

STANDARD ARTICLE

Prognostic value of left ventricular-arterial coupling estimated using echocardiography in dogs with myxomatous mitral valve disease

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Abstract

Background: The interaction between the left ventricle (LV) and systemic arterial systems, known as left ventricular-arterial coupling (VAC), has been evaluated based on the effective arterial elastance (Ea) to LV end-systolic elastance (Ees) ratio (Ea/Ees). The Ea reflects the total arterial load of LV, whereas Ees reflects the LV systolic function. A recent study found that inappropriate VAC based on increased Ea/Ees estimated by echocardiography is associated with advanced disease severity in dogs with myxomatous mitral valve disease (MMVD).

Hypothesis: Inappropriate VAC assessed by echocardiographic estimation of Ea/Ees is associated with a worse prognosis in dogs with MMVD.

Animals: Eighty-nine dogs with MMVD.

Methods: Prospective cohort study. Dogs underwent echocardiographic examinations at enrollment. The Ea was estimated using the formula: mean blood pressure/(forward stroke volume/body weight). The Ees was estimated using the formula: mean blood pressure/(LV end-systolic volume/body weight). The Ea/Ees was calculated.

Results: By end of study, 22 dogs died of cardiac-related causes with 67 dogs censored. Dogs with increased Ea/Ees (Ea/Ees >0.34; median survival time, 527 days; 95% confidence interval [CI], 322 days-not determinable) had a shorter survival time ($P < .0001$) than those without increased Ea/Ees (Ea/Ees ≤0.34; median survival time, >1112 days; 95% CI, not determinable). Multivariate Cox proportional hazard analysis showed that Ea/Ees, body weight, peak systolic mitral annular velocity, and the peak early diastolic transmitral velocity-to-peak early diastolic mitral annular velocity

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; 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; 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; S', peak velocity of the systolic wave of myocardial velocity; VAC, left ventricular-arterial coupling.

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ratio were independent predictors of cardiac-related death among echocardiographic indices.

Conclusions and Clinical Importance: Inappropriate VAC assessed based on echocardiographically-estimated Ea/Ees is associated with a worse prognosis in dogs with MMVD.

KEYWORDS

canine, Ea/Ees, elastance, mitral regurgitation, survival time

1 | INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the most common adult-onset heart disease of dogs worldwide, accounting for 75% to 80% of heart disease cases identified in dogs.^{1,2} This disease is characterized by progressive myxomatous degeneration of the mitral valve apparatus, which leads to mitral regurgitation. Severe volume overload of the left ventricle and atrium eventually occurs secondary to progressive mitral regurgitation, finally leading to left-sided congestive heart failure and death.^{1,2}

Left ventricular-arterial coupling (VAC) refers to the interaction between the left ventricle and systemic arterial systems. It is a determinant of the pump efficiency of the left ventricle, and deterioration of VAC plays a pivotal role in the pathophysiology of various heart diseases.^{3,4} In humans, VAC has been assessed based on the effective arterial elastance (Ea) to the left ventricular end-systolic elastance (Ees) ratio (Ea/Ees) determined using cardiac catheterization-derived left ventricular pressure-volume loops.^{3,4} Left ventricular end-systolic elastance is an index of left ventricular systolic function, and has been calculated as the slope of the end-systolic pressure-volume relationship of left ventricle pressure-volume loops obtained when left ventricular loading conditions are acutely altered.^{3,4} Effective arterial elastance is an index of the total arterial load of the left ventricle, and has been calculated as the ratio of the left ventricular end-systolic pressure to the left ventricular stroke volume in a single left ventricular pressure-volume loop.^{3,4} Recently, in humans, echocardiography has been used for the noninvasive estimation of Ea/Ees.⁴⁻⁸ Interestingly, previous studies showed that inappropriate VAC indicated by increased Ea/Ees estimated using echocardiography is related to worse New York Heart Association heart failure class or worse prognosis in human patients with heart disease.^{7,8}

In dogs with MMVD, a recent study found that inappropriate VAC based on increased Ea/Ees estimated using echocardiography is associated with more advanced American College of Veterinary Internal Medicine (ACVIM) stage.⁹ However, no reports have investigated the relationship between echocardiographically-estimated VAC and prognosis in dogs with MMVD. Therefore, our aim was to investigate the prognostic value of VAC estimated using echocardiography in dogs with MMVD. Our hypothesis was that inappropriate VAC assessed by echocardiographic estimation of Ea/Ees is associated with a worse prognosis in dogs with MMVD.

2 | MATERIALS AND METHODS

This prospective cohort study received ethical approval from the Hokkaido University, Sapporo, Hokkaido, Japan (Approval No. 18-0152). All owners signed an informed consent form before recruitment into this study.

2.1 | Animals

Client-owned 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 December 2018. These dogs underwent standard echocardiographic studies (B-mode, M-mode, pulsed-wave Doppler, continuous-wave Doppler, and color flow Doppler imaging) for various reasons, including cardiac murmur, clinical signs possibly related to heart disease (eg, cough, respiratory distress, syncope), and preanesthetic evaluation.

Dogs were diagnosed with MMVD and included in this study: (a) if they had a systolic cardiac murmur with point of maximum intensity over the left cardiac apex, and (b) if they were echocardiographically diagnosed with MMVD based on identification of mitral regurgitation by color flow Doppler imaging with the presence of mitral valve prolapse or any degree of mitral valve thickening on B-mode imaging. Dogs were excluded from the study: (a) if their survival information could not be obtained, (b) if their body weights were >15 kg (the study aimed to enroll only small breed dogs), (c) if they had other heart disease (eg, congenital heart disease, dilated cardiomyopathy, infective endocarditis), (d) if they had hemodynamically relevant arrhythmia (eg, atrial fibrillation, ventricular tachycardia), (e) if they had clinically relevant extracardiac disease that might affect cardiac function, hemodynamics, or survival time (eg, chronic kidney disease [plasma creatinine concentration ≥ 1.4 mg/dL], systemic hypertension [systolic blood pressure >170 mm Hg], hyperadrenocorticism, malignant tumors), or (f) if they were so anxious that their motion (ie, trembling) was deemed likely to make systemic arterial blood pressure measurement unreliable. Azotemia that had occurred after initiation of cardiovascular drugs (eg, loop diuretics) was permitted. Most of the dogs included in the study were enrolled in a previous study investigating the relationship between echocardiographically-estimated VAC and ACVIM stage.⁹ If the dogs

in this study underwent multiple echocardiographic studies during the above-mentioned recruitment period, the clinical data recorded the first time during the period were used.

Age, sex, body weight, breed, and medical history were recorded based on interviews with owners and physical examinations at enrollment. Also, dogs were classified into stage B1, B2, or C according to the ACVIM consensus statement at enrollment.¹ Dogs in stage B1 had asymptomatic MMVD that was not severe enough to meet echocardiographic criteria of cardiomegaly (left atrial to aortic ratio [LA/Ao] <1.6 or left ventricular end-diastolic internal diameter normalized for body weight [LVIDDN] <1.7).¹ Dogs in stage B2 had asymptomatic MMVD that was severe enough to meet echocardiographic criteria of cardiomegaly (LA/Ao \geq 1.6 and LVIDDN \geq 1.7).¹ Dogs in stage C had MMVD with current or past clinical and radiographic evidence of left-sided congestive heart failure (cardiogenic pulmonary edema).¹ Left-sided congestive heart failure was diagnosed on the basis of clinical signs consistent with left-sided congestive heart failure (eg, dyspnea, tachypnea) and radiographic findings indicating cardiogenic pulmonary edema including cardiomegaly and an interstitial or alveolar lung pattern.

Based on the ACVIM consensus statement,¹⁰ systemic systolic, diastolic, and mean (MBP) pressures were measured using an oscillometric blood pressure device (petMAP graphic, Ramsey Medical Inc, Tampa, FL) at enrollment. Blood pressure measurement was performed on 1 occasion in a single day when echocardiographic examination was performed. Each dog was manually restrained in ventral or lateral recumbency without use of sedation. An appropriately-sized cuff (cuff width 30%-40% of the circumference of the cuff site) was placed on the left or right forelimb. Blood pressure was measured repeatedly until a total of 5 consecutive or near-consecutive, consistent (<20% variability) results were recorded. The mean of the 5 recorded results was used as the final blood pressure measurement.

2.2 | Echocardiographic measurements

Echocardiographic examinations and off-line analysis were performed by 1 investigator (TO) using a commercially available ultrasonographic machine equipped with a 3-6 MHz sector probe and simultaneous ECG recording (Artida, Canon Medical Systems Corp., Ohtawara, Tochigi, Japan). Each dog was manually restrained in left and right lateral recumbency without sedation. All data were digitally stored for off-line analysis. The investigator (TO) was not blinded to the dogs' ACVIM stage, but was blinded to the dogs' survival information. The heart rate was calculated using RR intervals between 5 consecutive cardiac cycles on ECG at the time when aortic Doppler flow was recorded. Left ventricular end-diastolic and end-systolic internal diameters and left ventricular fractional shortening were obtained from an M-mode image acquired from a right parasternal short axis-view at the chordae tendineae level using the leading edge-to-leading edge method.^{1,11} The left ventricular end-diastolic internal diameter normalized for body weight (LVIDDN) was calculated using the formula: LVIDDN = left ventricular end-diastolic internal diameter (cm)/body

weight (kg)^{0.294, 1,11} The left ventricular end-systolic internal diameter normalized for body weight (LVIDSN) was calculated using the formula: LVIDSN = left ventricular end-systolic internal diameter (cm)/body weight (kg)^{0.315, 11} The left atrial to aortic ratio was determined from a 2-dimensional image of the right parasternal short-axis view at the aortic root level using the "Swedish" method.^{1,12} Doppler indices of transmitral flow including peak velocities of the early diastolic (E) and late diastolic (A) waves were recorded from a left apical 4-chamber view. The E to A ratio (E/A) was determined. Only E was measured when E and A waves were partially fused (E and A waves were completely fused in no enrolled dogs). Myocardial tissue Doppler indices including peak velocities of the early diastolic (E'), late diastolic (A'), and systolic (S') waves were recorded from a left apical 4-chamber view with sample volume positioned at the lateral mitral annulus. Only E' and S' were measured when E' and A' waves were partially fused (E' and A' waves were completely fused in no enrolled dogs). The E to E' ratio (E/E') was determined. From a left-apical 5-chamber view, the isovolumic relaxation time (IVRT) was measured as the time interval between aortic valve closure and beginning of the early diastolic wave of transmitral flow with a sample volume of 6 to 8 mm placed at an intermediate position between the left ventricular inflow and outflow tracts.¹³ The E to IVRT ratio (E/IVRT) was determined.

Based on previous studies, Ees was estimated using the formula: Ees = MBP/(left ventricular end-systolic volume [mL]/body weight [kg]).^{5,6,9} The left ventricular end-systolic volume was computed using the monoplane Simpson method of disc from a 2-dimensional image of the left apical 4-chamber view.^{9,14} Briefly, in the frame before mitral valve opening, the endocardial border was manually traced from the septal side of the mitral annulus to the other side with papillary muscles included in the volume calculation. Then, the left ventricular maximal length was measured from the middle of the mitral annulus to the endocardial border of the left ventricular apex. After these procedures, the left ventricular end-systolic volume was determined automatically by the ultrasonography machine. Effective arterial elastance was estimated using the formula: Ea = MBP/(forward stroke volume [mL]/body weight [kg]).^{9,15} The forward stroke volume was calculated using the formula: forward stroke volume = time velocity integral of the aortic Doppler flow \times aortic luminal area. Aortic pulsed-wave Doppler flow was recorded from the subcostal 5-chamber view with a sample volume placed just distal to the aortic valve. The time velocity integral of the aortic Doppler flow was obtained by manually tracing it. The aortic luminal area was calculated by tracing the aortic lumen on a 2-dimensional image of the right parasternal short-axis view at the aortic root level (the same image used for determination of LA/Ao).¹⁶ In a previous report, a repeatability study using healthy dogs showed that the within- and between-day coefficients of variation for Ees, Ea, and Ea/Ees were 5.4% to 10.7%.⁹ The forward cardiac output was calculated using the formula: forward cardiac output = forward stroke volume \times heart rate. The forward cardiac output was normalized for body weight by dividing it by body weight.

The mean of 5 consecutive cardiac cycles was determined for the left ventricular end-systolic volume and forward stroke volume,

whereas the mean of 3 consecutive cardiac cycles was determined for the other echocardiographic indices.

2.3 | Survival information

Review of the electronic medical records of the institution was performed to obtain survival information for dogs. If survival information could not be obtained from the medical records, it was collected by contacting referring veterinarians or owners in April 2020. The date and cause of death (cardiac-related or noncardiac-related) were recorded for dogs that died. Cardiac-related death was defined as natural death or euthanasia because of congestive heart failure refractory to medical treatment, or sudden death. The cardiovascular drugs used during follow-up were not standardized in all dogs; some dogs were treated at referring hospitals. However, medical treatment was always performed following the ACVIM consensus statement.¹

2.4 | Statistical analysis

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

The Shapiro-Wilk test was performed to confirm the normal distribution of continuous data at enrollment. Continuous data at enrollment are reported as the mean (SD) for normally distributed data and median (25th-75th percentile) for nonnormally distributed data.

Survival time was counted from the day of enrollment to the day of death or last contact. Dogs that were lost to follow-up were right-censored after their last contact. Dogs that died of noncardiac-related causes or were alive at the time of contact in April 2020 also were right-censored. Kaplan-Meier analysis with a log-rank test was performed to determine the effects of Ees, Ea, and Ea/Ees at enrollment on survival. The 95% upper and lower prediction limits of Ees, Ea, and Ea/Ees reported in a previous study⁹ were used as the cutoff values to dichotomize them: Ees < 86.3 mm Hg/(mL/kg), Ea > 45.3 mm Hg/(mL/kg), and Ea/Ees > 0.34 .

Two separate multivariable Cox's proportional hazard analyses were performed to determine independent echocardiographic predictors of survival at enrollment. One multivariable Cox's proportional hazard analysis used continuous echocardiographic variables, and the other multivariable analysis used dichotomized echocardiographic variables. The Ees, Ea, and Ea/Ees were dichotomized by cutoff values mentioned above: Ees < 86.3 mm Hg/(mL/kg), Ea > 45.3 mm Hg/(mL/kg), and Ea/Ees > 0.34 .⁹ The LVIDDN, LA/Ao, and E were dichotomized by cutoff values chosen based on prognostic relevance in previous studies as follows: LVIDDN > 1.7 ,^{1,17} LA/Ao > 1.7 ,^{1,17,18} and E > 1.2 m/s.¹⁸ Cutoff values for other echocardiographic indices were chosen by dividing them into quartile groups and evaluating the effect

TABLE 1 Clinical and echocardiographic data at enrollment of 89 dogs with myxomatous mitral valve disease

	Observed values
Age (years)	11.7 ± 2.4
Sex (female/male)	36/53
Body weight (kg)	4.4 (3.2-6.4)
Cardiovascular drugs (yes/no)	
ACEI	44/45
Pimobendan	38/51
Loop diuretics	14/75
Spironolactone	12/77
SBP (mm Hg)	148 ± 13
DBP (mm Hg)	86 ± 11
MBP (mm Hg)	107 ± 11
Heart rate (bpm)	127 (105-151)
LVIDDN	1.8 ± 0.37
LVIDSN	0.85 ± 0.19
FS (%)	51 ± 7
LA/Ao	1.86 (1.54-2.24)
E (m/s)	0.96 (0.77-1.3)
A (m/s, n = 88)	0.81 ± 0.27
E/A (n = 88)	1.15 (0.93-1.58)
E' (cm/s)	9.3 (7.3-10.8)
A' (cm/s, n = 88)	9.9 ± 2.7
S' (cm/s)	9.2 (8-11.3)
E/E'	10.4 (9.2-12.9)
IVRT (ms)	48 ± 14
E/IVRT	2.02 (1.52-2.9)
FCO/BW (mL/min/kg)	346 (265-454)
Ees [mm Hg/(mL/kg)]	111 (80-160)
Ea [mm Hg/(mL/kg)]	39 (29-48)
Ea/Ees	0.34 (0.22-0.58)

Note: Mean ± SD for normally distributed continuous data, median (25th-75th percentile) for nonnormally distributed continuous data, and number (n) for categorical data. One dog in stage C had a heart rate so fast that A and A' could not be determined (E and A waves and E' and A' waves were partially fused).

Abbreviations: A, peak velocity of the late diastolic wave of transmitral flow; A', peak velocity of the late diastolic wave of myocardial velocity; ACEI, angiotensin-converting enzyme inhibitors; DBP, diastolic blood pressure; E, peak velocity of the early diastolic wave of transmitral flow; E', peak velocity of the early diastolic wave of myocardial velocity; 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; FS, left ventricular fractional shortening; FCO/BW, forward cardiac output 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; MBP, mean blood pressure; S', peak velocity of the systolic wave of myocardial velocity; SBP, systolic blood pressure.

of these quartiles on survival using Kaplan-Meier analysis with a log-rank test. In both multivariable analyses, age, body weight, systemic blood pressures, and heart rate were used as continuous variables. For each multivariable analysis, univariable Cox's proportional hazard analysis was performed for age, sex, body weight, systemic blood pressures, heart rate, and continuous or dichotomized echocardiographic variables. Then, explanatory variables with $P < .2$ on univariable Cox's proportional hazard analysis were selected and a stepwise forward selection method with Akaike's information criterion was used for generation of each multivariable model. The cardiovascular drugs used during follow-up were not used for multivariable Cox's proportional hazard analyses because they were not standardized in all dogs. In the generated multivariable models, proportionality of hazards was confirmed by Schoenfeld residuals.

3 | RESULTS

Eighty-nine dogs with MMVD, including 35 dogs in stage B1, 30 dogs in stage B2, and 24 dogs in stage C, were enrolled in the study. Clinical and echocardiographic data at enrollment are summarized in Table 1. At enrollment, among the dogs in stage C, cardiogenic pulmonary edema was ongoing on the basis of evaluation of thoracic radiographs in 9 dogs (pulmonary edema had been partially stabilized by oxygenation with or without cardiovascular drugs before echocardiographic examinations), whereas it had been successfully controlled with cardiovascular drugs in 15 dogs. Ten dogs in stage C were not receiving loop diuretics. Among them, 7 dogs underwent echocardiographic examinations before discharge on PO cardiovascular drugs including loop diuretics for home care after the radiographic diagnosis of cardiogenic pulmonary edema. In the other 3 dogs, after cardiogenic pulmonary edema had been successfully controlled by cardiovascular drugs including loop diuretics, loop diuretics could be tapered and finally discontinued before echocardiographic examinations. The most commonly represented breed was Chihuahua ($n = 27$), followed by Pomeranian

($n = 9$), Toy Poodle ($n = 8$), Cavalier King Charles Spaniel ($n = 8$), Maltese ($n = 7$), Miniature Dachshund ($n = 6$), and Shih tzu ($n = 6$).

At the time when the survival information was obtained (April 2020), 22 dogs (25%) had died of cardiac-related causes (21 dogs died naturally; 1 dog was euthanized), 26 dogs (29%) had died of noncardiac-related causes, 39 dogs (44%) were still alive, and 2 dogs (2%) had been lost to follow-up. The median survival time for all enrolled dogs could not be calculated (median survival time >1122 days).

Kaplan-Meier analysis with a log-rank test showed the significant effects of Ees, Ea, and Ea/Ees at enrollment on survival (Table 2, Figure 1). Dogs with Ees $<$ its 95% lower prediction limit (Ees <86.3 mm Hg/[mL/kg]) had shorter survival times ($P < .0001$) than those with Ees \geq its 95% lower prediction limit (Ees ≥86.3 mm Hg/[mL/kg]). Dogs with Ea $>$ its 95% upper prediction limit (Ea >45.3 mm Hg/[mL/kg]) had shorter survival times ($P = .0002$) than those with Ea \leq its 95% upper prediction limit (Ea ≤45.3 mm Hg/[mL/kg]). Dogs with Ea/Ees $>$ its 95% upper prediction limit (Ea/Ees >0.34) had shorter survival times ($P < .0001$) than those with Ea/Ees \leq its 95% upper prediction limit (Ea/Ees ≤0.34).

Based on the univariable Cox's proportional hazard analysis, body weight, systolic blood pressure, heart rate, LVIDDN, LVIDSN, LA/Ao, E, E', S', E/E', IVRT, E/IVRT, forward cardiac output divided by body weight, Ees, Ea, and Ea/Ees were selected for the multivariable Cox's proportional hazard analysis using continuous echocardiographic variables ($P < .2$; Table 3). The E/A and A' were not selected despite their P values on univariable analysis ($P < .2$) because these could not be measured in all dogs. In the multivariable Cox's proportional hazard analysis using continuous echocardiographic variables, Ea/Ees, body weight, S', and E/E' were identified as independent predictors of cardiac-related death (Table 4).

On the basis of the univariate Cox's proportional hazard analysis, body weight, systolic blood pressure, heart rate, LVIDDN >1.7 , LVIDSN >0.98 , LA/Ao >1.7 , E >1.2 m/s, S' >11.3 cm/s, E/E' >12.9 , IVRT <38 ms, E/IVRT >2.9 , forward cardiac output divided by body

TABLE 2 Kaplan-Meier analysis with a log-rank test in 89 dogs with myxomatous mitral valve disease

Subgroup	n	Median survival time (d)	95% CI	P
Ees				
<86.3 mm Hg/(mL/kg)	29	484	263-ND	<.0001
≥86.3 mm Hg/(mL/kg)	60	>1122	ND	
Ea				
≤45.3 mm Hg/(mL/kg)	59	>1122	ND	.0002
>45.3 mm Hg/(mL/kg)	30	484	239-ND	
Ea/Ees				
≤0.34	46	>1122	ND	<.0001
>0.34	43	527	322-ND	

Note: The 95% upper and lower prediction limits of Ees, Ea, and Ea/Ees reported in a previous study⁹ were used as the cutoff values to dichotomize them.

Abbreviations: CI, confidence interval; Ea, effective arterial elastance; Ea/Ees, Ea to Ees ratio; Ees, left ventricular end-systolic elastance; ND, not determinable.

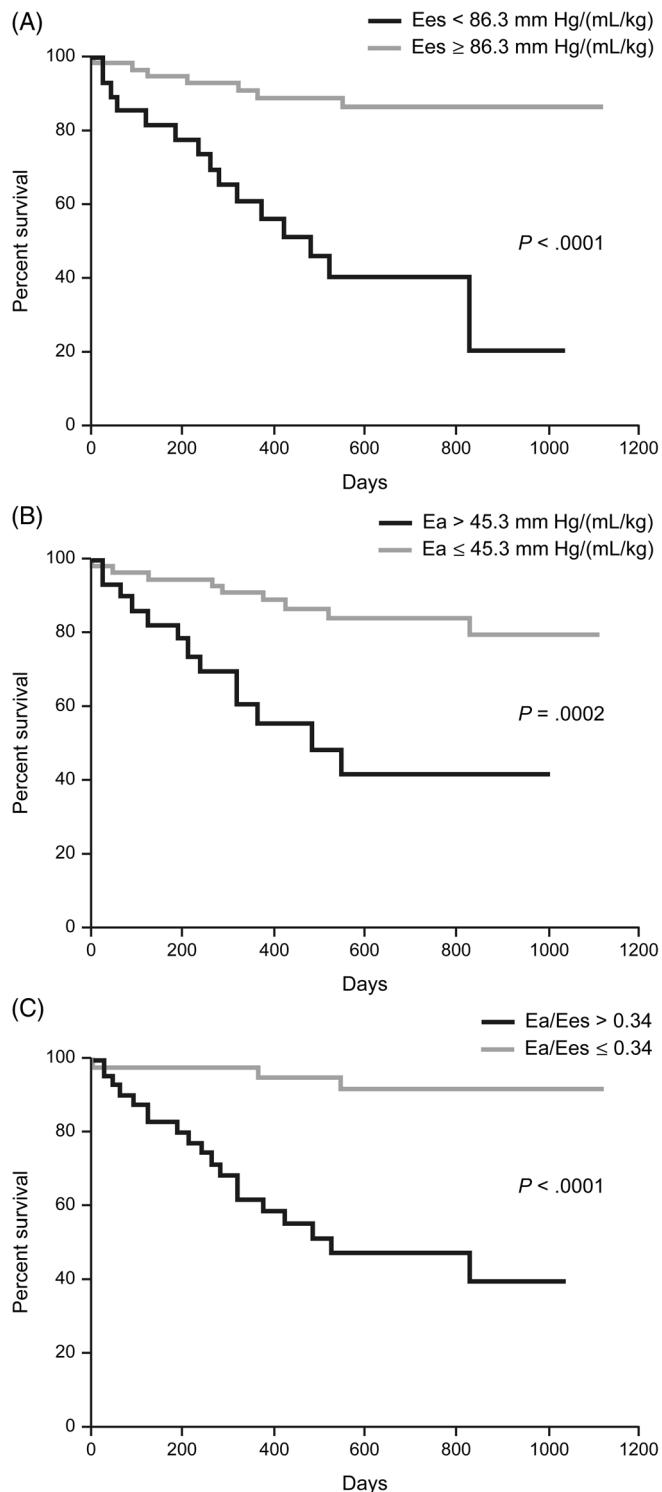


FIGURE 1 Kaplan–Meier survival curves showing the significant effects of Ees (log-rank test: $P < .0001$, A), Ea (log-rank test: $P = .0002$, B), and Ea/Ees (log-rank test: $P < .0001$, C) at enrollment on the survival of 89 dogs with myxomatous mitral valve disease. Ea, effective arterial elastance; Ea/Ees, Ea to Ees ratio; Ees, left ventricular end-systolic elastance

weight $<454 \text{ mL}/\text{min}/\text{kg}$, $Ees < 86.3 \text{ mm Hg}/(\text{mL}/\text{kg})$, $Ea > 45.3 \text{ mm Hg}/(\text{mL}/\text{kg})$, and $Ea/Ees > 0.34$ were selected for the multivariable Cox's proportional hazard analysis using dichotomized

echocardiographic variables ($P < .2$; Tables 3 and 5). The $E/A > 1.58$ and $A' < 9.7 \text{ cm}/\text{s}$ were not selected despite their P values on univariable analysis ($P < .2$) because they could not be measured in all dogs. In the multivariable Cox's proportional hazard analysis using dichotomized echocardiographic variables, $Ea/Ees > 0.34$, $E/E' > 12.9$, $S' > 11.3 \text{ cm}/\text{s}$, and body weight were identified as independent predictors of cardiac-related death (Table 6).

4 | DISCUSSION

Our results show that assessment of VAC with echocardiographic estimation of Ea/Ees provides important prognostic information in dogs with MMVD. Inappropriate VAC indicated by an increase in Ea/Ees was associated with shortened survival time in dogs with MMVD. Our study is the first to investigate the prognostic value of VAC estimated by echocardiography in dogs with naturally occurring heart disease.

Recently, a few studies in human patients with heart disease found that inappropriate VAC indicated by an increase in echocardiographically-estimated Ea/Ees is an indicator of a poor prognosis.^{7,8} In a study that enrolled human patients with heart failure caused by left ventricular systolic dysfunction, an increase in Ea/Ees was associated with adverse cardiac outcomes including death and cardiac transplantation.⁷ In another study, an increase in Ea/Ees was a predictor of adverse cardiac events including death, stroke, and recurrent myocardial infarction in human patients with acute coronary syndrome.⁸ However, to our knowledge, there have been no reports on the relationship between VAC estimated by echocardiography and the prognosis of human patients with mitral regurgitation.

In our study, the decrease in echocardiographically-estimated Ees, which was suggestive of impairment of the left ventricular systolic function, was associated with decreased survival time in dogs with MMVD. In humans with mitral regurgitation, to our knowledge, no studies have reported on the relationship between Ees estimated by echocardiography and prognosis. In dogs with MMVD, previous studies showed that impairment of some indices of left ventricular systolic function including left ventricular end-systolic internal diameter and volume was associated with poor prognosis.^{18,19} On the other hand, as for other indices of the left ventricular systolic function including left ventricular fractional shortening and ejection fraction, the “enhancement” of these indices because of the enhancing effect of volume overload combined with decreased total left ventricular afterload (distinct from total arterial load) and increased sympathetic tone was associated with a poor prognosis.^{19,20} Indeed, in our study, the “enhancement” of S' was associated with shortened survival time in dogs with MMVD.

According to a previous study in dogs with MMVD,⁹ Ea was echocardiographically estimated by the forward stroke volume so that Ea should be used as the index of the total arterial load of the left ventricle. Another way to estimate Ea is by the total stroke volume (left ventricular end-diastolic volume minus left ventricular end-systolic volume) instead of forward stroke volume.^{5–7} However, in mitral

TABLE 3 Univariable Cox's proportional hazard analysis for age, sex, body weight, systemic blood pressures, and continuous echocardiographic variables in 89 dogs with myxomatous mitral valve disease

	HR	95% CI	P
Age per 1 year increase	1	0.85-1.19	1
Male	0.68	0.29-1.57	.36
Body weight per 1 kg increase	0.82	0.66-1.01	.06
SBP per 10 mm Hg increase	0.62	0.44-0.86	.004
DBP per 10 mm Hg increase	1.08	0.74-1.56	.69
MBP per 10 mm Hg increase	0.91	0.62-1.32	.61
Heart rate per 10 bpm increase	1.26	1.1-1.43	.0004
LVIDDN per 0.1 unit increase	1.55	1.32-1.82	<.0001
LVIDSN per 0.1 unit increase	1.78	1.38-2.28	<.0001
FS per 1% increase	1.04	0.98-1.1	.23
LA/Ao per 0.1 unit increase	1.29	1.18-1.41	<.0001
E per 0.1 m/s increase	1.52	1.29-1.79	<.0001
A per 0.1 m/s increase (n = 88)	0.97	0.82-1.16	.76
E/A per 0.1 unit increase (n = 88)	1.06	1.03-1.09	<.0001
E' per 1 cm/s increase	1.15	0.99-1.34	.07
A' per 1 cm/s increase (n = 88)	0.83	0.7-0.99	.04
S' per 1 cm/s increase	1.31	1.13-1.52	.0002
E/E' per 1 unit increase	1.24	1.11-1.38	<.0001
IVRT per 10 ms increase	0.69	0.48-1.01	.05
E/IVRT per 1 unit increase	1.94	1.45-2.6	<.0001
FCO/BW per 100 mL/min/kg increase	0.74	0.5-1.08	.11
Ees per 10 mm Hg/(mL/kg) increase	0.75	0.66-0.87	<.0001
Ea per 10 mm Hg/(mL/kg) increase	1.74	1.33-2.28	<.0001
Ea/Ees per 0.1 unit increase	1.4	1.26-1.56	<.0001

Note: One dog in stage C had a heart rate so fast that A and A' could not be determined (E and A waves and E' and A' waves were partially fused). Abbreviations: A, peak velocity of the late diastolic wave of transmitral flow; A', peak velocity of the late diastolic wave of myocardial velocity; CI, confidence interval; DBP, diastolic blood pressure; E, peak velocity of the early diastolic wave of transmitral flow; E', peak velocity of the early diastolic wave of myocardial velocity; 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; FS, left ventricular fractional shortening; FCO/BW, forward cardiac output divided by body weight; HR, hazard ratio; 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; S', peak velocity of the systolic wave of myocardial velocity; SBP, systolic blood pressure.

regurgitation, assessment of the total arterial load of the left ventricle on the basis of Ea estimated using the total stroke volume is difficult because Ea estimated based on total stroke volume is influenced by the low impedance provided by the left atrium.¹⁵ In addition, mathematically, Ea/Ees calculated using Ea estimated by the total stroke volume should not provide additional information for the determination of the left ventricular ejection or fractional shortening (Ea/Ees = 1/ left ventricular ejection fraction - 1).^{3,4}

We found that an increase in echocardiographically-estimated Ea, which was indicative of an increase in the total arterial load of the left ventricle, was associated with a poor prognosis in dogs with MMVD. In humans, the above-mentioned previous study indicated that the increase in Ea estimated by echocardiography was associated with adverse cardiac outcomes including death in human patients with left ventricular systolic heart failure.⁷ However, to our knowledge, no studies have investigated the association between echocardiographically-estimated Ea and prognosis in human patients with mitral regurgitation. Generally, Ea is mainly determined by peripheral vascular resistance and heart rate (increases in peripheral vascular resistance and heart rate cause an increase in Ea).^{3,4} Given that increased sympathetic activation and decreased parasympathetic activation may occur in dogs with advanced MMVD,²¹ our results suggest that the increases in peripheral vascular resistance and heart rate associated with sympathetic activation and parasympathetic withdrawal might be related to decreased survival time in dogs with MMVD.

Our results from multivariable Cox's proportional hazard analysis indicate that Ea/Ees estimated by echocardiography can be a useful prognostic indicator in dogs with MMVD. The formulae used for the estimation of Ees, Ea, and Ea/Ees in our study are simple, and these indices can be determined using commercially available echocardiographic equipment and application software in <5 minutes. In humans, the echocardiographic estimation of Ea/Ees is considered a useful tool for predicting outcomes and guiding treatment of patients with heart disease.⁴

Surprisingly, in our study, indices of left atrial and ventricular sizes (LA/Ao and LVIDDN) were not identified as independent predictors of cardiac-related death in multivariable analysis. The increases in left atrial and ventricular size (eg, LA/Ao and LVIDDN) are well-established important prognostic indicators in dogs with MMVD.^{1,2,17-19} Correlations between Ees and each of LA/Ao (Spearman's rho = -0.69) and LVIDDN (Spearman's rho = -0.78) and between Ea and each of LA/Ao (Spearman's rho = 0.21) and LVIDDN (Spearman's rho = 0.46) were identified in our population (data not shown). However, Ees was estimated by the left ventricular end-systolic volume, which is theoretically not an index dependent on mitral regurgitation volume, such as LA/Ao and LVIDDN. Additionally, in a previous study in dogs with MMVD, no significant difference in Ea was found between stages B1 and B2.⁹ Considering that Ees and Ea seem not to be closely related to left atrial and ventricular size as mentioned above, echocardiographic estimation of Ea/Ees in addition to evaluation of left atrial and ventricular size might enable more accurate prognostication in dogs with MMVD.

Our study had some limitations. First, left ventricular pressure-volume loop analysis by use of cardiac catheterization, which is the gold standard for the determination of Ea/Ees, was not performed. Second, the effects of cardiovascular drugs administered to dogs at enrollment on Ea/Ees are unknown. Third, the cardiovascular medications used during follow-up were not standardized in all dogs (some dogs were treated at referring hospitals) although the ACVIM consensus guidelines for the management of dogs with MMVD always were followed.¹ Fourth, a relatively small number of dogs (approximately 25% of included dogs) died of cardiac-related causes. Fifth, the

TABLE 4 Multivariable Cox's proportional hazard analysis using continuous echocardiographic variables in 89 dogs with myxomatous mitral valve disease

	HR	95% CI	P
Ea/Ees per 0.1 unit increase	1.46	1.25-1.71	<.0001
Body weight per 1 kg increase	0.69	0.54-0.88	.003
S' per 1 cm/s increase	1.21	1.03-1.43	.02
E/E' per 1 unit increase	1.15	1.02-1.3	.02

Abbreviations: CI, confidence interval; 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; Ea/Ees, Ea to Ees ratio; E/E', E to E' ratio; Ees, left ventricular end-systolic elastance; HR, hazard ratio; S', peak velocity of the systolic wave of myocardial velocity.

TABLE 5 Univariable Cox's proportional hazard analysis for dichotomized echocardiographic variables in 89 dogs with myxomatous mitral valve disease

	HR	95% CI	P
LVIDDN >1.7	3.42	1.84-8.56	<.0001
LVIDSN >0.98	2.59	1.69-4.11	<.0001
FS >45.5%	1.4	0.85-2.6	.2
LA/Ao >1.7	2.99	1.61-7.49	.0001
E >1.2 m/s	2.34	1.54-3.67	.0001
A <0.60 m/s (n = 88)	1.37	0.84-2.12	.2
E/A >1.58 (n = 88)	2.35	1.52-3.66	.0002
E' >9.3 cm/s	1.28	0.84-2	.25
A' <9.7 cm/s (n = 88)	1.59	1.02-2.59	.04
S' >11.3 cm/s	1.9	1.23-2.9	.004
E/E' >12.9	2.25	1.46-3.47	.0004
IVRT <38 ms	1.46	0.92-2.24	.1
E/IVRT >2.90	2.59	1.68-4.01	<.0001
FCO/BW <454 mL/min/kg	2	1.08-5.01	<.0001
Ees <86.3 mm Hg/(mL/kg)	2.53	1.63-4.11	<.0001
Ea >45.3 mm Hg/(mL/kg)	2.12	1.38-3.34	.0007
Ea/Ees >0.34	3.15	1.83-6.51	<.0001

Note: One dog in stage C had a heart rate so fast that A and A' could not be determined (E and A waves and E' and A' waves were partially fused). Abbreviations: A, peak velocity of the late diastolic wave of transmitral flow; A', peak velocity of the late diastolic wave of myocardial velocity; CI, confidence interval; 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; FS, left ventricular fractional shortening; FCO/BW, forward cardiac output divided by body weight; HR, hazard ratio; 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.

investigator performing echocardiographic examinations and off-line analysis was not blinded to the dog's ACVIM stage, which might have caused a bias in the estimation of Ea/Ees.

TABLE 6 Multivariable Cox's proportional hazard analysis using dichotomized echocardiographic variables in 89 dogs with myxomatous mitral valve disease

	HR	95% CI	P
Ea/Ees >0.34	2.67	1.48-5.68	.0006
E/E' >12.9	1.93	1.15-3.33	.01
S' >11.3 cm/s	2.44	1.46-4.17	.0007
Body weight per 1 kg increase	0.75	0.57-0.96	.02

Abbreviations: CI, confidence interval; 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; Ea/Ees, Ea to Ees ratio; E/E', E to E' ratio; Ees, left ventricular end-systolic elastance; HR, hazard ratio; S', peak velocity of the systolic wave of myocardial velocity.

In conclusion, our study found that inappropriate VAC indicated by an increase in Ea/Ees estimated by echocardiography is associated with worse prognosis in dogs with MMVD. Multivariable Cox's proportional hazard analysis indicated that Ea/Ees was an independent predictor of decreased survival time in dogs with MMVD among various echocardiographic indices assessed in the study. Additional studies including a larger number of MMVD dogs that died of cardiac-related causes are warranted.

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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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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