, prediction interval; S′, peak velocity of the systolic wave of myocardial velocity; VAC, left ventricular-arterial coupling.

Conclusions and Clinical Importance: Inappropriate VAC assessed by echocardiographically estimated Ea/Ees is associated with advanced disease severity in dogs with MMVD.

KEYWORDS
dogs, Ea/Ees, elastance, heart failure, mitral regurgitation

1 | INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the most common acquired heart disease of dogs in many countries.[1,2] Progressive myxomatous degeneration of mitral valve apparatus leads to mitral regurgitation, which eventually can cause severe left-sided volume overload, ultimately leading to left-sided heart failure and death.[1,2]

The interaction between the left ventricle and systemic arterial systems is termed left ventricular-arterial coupling (VAC). It is related to the pump efficiency of the left ventricle, and the deterioration of VAC plays an important role in the pathophysiology of various heart diseases.[3,4] In humans, VAC has been assessed invasively by obtaining left ventricular pressure-volume loops during cardiac catheterization to determine the effective arterial elastance (Ea) to the left ventricular end-systolic elastance (Ees) ratio (Ea/Ees).[3,4] End-systolic elastance is an index of left ventricular systolic function and has been determined as the slope of the end-systolic pressure-volume relationship of left ventricular pressure-volume loops obtained during acutely altered loading conditions.[3,4] Effective arterial elastance is an index of the total arterial load of the left ventricle, and has been determined as the ratio of the left ventricular end-systolic pressure to the left ventricular stroke volume.[3,4] Recently, in humans, Ea/Ees has been noninvasively estimated by echocardiography using various approaches.[3,5-8] Notably, previous studies found that inappropriate VAC on the basis of increased Ea/Ees estimated by echocardiography is associated with a more advanced heart failure function class (New York Heart Association function class) or poorer prognosis in human patients with heart disease.[7,8]

To our knowledge, echocardiographic estimation of VAC has not been reported in dogs with naturally occurring heart disease. Our aim was to determine the VAC status estimated by echocardiography in dogs with MMVD. Our hypothesis was that inappropriate VAC assessed by echocardiographic estimation of Ea/Ees would be associated with advanced disease severity in dogs with MMVD.

2 | MATERIALS AND METHODS

The study received ethical approval from the Hokkaido University, Sapporo, Hokkaido, Japan (Approval No. 18-0152). The study consisted of a clinical cross-sectional study and a repeatability study. Each owner signed an informed consent form before recruitment into the clinical cross-sectional study.

2.1 | Clinical cross-sectional study

Dogs that were presented to the Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University and underwent echocardiographic examination were prospectively recruited into the study from April 2017 to August 2018. Recruited dogs underwent standard echocardiographic studies including B-mode, M-mode, pulsed-wave Doppler, and color Doppler imaging for various reasons, including cardiac murmur, clinical signs possibly associated with cardiac disease (eg, cough, respiratory distress, syncope), and pre-anesthetic assessment. Among the recruited dogs, dogs were included as MMVD dogs in the study: (a) if they had a systolic cardiac murmur with a point of maximum intensity over the left cardiac apex and (b) if they were echocardiographically diagnosed with MMVD on the basis of the identification of mitral regurgitation by color Doppler imaging with the presence of mitral valve prolapse or any degree of mitral valve thickening on B-mode imaging. In addition, among the recruited dogs, dogs were included as healthy dogs if they had no cardiac abnormalities on the basis of complete physical examination, measurement of systemic arterial blood pressure, ECG, and abovementioned standard echocardiographic studies. Dogs were excluded from the study: (a) if their body weights were >15 kg (the study was intended to include only small breed dogs), (b) if they had congenital heart disease, dilated cardiomyopathy, or other acquired heart disease (eg, infective endocarditis), (c) if they had a hemodynamically relevant arrhythmia (ie, arrhythmias other than sinus arrhythmia, sinus bradycardia, sinus tachycardia, a single atrial premature complex, or a single ventricular premature complex), (d) if they had clinically relevant extracardiac disease that might affect cardiac function or hemodynamics (eg, chronic kidney disease [plasma creatinine concentration ≥1.4 mg/dL]; azotemia that had developed after commencement of cardiovascular medications including loop diuretics was permitted), systemic hypertension (systolic blood pressure >170 mm Hg), hyperadrenocorticism, or (e) if they were sufficiently anxious that their motion (eg, trembling) was deemed likely to make the systemic arterial blood pressure measurement unreliable. Each dog was included only once in the study.

The MMVD dogs were classified into stage B1, B2, or C according to the American College of Veterinary Internal Medicine (ACVIM) consensus statement.[1] Stage B1 included asymptomatic dogs with MMVD that was not sufficiently severe to meet echocardiographic criteria of left ventricular and atrial enlargement and trigger the use of pimobendan to delay the onset of heart failure (ie, left atrial to aortic ratio [LA/Ao] <1.6 or left ventricular end-diastolic internal diameter normalized for body weight [LVIDDN] <1.7).[1] Stage B2 included asymptomatic dogs with MMVD that

was sufficiently severe to meet echocardiographic criteria of left ventricular and atrial enlargement and trigger the use of pimobendan to delay the onset of heart failure (ie, LA/Ao ≥1.6 and LVIDDN ≥1.7).[1] Stage C included MMVD dogs with current or past clinical and radiographic evidence of cardiogenic pulmonary edema.[1]

The following data were obtained by owner interviews and physical examinations: age, sex, body weight, breed, and medical history.

An oscillometric blood pressure device (petMAP graphic, Ramsey Medical, Inc, Tampa, Florida) was used to obtain systolic, diastolic, and mean (MBP) blood pressures according to the ACVIM consensus statement.[9] Dogs were manually restrained in ventral or lateral recumbency without sedation. An appropriately-sized cuff with a cuff width 30% to 40% of the circumference of the limb cuff site was placed on the right or left forelimb. Blood pressure measurements were taken repeatedly until 5 consecutive or nearly consecutive consistent (<20% variability) values were recorded. The 5 recorded values were averaged and used as the final result of blood pressure measurement.

Echocardiographic examinations were performed by 1 operator (TO) using a commercially available ultrasonographic machine with a 3 to 6 MHz sector probe and simultaneous ECG recording (Artida, Canon Medical Systems Corp., Ohtawara, Tochigi, Japan). Dogs were manually restrained in right and left lateral recumbency without sedation. All data were digitally stored and analyzed off-line by 1 investigator (TO). Echocardiographic examinations and analysis were performed without blinding to clinical data and dog identity. Heart rate was determined using RR intervals between 5 consecutive cardiac cycles on ECG at the time when aortic Doppler flow was recorded. From a right parasternal short axis view at the chordae tendineae level, left ventricular M-mode variables including left ventricular end-diastolic and end-systolic internal diameters and left ventricular fractional shortening were measured using the leading edge-to-leading edge method. Left ventricular end-diastolic internal diameter normalized for body weight (LVIDDN) was calculated using the following formula: left ventricular end-diastolic internal diameter (cm)/body weight (kg)$^{0.294}$.[1,10] Left ventricular end-systolic internal diameter normalized for body weight (LVIDSN) was calculated using the following formula: left ventricular end-systolic internal diameter (cm)/body weight (kg)$^{0.315}$.[10] From a 2-dimensional image of the right parasternal short-axis view at the aortic root level, LA/Ao was determined.[1] Briefly, at a frame soon after the end of the T wave on ECG, the aortic diameter was measured from inside edge to inside edge along the junction of the noncoronary and left coronary cusps, and the left atrial diameter was measured from inside edge to inside edge on the same line as the aortic diameter (ie, Swedish method).[1] From a left apical 4-chamber view, transmitral Doppler indices including peak velocities of the early diastolic (E) and late diastolic (A) waves and the E to A ratio (E/A) were recorded. When E and A waves were partially fused, only E was recorded. From a left apical 4-chamber view, tissue Doppler indices including peak velocities of the early diastolic (E′), late diastolic (A′), and systolic (S′) waves of myocardial velocity were recorded with sample volume positioned at the lateral mitral annulus. When E′ and A′ waves were partially fused, only E′ was recorded. No dogs had completely fused E′ and A′ waves. The E to E′ ratio (E/E′) was calculated. From a left apical 5-chamber view, the isovolumic relaxation time (IVRT) was determined with a sample volume of 6 to 8 mm placed at an intermediate position between the left ventricular inflow and outflow tracts.[11] The E to IVRT ratio (E/IVRT) was calculated.

The Ees was estimated using the following formula: MBP/(left ventricular end-systolic volume [[mL]/body weight kg]).[5,6] The left ventricular end-systolic volume (ESV) was determined using the monoplane Simpson method of disc from a 2-dimensional image of the left apical 4-chamber view.[12] Briefly, in the end-systolic frame, defined as the frame before mitral valve opening, manual tracing along the endocardial border with papillary muscles included in the ESV calculation from the septal side of the mitral annulus to the other side was performed. Then, the left ventricular maximal length was measured from the middle of the mitral annuli to the endocardial border of the left ventricular apex. After these procedures, ESV was calculated automatically by the ultrasonographic machine.[12] The Ea was estimated using the following formula: MBP/(forward stroke volume [mL]/body weight [kg]).[13,14] The forward stroke volume (FSV) was calculated by multiplying the time velocity integral of the aortic Doppler flow by the aortic luminal area. The aortic Doppler flow was recorded from the subcostal 5-chamber view with sample volume placed just distal to the aortic valve and manually traced to obtain the time velocity integral. The aortic luminal area was determined by tracing the aortic lumen on the 2-dimensional image of the right parasternal short axis view at the aortic root level,[15] which was used for the determination of LA/Ao. The Ea to Ees ratio (Ea/Ees) was determined. As described above, ESV and FSV were normalized for body weight (ie, divided by body weight) for the determination of Ees and Ea, respectively. This was done because linear regression analysis after logarithmic transformation of the data indicated that the relationships between body weight and each of ESV and FSV were linear in the healthy dogs enrolled in the study; the scaling exponent (b) in the allometric equation ($Y = aX^b$) was close to 1 for ESV (b = 1.13) and FSV (b = 0.85).[10] Forward cardiac output was calculated by multiplying FSV by heart rate and normalized for body weight by dividing it by body weight.

The mean of 5 consecutive cardiac cycles was calculated for ESV and FSV, and the mean of 3 consecutive cardiac cycles was calculated for the other conventional echocardiographic indices.

2.2 | Repeatability study

Six intact female beagle dogs (age, 1-3 years; body weight, 9.2-14.5 kg) that were part of a research colony at the investigators' laboratory were used in the repeatability study. All dogs were confirmed to be healthy and to have no cardiac abnormalities on the basis of complete physical examination, ECG, and standard echocardiographic studies including B-mode, M-mode, pulsed-wave Doppler, and color Doppler imaging.

Each dog underwent echocardiographic examinations and blood pressure measurements on 3 different days 1 week apart conducted by 1 operator (TO). On a given day, each dog was examined 3 times

(8 am-12 pm, 12-4 pm, and 4-6 pm). During each examination, Ees, Ea, and Ea/Ees were estimated as described above.

2.3 | Statistical analysis

Statistical analysis was performed using commercially available software (JMP pro version 14.0.0, SAS Institute, Inc, Cary, North Carolina; IBM SPSS Statistics version 21, IBM Corp, Armonk, New York). The level of significance was set at $P < .05$.

In this clinical cross-sectional study, the normal distribution of continuous data was confirmed using the Shapiro-Wilk test. Continuous data are reported as mean (SD) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. The overall difference among stages was determined by 1-way analysis of variance for normally distributed data and using the Kruskal-Wallis test for non-normally distributed data. Post hoc multiple comparisons were performed by Tukey's honest significant difference test for normally distributed data and using the Steel-Dwass test for non-normally distributed data. For categorical data, the overall difference among stages was determined using Fisher's exact test and post hoc multiple comparisons were made using Fisher's exact test with Bonferroni correction. Multivariable logistic regression analysis was performed to determine independent predictors of stage C in MMVD dogs. Explanatory variables with $P < .20$ on univariable logistic regression analysis including heart rate, conventional echocardiographic indices, Ees, Ea, and Ea/Ees were selected and a stepwise forward selection method with an entry criterion of $P < .05$ was used. The Hosmer-Lemeshow test was performed to evaluate the goodness-of-fit of the generated model. Multicollinearity of explanatory variables in the generated model was assessed using the variance inflation factor. The 95% prediction intervals (PIs) of Ees, Ea, and Ea/Ees were computed from the data in the healthy dogs using the Reference Value Advisor with the robust method with Box-Cox transformation.[16,17]

In the repeatability study, within-day and between-day coefficients of variation (CVs) were determined using the following linear model:[18]

$$Y_{ijk} = \mu + \text{day}_i + \text{dog}_j + (\text{day} \times \text{dog})_{ij} + \varepsilon_{ijk}$$

where Y_{ijk} represents the kth value measured for dog j on day i, μ represents the general mean, day_i represents the differential effect of day i, dog_j is the differential effect of dog j, $(\text{day} \times \text{dog})_{ij}$ represents the interaction term between day and dog, and ε_{ijk} represents the model error. The within-day SD was estimated as the residual SD of the model, whereas the between-day SD was estimated as the SD of the differential effect of day. The corresponding CVs were calculated by dividing each SD by the mean.

3 | RESULTS

In this clinical cross-sectional study, 90 MMVD dogs including 38 in stage B1, 32 in stage B2, and 20 in stage C, and 61 healthy dogs were included. At the time of echocardiographic examinations, cardiogenic pulmonary edema was present in 7 dogs in stage C and it had been successfully controlled using cardiovascular medications in 13 dogs in stage C. Demographic data, medical history, and results of blood pressure measurements are shown in Table 1. In MMVD dogs, the most commonly represented breed was Chihuahua (n = 26), followed by Pomeranian (n = 9), Toy Poodle (n = 9), Maltese (n = 6), Miniature Dachshund (n = 6), and Shih Tzu (n = 6). In healthy dogs, the most commonly represented breed was Chihuahua (n = 13), followed by Miniature Dachshund (n = 9), Yorkshire Terrier (n = 6), mixed breed (n = 5), Miniature Schnauzer (n = 4), and Pomeranian (n = 3). Age was older in stages B1, B2, and C than in healthy dogs. Sex and body weight were not different among the stages. The MMVD dogs in the more advanced stage were more likely to have received cardiovascular drugs. Eight dogs in stage C were not receiving any diuretic. Among them, 5 dogs underwent echocardiographic examinations before discharge on PO cardiovascular drugs including a loop diuretic for home care after the diagnosis of cardiogenic pulmonary edema. In the other 3 dogs, after cardiogenic pulmonary edema had been successfully controlled using angiotensin-converting enzyme inhibitors, pimobendan, and diuretics, diuretics could be tapered and finally discontinued before echocardiographic examinations. These 3 dogs were successfully tapered off diuretics 2, 3, and 8 months before echocardiographic evaluations. The MBP was not different among stages.

Results of echocardiographic examination are summarized in Table 2. Heart rates were higher in stages B2 and C than in healthy dogs. The LVIDDN and LA/Ao values increased with disease severity. The LVIDSN and left ventricular fractional shortening were higher in stage B2 and C dogs than in healthy dogs and stage B1 dogs. One dog in stage C had a heart rate so rapid that transmitral E and A waves and myocardial E′ and A′ waves were partially fused; A and A′ could not be determined in this dog. No dogs had completely fused E and A waves or fused E′ and A′ waves. The E, E/A, E/E′, and E/IVRT values increased with disease severity. The E′ and S′ values were higher in stage B2 and C dogs than in healthy dogs and stage B1 dogs. The A values were higher in stage B1 and B2 dogs than in healthy dogs. The A′ values were higher in stage B2 dogs than in dogs of the other 3 stages. The IVRT values were shorter in stage C dogs than in dogs of the other 3 stages. The ESV values normalized for body weight were higher in stage B2 and C dogs than in healthy dogs and stage B1 dogs. The FSV values normalized for body weight were lower in stage C dogs than in dogs of the other 3 stages. Forward cardiac output values normalized for body weight were not different among the stages.

The Ees values were lower in stage B2 and C dogs than in healthy dogs and stage B1 dogs (Table 2; Figure 1A). The Ea values were higher in stage C dogs than in dogs of the other 3 stages (Figure 1B). The Ea/Ees values were higher in stage B2 dogs than in healthy dogs and stage B1 dogs, and higher in stage C dogs than in dogs of the other 3 stages (Figure 1C).

On the basis of univariable logistic regression analysis, heart rate, LVIDDN, LVIDSN, LA/Ao, E, IVRT, E/IVRT, E′, S′, E/E′, Ees, Ea, and Ea/Ees were selected (ie, $P < .20$) for multivariable logistic regression

TABLE 1 Demographic data, medical history, and results of blood pressure measurements in 90 dogs with myxomatous mitral valve disease and 61 healthy dogs

					P						
	Healthy (n = 61)	**Stage B1 (n = 38)**	**Stage B2 (n = 32)**	**Stage C (n = 20)**	**Overall**	**Healthy vs B1**	**Healthy vs B2**	**Healthy vs C**	**B1 vs B2**	**B1 vs C**	**B2 vs C**
Age (years)	7.5 (4.3-9.9)	11 (9.0-13.2)	11.8 (10.0-13.8)	12.3 (10.2-13.1)	<.0001	<.0001	<.0001	<.0001	.7	.59	.98
Sex (female/male)	31/30	13/25	13/19	9/11	.43						
Body weight (kg)	4.5 (3.1-6.6)	5.0 (3.4-7.0)	4.5 (3.4-6.4)	4.2 (2.7-6.7)	.7						
Cardiovascular drugs (yes/no)											
ACEI	0/61	7/31	15/17	19/1	<.0001	.005	<.0001	<.0001	.11	<.0001	.002
Pimobendan	0/61	0/38	12/20	20/0	<.0001	.87	<.0001	<.0001	.005	<.0001	<.0001
Loop diuretics	0/61	0/38	0/32	11/9	<.0001	1.00	1.00	<.0001	1.00	<.0001	<.0001
Spironolactone	0/61	0/38	4/28	5/15	<.0001	1.00	.07	.004	.23	.02	1.00
SBP (mm Hg)	148 ± 12	153 ± 11	143 ± 12	146 ± 12	.008	.18	.25	.94	.004	.18	.8
DBP (mm Hg)	83 ± 10	87 ± 12	83 ± 10	88 ± 11	.16						
MBP (mm Hg)	105 ± 10	109 ± 11	104 ± 9	108 ± 10	.07						

Note: Mean ± SD for normally distributed continuous data, median (interquartile range) for non-normally distributed continuous data, and number (n) for categorical data.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

TABLE 2 Results of echocardiographic examination in 90 dogs with myxomatous mitral valve disease and 61 healthy dogs

					P						
	Healthy (n = 61)	Stage B1 (n = 38)	Stage B2 (n = 32)	Stage C (n = 20)	Overall	Healthy vs B1	Healthy vs B2	Healthy vs C	B1 vs B2	B1 vs C	B2 vs C
Heart rate (bpm)	109 ± 26	116 ± 26	128 ± 38	148 ± 28	<.0001	.65	.01	<.0001	.27	.0007	.1
LVIDDN	1.34 (1.25-1.40)	1.44 (1.35-1.54)	1.96 (1.79-2.09)	2.15 (2.03-2.29)	<.0001	.001	<.0001	<.0001	<.0001	<.0001	.02
LVIDSN	0.71 ± 0.13	0.70 ± 0.12	0.92 ± 0.14	0.99 ± 0.18	<.0001	.97	<.0001	<.0001	<.0001	<.0001	.22
FS (%)	44.7 ± 8.5	49.5 ± 7.0	51.7 ± 6.4	52.0 ± 6.4	<.0001	.01	.0002	.001	.6	.6	1.00
LA/Ao	1.38 (1.28-1.46)	1.52 (1.43-1.59)	1.96 (1.82-2.22)	2.48 (2.18-2.78)	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.002
E (m/s)	0.60 (0.52-0.72)	0.74 (0.65-0.90)	1.11 (0.95-1.35)	1.29 (1.13-1.54)	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.14
A (m/s, n = 150)	0.54 (0.46-0.64)	0.78 (0.63-0.96)	0.84 (0.69-1.07)	0.59 (0.53-0.99, n = 19)	<.0001	<.0001	<.0001	.20	.38	.62	.14
E/A (n = 150)	1.09 (0.85-1.43)	0.96 (0.85-1.08)	1.22 (1.06-1.51)	2.14 (1.15-2.99, n = 19)	<.0001	.37	.24	.001	.001	.0002	.07
E′ (cm/s)	8.2 ± 2.1	8.0 ± 2.0	10.4 ± 2.2	10.8 ± 3.4	<.0001	.97	.0001	.0002	.0001	.0002	.95
A′ (cm/s, n = 150)	9.0 ± 2.5	9.4 ± 2.5	11.3 ± 2.4	8.9 ± 2.8 (n = 19)	.0003	.81	.0002	1.00	.01	.84	.005
S′ (cm/s)	7.8 (6.3-9.2)	8.4 (7.1-9.2)	10.0 (8.5-12.3)	11.0 (8.2-13.4)	<.0001	.39	<.0001	.0004	.001	.01	.97
E/E'	7.3 (6.6-8.7)	9.9 (8.6-11.1)	10.0 (8.8-12.6)	12.1 (10.0-15.5)	<.0001	<.0001	<.0001	<.0001	.79	.01	.16
IVRT (ms)	53 (47-59)	47 (42-56)	53 (42-65)	39 (32-48)	<.0001	.08	1.00	<.0001	.58	.007	.009
E/IVRT	1.12 (0.90 -1.43)	1.54 (1.27-1.84)	2.11 (1.55-2.72)	3.63 (2.36-4.45)	<.0001	<.0001	<.0001	<.0001	.008	<.0001	.009
ESV/BW (mL/kg)	0.68 (0.52-0.85)	0.64 (0.49-0.83)	1.12 (0.76-1.38)	1.43 (1.15-1.69)	<.0001	1.00	<.0001	<.0001	<.0001	<.0001	.09
FSV/BW (mL/kg)	3.41 (3.00-3.84)	2.87 (2.57-3.60)	2.90 (2.54-3.63)	2.11 (1.62-2.63)	<.0001	.04	.07	<.0001	1.00	.0002	.001
FCO/BW (mL/min/kg)	3.65 (3.07-4.55)	3.39 (2.75-3.94)	3.70 (2.71-4.74)	3.07 (2.48-3.79)	.1						
Ees (mm Hg/mL/kg)	154 (121-205)	170 (125-226)	96 (73-125)	72 (66-101)	<.0001	.96	<.0001	<.0001	<.0001	<.0001	.21
Ea (mm Hg/mL/kg)	31 (27-35)	38 (28-43)	36 (28-40)	52 (39-70)	<.0001	.02	.32	<.0001	.86	.0007	.0006
Ea/Ees	0.18 (0.14-0.26)	0.21 (0.16-0.29)	0.35 (0.28-0.55)	0.72 (0.46-0.99)	<.0001	.41	<.0001	<.0001	<.0001	<.0001	.0005

Note: Mean ± SD for normally distributed continuous data and median (interquartile range) for non-normally distributed continuous data.

Abbreviations: A, peak velocity of the late diastolic wave of transmitral flow; A′, peak velocity of the late diastolic wave of myocardial velocity; E, peak velocity of the early diastolic wave of transmitral flow; E′, peak velocity of the early diastolic wave of transmitral flow; Ea, effective arterial elastance; E/A, E to A ratio; Ea/Ees, Ea to Ees ratio; E/E′, E to E′ ratio; Ees, left ventricular end-systolic elastance; E/IVRT, E to IVRT ratio; ESV/BW, left ventricular end-systolic volume divided by body weight; FS, left ventricular fractional shortening; FCO/BW, forward cardiac output divided by body weight; FSV/BW, forward stroke volume divided by body weight; IVRT, isovolumic relaxation time; LA/Ao, left atrial to aortic ratio; LVIDDN, left ventricular end-diastolic internal diameter normalized for body weight; LVIDSN, left ventricular end-systolic internal diameter normalized for body weight; S′, peak velocity of the systolic wave of myocardial velocity.

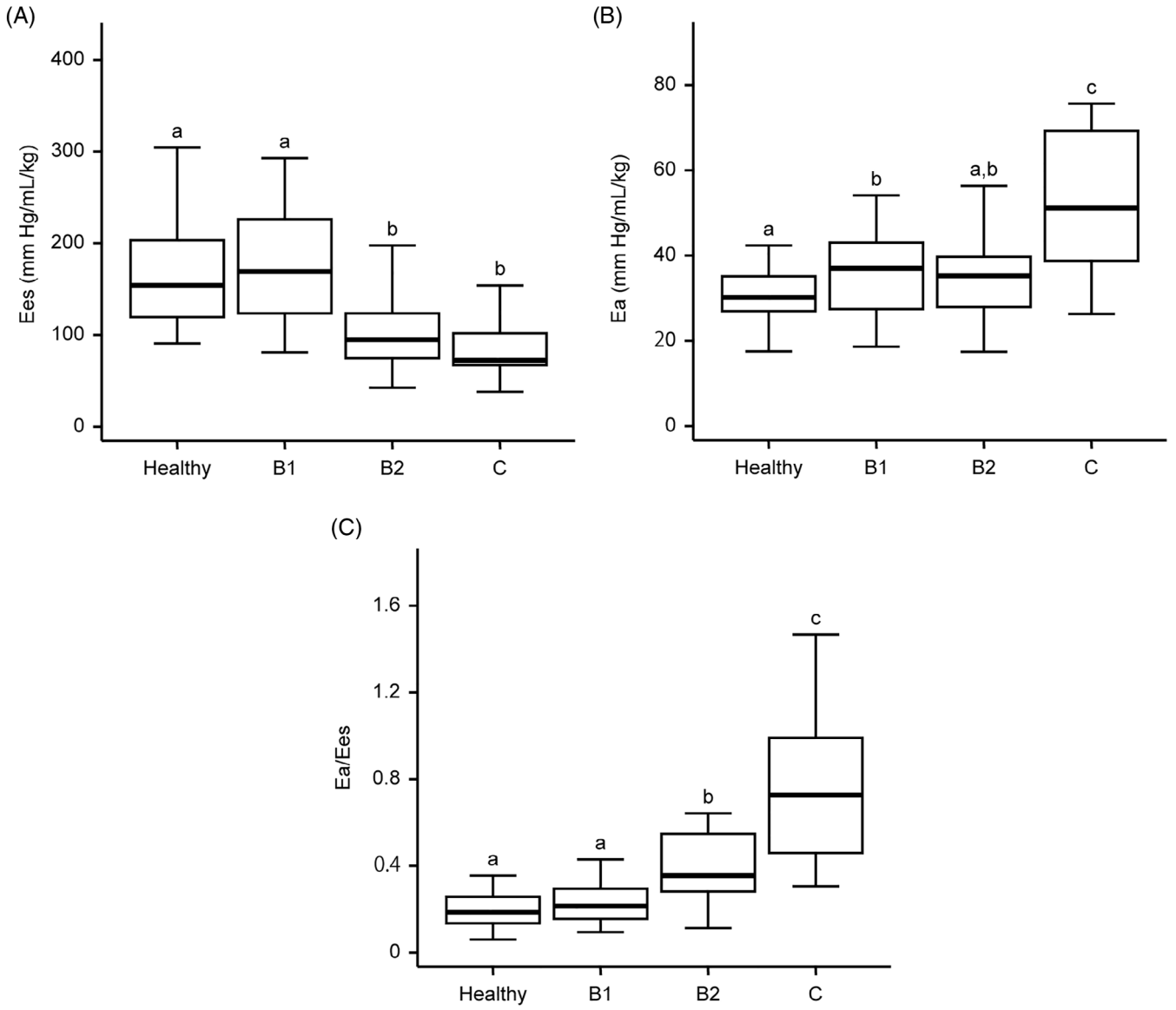

FIGURE 1 Box and whisker plot showing Ees (1A), Ea (1B), and Ea/Ees (1C) estimated by echocardiography in 90 dogs with MMVD (38 in stage B1, 32 in stage B2, and 20 in stage C) and 61 healthy dogs. The boxes represent the interquartile range, with the horizontal lines within each box representing medians. The vertical lines represent ranges. Different lower case letters above the vertical lines indicate significant differences among stages. B1, stage B1; B2, stage B2; C, stage C; Ea, effective arterial elastance; Ea/Ees, Ea to Ees ratio; Ees, left ventricular end-systolic elastance

TABLE 3 Multivariable logistic regression analysis to identify independent predictors of stage C in dogs with myxomatous mitral valve disease

Variable	Odds ratio	95% CI	*P*
Ea/Ees (per 0.1-unit increase)	1.628	1.228-2.158	.0007
E/IVRT (per 0.1-unit increase)	1.070	1.013-1.131	.02

Notes: Hosmer-Lemeshow test χ^2 = 3.134, *P* = .93. This analysis included 90 dogs with myxomatous mitral valve disease, including 38 in stage B1, 32 in stage B2, and 20 in stage C.
Abbreviations: CI, confidence interval; E, peak velocity of the early diastolic wave of transmitral flow; Ea, effective arterial elastance; Ees, left ventricular end-systolic elastance; Ea/Ees, Ea to Ees ratio; E/IVRT, E to IVRT ratio; IVRT, isovolumic relaxation time.

analysis to identify independent predictors of stage C in MMVD dogs. The A, E/A, and A′ values were not selected despite their *P* value on univariable logistic regression analysis (*P* < .20) because these indices could not be determined in all enrolled dogs. In multivariable logistic regression analysis with stepwise forward selection, among abovementioned indices, Ea/Ees and E/IVRT were identified as independent predictors of stage C in MMVD dogs (Table 3).

The 95% PIs for Ees, Ea, and Ea/Ees were: Ees, 86.3-375.3 mm Hg/mL/kg; Ea, 17.5-45.3 mm Hg/mL/kg; Ea/Ees, 0.05-0.34. The numbers of dogs for which Ees, Ea, and Ea/Ees were outside of the 95% PIs in each stage are shown in Table 4.

TABLE 4 The numbers of dogs of which Ees, Ea, Ea/Ees values were outside of the 95% prediction intervals in each stage

	Healthy (n = 61)	Stage B1 (n = 38)	Stage B2 (n = 32)	Stage C (n = 20)	*P*						
					Overall	Healthy vs B1	Healthy vs B2	Healthy vs C	B1 vs B2	B1 vs C	B2 vs C
Outside of 95% PI (yes/no)											
Ees	0/61	3/35	14/18	13/7	<.0001	.32	<.0001	<.0001	.004	<.0001	.98
Ea	1/60	8/30	5/27	14/6	<.0001	.01	.1	<.0001	1.00	.003	.0006
Ea/Ees	1/60	4/34	19/13	18/2	<.0001	.42	<.0001	<.0001	<.0001	<.0001	.16

Note: Number (n) for categorical data.

Abbreviations: Ea, effective arterial elastance; Ea/Ees, Ea to Ees ratio; Ees, left ventricular end-systolic elastance; PI, prediction interval.

In the repeatability study, the within-day and between-day CVs for Ees were 5.4% and 7.6%, respectively. The within-day and between-day CVs for Ea were 10.7% and 9.5%, respectively. The within-day and between-day CVs for Ea/Ees were 6.5% and 6.1%, respectively.

4 | DISCUSSION

Our results show that inappropriate VAC indicated by an increase in echocardiographically estimated Ea/Ees is associated with advanced disease severity in dogs with MMVD. The increase in Ea/Ees in stage B2 mainly was associated with the decrease in Ees, suggesting that left ventricular systolic dysfunction mainly contributed to inappropriate VAC in this stage. On the other hand, the increase in Ea/Ees in stage C was associated with both the decrease in Ees and increase in Ea, suggesting that both left ventricular systolic dysfunction and increase in the total arterial load of the left ventricle contributed to inappropriate VAC in this stage. Our study is the first to estimate VAC using echocardiography in dogs clinically affected by MMVD.

In humans, several studies have reported that VAC assessed by cardiac catherization or estimated by echocardiography was associated with disease severity or prognosis in patients with heart failure with left ventricular systolic dysfunction.[3,7,8] Nonetheless, few studies have investigated the clinical relevance of VAC in patients with heart failure associated with mitral regurgitation. A previous study that enrolled a relatively small number of human patients with chronic mitral regurgitation found that VAC assessed by cardiac catheterization progressively deteriorated, mainly secondary to a progressive decrease in Ees.[14] In the previous study, Ea did not change significantly with disease progression but a slight increase in Ea was observed in patients with more advanced mitral regurgitation.[14]

Our results on the estimation of Ees suggest that left ventricular systolic function worsens progressively with disease severity, leading to inappropriate VAC in stages B2 and C. This finding is in agreement with the abovementioned study that enrolled human patients with chronic mitral regurgitation whose left ventricular systolic function was assessed on the basis of Ees determined by cardiac catheterization.[14] Echocardiographic evaluation of left ventricular systolic function in dogs with MMVD has been performed using conventional indices (eg, left ventricular fractional shortening and ejection fraction) and novel indices (eg, systolic tissue Doppler velocity, left ventricular systolic strain). However, evaluation of left ventricular systolic function on the basis of these echocardiographic indices has been problematic in dogs with MMVD because of the enhancing effect of volume overload combined with decreased total left ventricular afterload (distinct from total arterial load) and increased sympathetic tone on echocardiographic indices of left ventricular systolic function.[19] For example, in a previous study that included dogs with MMVD, left ventricular fractional shortening and left ventricular systolic strain determined by 2-dimensional tissue tracking echocardiography were enhanced in stage B2 and returned to normal in stage C when compared with results in healthy dogs and stage B1 dogs.[19] This normalization of these indices in stage C may indicate left ventricular systolic dysfunction. In another study, left ventricular systolic

velocities recorded from various sites using tissue Doppler imaging were enhanced or unchanged in MMVD dogs with congestive heart failure when compared with those in MMVD dogs without congestive heart failure and those of healthy dogs.[20] Furthermore, in the previous study, left-sided volume overload assessed by LA/Ao was positively correlated with left ventricular systolic velocity recorded by tissue Doppler imaging.[20]

In our study, Ea was estimated using FSV so that Ea should reflect the total arterial load of the left ventricle, as in a previous study that enrolled human patients with mitral regurgitation.[14] Although Ea can be estimated using total stroke volume (ie, left ventricular end-diastolic volume minus ESV) instead of FSV, so that Ea should reflect total left ventricular afterload,[5-7] Ea estimated by this method is affected by the low impedance provided by the left atrium in mitral regurgitation, leading to difficulty in assessing the total arterial load of the left ventricle and its interaction with the ventricular systolic function (ie, VAC).[14] In addition, if Ea is estimated using the total stroke volume, Ea/Ees is mathematically related to left ventricular ejection fraction (ie, Ea/Ees equals [1/left ventricular ejection fraction] −1), and therefore should not provide additional information to measurement of left ventricular ejection fraction or fractional shortening.[3]

The results on Ea in our study suggest that the total arterial load of the left ventricle increases in stage C, leading to more inappropriate VAC in stage C when compared with stage B2. The total arterial load of the left ventricle consists of steady and pulsatile components.[3,4] The steady component depends largely on peripheral vascular resistance. On the other hand, the pulsatile component is dependent mainly on the properties of conduit arteries (eg, characteristic impedance of aorta, arterial compliance). In general, Ea is mainly dependent on the steady component of the arterial load with pulsatile components of the arterial load minimally affecting Ea.[3,4] Considering the sympathetic activation and parasympathetic withdrawal associated with advanced disease severity in MMVD,[21] the increase in Ea in stage C in our study could have been associated with the increase in peripheral vascular resistance caused by the abovementioned changes in sympathetic and parasympathetic activity. In addition, in theory, Ea is highly affected by heart rate (ie, high heart rate leads to high Ea).[3,4] Thus, the increase in heart rate associated with the abovementioned changes in sympathetic and parasympathetic activity also might have contributed to the increase in Ea in stage C in our study.

Notably, in our study, multivariable logistic regression analysis showed that Ea/Ees was an independent predictor of stage C among the various echocardiographic indices evaluated in MMVD dogs. In addition, the determination of Ea/Ees used in our study can be accomplished easily by using application software generally provided on commercially available echocardiographic machines, and requires <5 minutes. These factors will motivate further studies to evaluate the prognostic value of Ea/Ees in dogs with MMVD. In humans with heart disease, Ea/Ees estimated using echocardiography is a promising marker for prognostication and guidance of treatment,[3] although recommendations for clinical use of this index remain to be established.

Unfortunately, comparison between our data and published experimental data obtained invasively by left ventricular pressure-volume loops in dogs is difficult for a number of reasons. Firstly, the body sizes of the dogs enrolled in our study (<15 kg) and dogs used in previous experimental studies (generally >15-20 kg) are quite different.[6] Secondly, in the previous experimental studies using dogs, general anesthesia, mechanical ventilation, thoracotomy, or pericardectomy were commonly used. Such procedures could have affected Ees, Ea, and Ea/Ees. Thirdly, in the previous experimental studies that enrolled dogs, Ea generally was determined using total stroke volume instead of FSV. Therefore, mitral regurgitation (if present) in heart disease model dogs makes the comparison between our data and published experimental data difficult.

Our study had several limitations. Firstly, we did not perform cardiac catherization for left ventricular pressure-volume loop analysis, the gold standard for the determination of Ees and Ea. The estimation accuracy of Ees and Ea in our study may not be high. In our study, MBP was used for estimation of Ees and Ea because the oscillometric blood pressure device used in our study was expected to predict MBP more accurately and precisely than systolic blood pressure.[22,23] In humans, it is more common to use systolic blood pressure instead of MBP for estimation for these indices.[3,7,8] Secondly, the effects of cardiovascular drugs administered to enrolled dogs on Ees, Ea, and Ea/Ees are unknown. Thirdly, ours was a cross-sectional study, which does not prove causality between the deterioration of VAC and disease severity of MMVD. Fourthly, sample sizes were small. Fifthly, our study lacked blinding to the clinical data and dog identity at the time when both a clinical cross-sectional study and repeatability study were performed. This design feature might have caused bias in calculation of Ees and Ea in our study.

In conclusion, inappropriate VAC assessed by echocardiographic estimation of Ea/Ees is associated with advanced disease severity in dogs with MMVD. Inappropriate VAC indicated by the increase in Ea/Ees was mainly associated with decreases in Ees in stage B2, and was associated with both a decrease in Ees and an increase in Ea in stage C. Multivariable logistic regression analysis showed that Ea/Ees was an independent predictor of stage C in dogs with MMVD among the various echocardiographic indices evaluated.

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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

Approval from Hokkaido University, Sapporo, Hokkaido, Japan (Approval No. 18-0152).

HUMAN ETHICS APPROVAL DECLARATION

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

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