**Left Atrial Strain at Different Stages of Myxomatous Mitral Valve Disease in Dogs**

K. Nakamura, S. Kawamoto, T. Osuga, T. Morita, N. Sasaki, K. Morishita, H. Ohta, and M. Takiguchi

**Background:** Decreased function of the left atrium (LA) is a useful prognostic indicator in dogs with myxomatous mitral valve disease (MMVD). In humans, LA strain is a novel severity indicator of mitral regurgitation, but its clinical utility in dogs has not been confirmed.

**Objectives:** To examine whether LA strain as evaluated with speckle-tracking echocardiography is associated with MMVD stage in dogs.

**Animals:** Fifty-two client-owned dogs with MMVD.

**Methods:** Cross-sectional study. Dogs were classified as stage B1, B2, C, or D, according to the American College of Veterinary Internal Medicine consensus. Physical examination findings and echocardiographic variables were compared among the groups. To assess the comparative accuracy of echocardiographic variables in identifying dogs with the presence or history congestive heart failure (CHF), receiver operating characteristic curves and multivariate logistic analysis were used.

**Results:** There were no significant differences in parameters of LA strain between B1 and B2 groups. However, LA longitudinal strain during atrial contraction ($e_A$) (median, 19.1%; interquartile range, 15.3–24.3% in B1, 19.6%; 14.1–21.4% in B2, 6.2%; 3.8–11.2% in C/D) and during ventricular systole ($e_m$) (32.7%; 28.9–39.2% in B1, 35.6%; 31.7–41.9% in B2, 23.6%; 16.9–26.1% in C/D) were significantly lower in stages C/D than in stages B1 and B2. In multivariate logistic regression analysis, $e_A$ and peak early diastolic mitral inflow velocity were identified as independent indicators of stage C/D.

**Conclusions and Clinical Importance:** $e_A$ was the best predictor of the presence or history of CHF. Further studies are needed to determine the clinical implications of these findings for treatment decisions and prognosis determination.

**Key words:** Booster pump; Echocardiography; Heart failure; Strain imaging.

The left atrium (LA) plays an important role in maintaining adequate cardiac performance, interdependently with the left ventricle (LV). The LA modulates LV filling with its reservoir, conduit, and booster pump functions. First, the LA functions as a reservoir, receiving blood from the pulmonary veins during LV systole and isovolumic relaxation. This function is influenced by LV contraction through the descent of the mitral annulus,1,2 by right ventricle (RV) contraction through the pulmonary blood flow3 and by LA compliance.4 Secondly, the LA functions as a conduit. Blood flows passively from the LA into the LV during early LV diastole and diastasis. Conduit function is influenced by LV relaxation and early diastolic pressure. Finally, the LA functions as a booster pump. Blood

**Abbreviations:**

AIC Akaike's information criteria  
A late diastolic mitral inflow velocity  
$A_m$ late diastolic velocity of the septal mitral annulus  
AUC area under the receiver operating characteristic curve  
BW body weight  
CHF congestive heart failure  
$E_m$ early diastolic velocity of the septal mitral annulus  
$E$ peak early diastolic mitral inflow velocity  
FAC fractional area change  
FS fractional shortening  
LA/Ao left atrial to aortic root ratio  
LAA$_{max}$ LA maximum area  
LAMA$_{min}$ LA minimum area  
LAPA LA area pre-atrial contraction  
LA left atrium  
LVIDd inc% percent increase in LVIDd  
LVIDd left ventricular diameter in diastole  
LVIDd inc% percent increase in LVIDd  
LVIDs left ventricular diameter in systole  
LV left ventricle  
MMVD myxomatous mitral valve disease  
MR mitral regurgitation  
ROC receiver operating characteristic  
RV right ventricle  
MR mitral regurgitation  
ROCHF congestive heart failure  
$S_A$ strain before atrial contraction  
$S_{max}$ maximum strain  
$S_{min}$ minimum strain  
SR$_A$ second negative peak strain rate during atrial contraction  
SR$_E$ first negative peak strain rate during early ventricular diastole  
SR$_S$ positive peak strain rate during ventricular systole  
SR strain rate  
STE speckle-tracking echocardiography  
$e_A$ left atrial longitudinal strain during atrial contraction  
$e_E$ left atrial longitudinal strain during early ventricular diastole  
$e_S$ left atrial longitudinal strain during ventricular systole

From the Veterinary Teaching Hospital, (Nakamura, Morishita); and the Laboratory of Veterinary Internal Medicine, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Hokkaido, Japan (Kawamoto, Osuga, Morita, Sasaki, Sasaki, Ohta, Takiguchi).

This study was performed at the Graduate School of Veterinary Medicine, Hokkaido University, Hokkaido, Japan.

Corresponding author: K. Nakamura, DVM, PhD, Laboratory of Veterinary Internal Medicine, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9 Sapporo, Hokkaido 060-0818, Japan; e-mail: ken-vet@vetmed.hokudai.ac.jp.

Submitted September 13, 2016; Revised December 6, 2016; Accepted December 28, 2016.  
Copyright © 2017 The Authors, Journal of Veterinary Internal Medicine published by Wiley Periodicals, Inc. on behalf of the American College of Veterinary Internal Medicine.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

DOI: 10.1111/jvim.14660
flows actively from the LA into the LV during LA contraction in late LV diastole. This function is influenced by LA contractility, LV compliance, and LV end-diastolic pressure.

The most accurate and representative index for characterizing LA mechanical function is the evaluation of volume–pressure curves. However, obtaining these curves requires combined invasive measurements, which limits their use to experimental studies. In contrast, echocardiography is a simple and widely available tool that has been increasingly used for the noninvasive assessment of LA function. The maximum size of the LA as assessed with 2D echocardiography is one of the best indicators of prognosis and severity in dogs with myxomatous mitral valve disease (MMVD). Decreased LA booster pump function as indicated by fractional area change (FAC) is a more precise indicator of severity and prognosis of MMVD than maximum LA size in dogs.

LA strain and strain rate (SR) describe the longitudinal shortening and lengthening of the LA wall, allowing the quantification of all 3 LA functions: as reservoir, conduit, and booster pump. Speckle-tracking echocardiography (STE) is a novel, angle-independent imaging method that allows assessment of strain and SR using the tracking of acoustic speckle patterns. In humans, assessing LA strain with STE is feasible and reproducible, and LA strain is a useful severity indicator of mitral regurgitation (MR). The clinical feasibility and reproducibility of tissue Doppler imaging (TDI) and STE in evaluating LA strain and SR in normal dogs have been reported. However, the clinical utility of these methods in veterinary medicine remains unclear.

The aim of this study was to examine whether STE-derived indicators of LA strain and SR are associated with MMVD stage in dogs.

Materials and Methods

Animals

Client-owned dogs with MMVD were enrolled prospectively between December 2013 and April 2015 at Hokkaido University Veterinary Teaching Hospital. All of the dogs included in this study underwent physical examination, routine hematology, and blood biochemistry with minimum database consisting of packed blood cell volume, total protein, ALT, blood urea nitrogen, creatinine, sodium, potassium, and chloride concentrations, thoracic radiographs, and echocardiography. Dogs with atrial flutter or fibrillation and those with other concurrent cardiac disease, such as cardiomyopathy, infective endocarditis, or congenital cardiac disease, were excluded.

Myxomatous mitral valve disease was classified as stage B1, B2, C, or D in each dog based on clinical signs, echocardiographic examination, and thoracic radiographs, according to the American College of Veterinary Internal Medicine consensus. Stage B1 includes dogs without clinical signs of MMVD, and radiographic and echocardiographic evidence of LA enlargement (left atrial to aortic root ratio [LA/Ao] < 1.6). Stage B2 includes animals with echocardiographic evidence of LA enlargement (LA/Ao ≥ 1.6), but without clinical signs of MMVD. Stages C and D include dogs with the presence or history of clinical and radiographic signs of left-sided congestive heart failure (CHF). Stages C and D dogs were united into 1 group (group C/D) because of the small sample size.

Echocardiography

Echocardiography was performed in all dogs by an experienced veterinarian (KN) with an ultrasound unit equipped with a 4.4–6.2 MHz sector probe. Dogs were not sedated and were gently restrained in left and right lateral recumbency during the examination.

The LA/Ao was obtained from the right parasternal short-axis 2D view on the first frame after closure of the aortic valve as previously described. The LV diameter in diastole (LVIDd) and LV diameter in systole (LVIDs) were measured on the M-mode echocardiogram from the right parasternal short-axis 2D view with concomitant ECG registration. M-mode values were used to derive the fractional shortening (FS) and the percent increase in LVIDd (LVIDd inc%) and LVIDs (LVIDs inc%), according to the following equation: % increase = 100 x (observed dimension – expected normal dimension)/expected normal dimension. Expected normal dimensions were calculated according to the following equations: expected normal LVIDd = 1.53 x (body weight [BW])^{0.294} and expected normal LVIDs = 0.95 x (BW)^{0.315}. From the left apical 4-chamber view, pulsed wave Doppler was used to measure the peak early (E) and late (A) diastolic mitral inflow velocity and tissue Doppler was used to measure the early diastolic (E_t) and late diastolic (A_t) velocity of the septal mitral annulus.

Parameters of LA phasic function as indicated by FAC were determined as previously reported. LA area was measured with planimetry in the left apical 4-chamber view by tracing the endocardial border, excluding the confluence of the pulmonary veins. LA area was measured at 3 time points: at ventricular end-systole as LA maximum area (LAA_{max}), at the onset of the P wave on the ECG as LA area pre-atrial contraction (LAA_p), and at ventricular end-diastole as LA minimum area (LAA_{min}). Total, passive, and active FAC of the LA were calculated as follows:

\[
\text{total FAC} = 100 \times \frac{\text{LAA}_{\text{max}} - \text{LAA}_{\text{min}}}{\text{LAA}_{\text{max}}} \\
\text{passive FAC} = 100 \times \frac{\text{LAA}_p - \text{LAA}_{\text{min}}}{\text{LAA}_{\text{max}}} \\
\text{active FAC} = 100 \times \frac{\text{LAA}_p - \text{LAA}_{\text{min}}}{\text{LAA}_p}
\]

Total, passive, and active FAC are indicators of LA reservoir, conduit, and booster pump functions, respectively.

LA strain and SR were analyzed with 2DSTE. For each analysis, 2D cine loops from the left apical 4-chamber view were obtained with simultaneous ECG trace recording (lead II) to be analyzed with offline software originally designed to conduct LV analysis. The depth and sector width were minimized for frame-rate maximization (between 96 and 164 frame per second). A frame corresponding to the end-diastolic phase was selected, and the endocardial border of the left atrium was manually defined using a point-and-click technique. Epicardial surface tracing was automatically generated by the system, creating a region of interest that was manually adjusted to cover the full thickness of the myocardium. After processing, the LA myocardium was separated into 6 segments. The software automatically produced time-longitudinal strain and time-longitudinal SR curves for each segment and their averaged values (global strain and SR) (Fig 1). A cine loop preview was used to confirm whether the internal line of the region of interest followed the LA endocardial border throughout the cardiac cycle. If the internal line stopped following the endocardial border, it was manually adjusted. LA strain was measured at 3 time points:
minimum strain at a negative peak during the ventricular end-diastolic phase ($S_{\text{min}}$), maximum strain at a peak during the ventricular systolic phase ($S_{\text{max}}$), and strain before atrial contraction ($S_{\text{a}}$) on the global strain curve (Fig 1A). Left atrial longitudinal strain during ventricular systole ($e_S$) was calculated as an indicator of reservoir function, strain during ventricular early diastole ($e_E$) as an indicator of conduit function, and strain during atrial contraction ($e_A$) as an indicator of booster pump function, as follows:

\[ e_S = \frac{S_{\text{max}}}{S_{\text{min}}} \]

\[ e_E = \frac{S_{\text{max}}}{S_{\text{a}}} \]

\[ e_A = \frac{S_{\text{a}}}{S_{\text{min}}} \]

Strain rate was measured at a positive peak during ventricular systole ($SR_s$), a first negative peak during early ventricular diastole ($SR_E$), and a second negative peak during atrial contraction ($SR_A$) (Fig 1B). The mean of 3 consecutive cardiac cycles was calculated for all variables of LA function. The intra- and interobserver variations in strain variables in healthy Beagle dogs obtained by this method showed adequate repeatability and reproducibility (all intraobserver coefficient of variation was under 15% and interobserver coefficient of variation was under 20% in all strain variables with 6 dogs and 2 observers) (data not yet published).

**Statistical Analysis**

Measurements are presented as the median (interquartile range). An overall difference between groups was determined with the Kruskal-Wallis test; posthoc multiple comparisons were
made with the Steel-Dwass test for continuous variables. Fisher’s exact test was used for categorical variables. The relationships between different parameters were assessed with Spearman’s correlation analysis. To assess the comparative accuracy of different echocardiography variables in differentiating patients with a history of CHF (stage C/D) versus those without a CHF history (stage B1/B2), receiver operating characteristic (ROC) curves and the respective area under the ROC curve (AUC) were calculated. Predictors of heart failure were assessed with binary logistic regression analysis. The effect of retaining or dropping variables from the model was assessed with Akaike’s information criteria (AIC) scores. AIC scores are statistical criteria that enable logistic regression model comparisons: the smaller the AIC, the better the model. For multivariate analysis, 5 echocardiographic variables without high correlation were selected based on the results of univariate analysis and a stepwise forward selection method with the lowest AIC was performed. All statistical analyses were performed with commercially available statistical software.\textsuperscript{4,5} A 2-sided P value < .05 was considered significant.

### Results

A total of 52 dogs with MMVD were enrolled, including 24 dogs (4 Pomeranians, 4 chihuahuas, 3 Miniature Schnauzers, 2 Miniature Dachshund, 2 Shi Tzu, 2 Malteses, 1 Toy Poodle, 1 Yorkshire Terrier, and 5 others) in stage B1, 15 dogs (4 Chihuahuas, 2 Cavalier King Charles Spaniels, 2 Papillons, 2 Miniature Schnauzers, 1 Maltese, 1 Shih Tzu, and 3 others) in stage B2, 10 dogs (2 Shih Tzus, 1 Chihuahua, 1 Maltese, 1 Miniature Schnauzer, 1 Yorkshire Terrier, and 4 others) in stage C, and 3 dogs (1 Shih Tzu, 1 Miniature Dachshund, and 1 Maltese) in stage D. Table 1 shows the demographic data, physical examination results, and radiographic and echocardiographic characteristics of the study population.

The echocardiographic variables of each study group are also shown in Table 1. For the conventional

| Table 1. Clinical and echocardiographic characteristics of dogs with MMVD at different stages (ACVIM consensus). |
|---------------------------------|---------------------------------|---------------------------------|
| Age (years)                     | B1 (n = 24)                     | B2 (n = 15)                     | C/D (n = 13)                     |
| Sex (male/female)              | 10\textsuperscript{a} (8–11)    | 10\textsuperscript{b} (9–13)   | 12\textsuperscript{b} (11–14)   |
| Body weight (kg)               | 4.5\textsuperscript{b} (3.4–6.5) | 4.6\textsuperscript{b} (3.2–7.0) | 5.9\textsuperscript{b} (4.0–7.5) |
| Heart rate (bpm)               | 138\textsuperscript{b} (114–144) | 150\textsuperscript{b} (124–167) | 139\textsuperscript{b} (115–157) |
| LA/Ao                          | 1.44\textsuperscript{b} (1.27–1.50) | 1.92\textsuperscript{b} (1.73–2.15) | 2.44\textsuperscript{b} (2.29–2.83) |
| Medication                     | ACE inhibitor*                  | 1 (4.2%)                       | 4 (26.7%)                      |
|                               | Pimobendan*                     | 1 (4.2%)                       | 1 (6.7%)                       |
|                               | Diuretics*                      | 1 (4.2%)                       | 4 (26.7%)                      |
| LVIdD inc%                     | 15.5\textsuperscript{b} (5.05–36.3) | 15.5\textsuperscript{b} (5.05–36.3) | 40.0\textsuperscript{b} (25.4–48.4) |
| LDVs inc%                      | 21.0\textsuperscript{b} (43.3–7.75) | 21.0\textsuperscript{b} (43.3–7.75) | 9.32\textsuperscript{b} (–0.29–24.2) |
| FS (%)                         | 50.7\textsuperscript{b} (41.8–58.4) | 50.7\textsuperscript{b} (42.1–55.4) | 46.0\textsuperscript{b} (43.8–51.6) |
| E (cm/s)                       | 66.5\textsuperscript{b} (55.5–92.5) | 97\textsuperscript{b} (84–118)  | 158\textsuperscript{b} (126–176) |
| A (cm/s)                       | 65\textsuperscript{b} (59.3–83.8)  | 94\textsuperscript{b} (82–110)  | 87\textsuperscript{b} (51.5–121) |
| E/A                            | 1.01\textsuperscript{b} (0.86–1.30) | 1.01\textsuperscript{b} (0.79–1.29) | 1.92\textsuperscript{b} (1.37–2.78) |
| E\textsubscript{es} (cm/s)     | 6.6\textsuperscript{b} (5.2–8.0)   | 8.2\textsuperscript{b} (6.4–9.0)  | 9.0\textsuperscript{b} (8.4–10.3) |
| A\textsubscript{es} (cm/s)     | 8.1\textsuperscript{b} (5.4–9.5)   | 7.8\textsuperscript{b} (7.1–10.7) | 6.2\textsuperscript{b} (5.4–10.2) |
| Sm\textsubscript{es} (cm/s)    | 8.3\textsuperscript{b} (6.7–10.0)  | 8.9\textsuperscript{b} (8.2–10.4) | 9.1\textsuperscript{b} (7.5–10.5) |
| E/F\textsubscript{es}          | 11.1\textsuperscript{b} (8.8–13.2) | 13.2\textsuperscript{b} (10.2–16.7) | 14.7\textsuperscript{b} (13.4–20.0) |
| Total FAC (%)                  | 59.7\textsuperscript{b} (54.6–65.4) | 61.9\textsuperscript{b} (58.4–66.8) | 44.6\textsuperscript{b} (35.5–50.9) |
| Passive FAC (%)                | 27.8\textsuperscript{b} (20.0–35.2) | 35.4\textsuperscript{b} (26.9–38.2) | 27.7\textsuperscript{b} (25.6–31.6) |
| Active FAC (%)                 | 46.1\textsuperscript{b} (38.6–50.1) | 44.5\textsuperscript{b} (37.9–49.8) | 18.9\textsuperscript{b} (11.4–26.7) |
| \(e\textsubscript{Es} (%)      | 32.7\textsuperscript{b} (28.9–39.2) | 35.6\textsuperscript{b} (31.7–41.9) | 23.6\textsuperscript{b} (16.9–26.1) |
| \(e\textsubscript{E} (%)       | 12.7\textsuperscript{b} (9.9–18.4)  | 16.8\textsuperscript{b} (13.3–22.7) | 13.3\textsuperscript{b} (11.7–17.8) |
| \(e\textsubscript{A} (%)       | 19.1\textsuperscript{b} (15.3–24.3) | 19.6\textsuperscript{b} (14.1–21.4) | 6.2\textsuperscript{b} (3.18–11.2) |
| SR\textsubscript{E} (m/s)      | 1.97\textsuperscript{b} (1.70–2.43) | 2.26\textsuperscript{b} (1.98–3.52) | 1.72\textsuperscript{b} (1.39–1.91) |
| SR\textsubscript{A} (m/s)      | 2.17\textsuperscript{b} (1.85–2.77) | 2.80\textsuperscript{b} (1.88–3.87) | 1.33\textsuperscript{b} (1.17–2.30) |
| A, late diastolic mitral inflow velocity; ACE, angiotensin-converting enzyme; ACVIM, American College of Veterinary Internal Medicine; \(A\textsubscript{es}\), late diastolic velocity of the septal mitral annulus; \(E\), peak early diastolic mitral inflow velocity; \(E\textsubscript{es}\), early diastolic velocity of the septal mitral annulus; \(e\textsubscript{Es}\), left atrial longitudinal strain during atrial contraction; \(e\textsubscript{E}\), left atrial longitudinal strain during ventricular early diastole; \(e\textsubscript{A}\), left atrial longitudinal strain during ventricular systole; FAC, fractional area change; FS, fractional shortening; LA/Ao, left atrial to aortic root ratio; LVIdD inc\%, percent increase in left ventricular diameter in diastole; LVIdDs inc\%, percent increase in left ventricular diameter in systole; \(SR\textsubscript{E}\), left atrial longitudinal strain rate during atrial contraction; \(SR\textsubscript{A}\), left atrial longitudinal strain rate during early ventricular diastole; \(SR\textsubscript{E}\), left atrial longitudinal strain rate during ventricular systole; \(SR\textsubscript{A}\), strain rate.

\textsuperscript{A} continuous data are expressed as median (interquartile range). Values with different superscripted letters indicate statistically significant differences between groups.

\textsuperscript{B} A 2-sided P value < .05 was considered significant.

\textsuperscript{C} indicates significant difference between groups (P < .05).

\textsuperscript{D} Evaluations of 8 dogs in the B1, 6 dogs in the B2, and 7 dogs in the C/D.
variables, LA/Ao and E wave velocity increased significantly with advancing stage. Although there were no significant differences in parameters indicating reservoir function (total FAC and $e_S$) or booster pump function (active FAC, $e_A$, and SR$_A$) between B1 and B2 groups, these values were significantly lower in the C/D group (Figs 2 and 3). SR could be measured in 8 of 24 dogs in the B1 group, in 6 of 15 in the B2 group, and 7 of 13 in the C/D group, because the exact peak of each phase could not be determined due to the corrugation of the SR curve in some dogs.

Variables indicating LA strain were significantly correlated with age, heart rate, and some conventional echocardiographic variables (Table 2). There were significant correlations between $e_S$ and total FAC ($R = 0.748$), $e_A$ ($R = 0.763$), and SR$_A$ ($R = 0.824$), and between $e_A$ and active FAC ($R = 0.711$). The correlation between LA/Ao and $e_S$ was weak ($R = -0.433$); that between LA/Ao and $e_A$ was moderate ($R = -0.684$).

The ROC curves and the corresponding AUC were calculated to facilitate comparison of the accuracy of the...
echocardiographic variables in identifying dogs in stage C/D. As shown in Table 3, the highest accuracy was obtained with $e_A$, followed by $E$, active FAC, and LA/Ao.

Based on univariate logistic regression analysis, 5 variables, including $e_A$, $E$, LA/Ao, LVIDd inc%, and $E/A$, were selected for multivariate logistic regression.
Mitral inflow velocity; late diastolic mitral inflow velocity; early diastolic mitral inflow velocity; $e_a$, left atrial longitudinal strain during atrial contraction; LA/Ao, left atrial to aortic root ratio; LV indexed volume by approximately 20%–25% and its superiority to $e_a$ during volume loading in normal dogs. 34 Although the degree of preload dependency of $e_a$ remains unclear, SR$_A$ is confirmed to be a relatively preload-independent parameter. 35 The difference in preload dependency may contribute to the superiority of lower active FAC over active FAC in the present study.

SR$_A$ is another measure of booster pump function, and its superiority to $e_a$ as a severity indicator has been demonstrated in human patients with heart failure and preserved left ventricular ejection fraction. 22 The present study also showed the utility of SR$_A$, but SR$_A$ could not be obtained in more than half of included dogs; this was because the exact peak could not be determined due to the corrugation of the SR curve in some dogs, especially in early cases. LA strain rate has been less studied because noises in LA strain rate curves make it difficult to obtain consistent data in human patients with various cardiovascular disease. 36 In contrast, a previous study demonstrated the feasibility of measuring LA strain and SR with STE in most healthy dogs. 11 Previous study demonstrated the feasibility of evaluating LA longitudinal strain and SR with STE in most healthy dogs. 11 There is a significant correlation between $e_a$ and active FAC, but $e_a$ has a higher predictive power for CHF. LA FAC derived from 2D echocardiography is one of the commonly used measures of LA function in dogs. 10,11,32,33 However, the main limitation of LA FAC is the inability to distinguish between the increase in LA function due to a larger volume of blood received/ejected and a real increase in intrinsic LA contractility. 6 We previously demonstrated that active FAC is increased during volume loading in normal dogs. 34 Although the degree of preload dependency of $e_a$ remains unclear, SR$_A$ is confirmed to be a relatively preload-independent parameter. 35 The difference in preload dependency may contribute to the superiority of lower active FAC over active FAC in the present study.

## Discussion

The present study demonstrates that LA longitudinal strain during atrial contraction (indicator of booster pump function) and during ventricular systole (indicator of reservoir function) was lower in dogs with CHF due to MMVD than in those without CHF. Although the LA enlarges in accordance with the ACVIM stage, LA strain was maintained until the onset of CHF.

Impaired LA booster pump function evaluated with strain imaging is related to the presence of heart failure symptoms in hypertrophic cardiomyopathy23 and aortic stenosis24 in humans. Whether the reduced LA booster pump function in heart failure patients results from impairment of LA intrinsic contraction or from LA afterload mismatch (elevated LV end-diastolic pressure) remains unclear.

LA booster pump function is determined by LV compliance, LV end-diastolic pressure, and intrinsic LA contractility. LA contraction augments LV stroke volume by approximately 20–30% in normal human subjects and substantially more in the presence of impaired LV relaxation. 25 In atrial fibrillation, LA booster pump function is lost, diminishing the LA stroke volume by as much as 20%. Consequently, blood accumulates in the LA, increasing LA pressure and in turn increasing pressure within the pulmonary veins. This process promotes fluid shift, initially from the intravascular to interstitial space and then to the alveoli, culminating in pulmonary congestion and edema. 26 In dogs with MR, regurgitant jet flow and/or increased LA pressure causes LA dilatation and degeneration, including interstitial fibrosis, fatty replacement, and chronic inflammation. 27–29 These pathological changes in the LA may contribute to decreased LA intrinsic booster pump function, leading to elevation of LA pressure and pulmonary edema.

LA booster pump dysfunction is attributable more to LA afterload mismatch than to LA intrinsic contraction abnormalities. 30,31 In chronically decompensated MR, LV stiffness and end-diastolic pressure rise with LA pressure. This situation contributes to decreased transmural flow during LA contraction (restrictive pattern). In human heart failure patients, reduced transmural A wave velocity is recovered after reduction in LV filling pressure with optimal treatment of heart failure. 30 This reversibility of mitral A flow suggests that LA dysfunction results from LA afterload mismatch rather than intrinsic LA abnormalities. 30 Another study demonstrated that LV filling during LA contraction was significantly reduced in a dog model of ischemic heart disease, while LA systolic shortening during atrial contraction was not changed. 31 The preserved LA systolic shortening resulted from LA afterload mismatch, which was closely linked to an increase in the volume of blood ejected from the LA backward into the pulmonary veins. These results indicate that the morphological assessment of LA function is less dependent on afterload than transmural blood flow analysis. Further studies are needed to investigate to what degree the variables of STE-derived strain imaging are dependent on afterload.

Active FAC, a measure of LA booster pump function, was significantly lower in CHF dogs than in those without CHF in the present study, as in our previous study. 11 There is a significant correlation between $e_a$ and active FAC, but $e_a$ has a higher predictive power for CHF. LA FAC derived from 2D echocardiography is one of the commonly used measures of LA function in dogs. 10,11,32,33 However, the main limitation of LA FAC is the inability to distinguish between the increase in LA function due to a larger volume of blood received/ejected and a real increase in intrinsic LA contractility. 6 We previously demonstrated that active FAC is increased during volume loading in normal dogs. 34 Although the degree of preload dependency of $e_a$ remains unclear, SR$_A$ is confirmed to be a relatively preload-independent parameter. 35 The difference in preload dependency may contribute to the superiority of lower active FAC over active FAC in the present study.

### Table 4. Binary logistic regression analysis between stages B1/B2 and C/D.

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
| OR       | 95% CI     | $P$          |
| $e_a$ (%)| 0.24       | 0.03–0.60    | <.0001       |
| E (cm/s) | 1.17       | 1.07–1.40    | <.0001       |
| LA/Ao (%)| 1.07       | 1.04–1.12    | –            |
| LV indexed (%)| 1.09 | 1.05–1.16 | –            |
| $E/A$    | 1.42       | 1.18–1.84    | –            |

This study included 52 client-owned dogs with MMVD; 24 dogs were classified as stage B1, 15 as stage B2, and 13 as stage C/D.
or zooming might be needed to get appropriate image. Further studies are needed to examine the exact cause of this failure and to improve the feasibility of this technique.

A combined model with $e_A$ and $E$ wave was the best predictor of CHF in the present study. $E$ wave velocity is an indicator of peak LA pressure, representing LA preload. Increased preload augments LA contraction, according to the Frank-Starling law. In other words, the greater the preload, the weaker the LA contraction. In the present study, some dogs in stage B1 without $E$ wave elevation showed low $e_A$ similar to those in C/D. Therefore, this combined model may diminish the drawback of $e_A$ resulting from its preload dependency.

LA reservoir function as assessed with $e_S$ and total FAC was also a useful predictor of CHF in the present study. LA reservoir function is modulated by LV contraction, RV systolic pressure transmitted through the pulmonary circulation, and LA relaxation and stiffness. Impaired LA reservoir strain in human patients is associated with MR severity and worse prognosis. The impairment of LA reservoir function in MR may be caused by LA fibrosis due to severe LA dilation and RV enlargement. Although the utility of $e_S$ as predictor of CHF was lower than that of $e_A$ in this study, the feasibility of using $e_S$ in dogs with atrial fibrillation that lack booster pump function is a major advantage over $e_A$. Impaired LA reservoir function was demonstrated by $SR_S$ in human patients with persistent atrial fibrillation who lacked booster pump function, and $e_S$ was the only echocardiographic variable associated with CHADS2 score estimating the risk of stroke in atrial fibrillation. LA conduit function is mainly modulated by LV diastolic properties (LV relaxation and early diastolic pressure). Both $E$ and $E’$ velocity, conventional variables of LV diastolic function, were higher in dogs with CHF in the present study. In MR, the decrease in LV relaxation coexists with the increase in the pressure gradient between LA and LV. The more severe the MR, the greater the LA pressure becomes, leading to the increase in $E$ wave velocity. Although $E’$ is considered as a preload-independent index of LV relaxation, $E’$ is positively correlated with MR volume in human patients, and was higher in MR dogs with CHF than in those without CHF. LA conduit function as assessed with $e_S$ and passive FAC was not a statistically useful predictor of CHF in the present study; however, strain-derived variables of LA conduit function were decreased with MR severity in humans. These results may indicate that LA strain could be less load-dependent and more reliable for evaluation of LV diastolic function than conventional Doppler-derived variables.

Some limitations of this study must be considered. First, no invasive assessment of LA mechanical properties or afterload was performed to confirm the determinations of reduced LA function. Such assessments must be the focus of further specific studies. Second, the study lacked a control group. Investigation into the reference value of LA function in stage A with the same ultrasound machine and software used in this study is needed to strengthen the clinical importance of the LA strain in dogs with MMVD. Third, the number of dogs studied was small, especially strain rate, rendering the study underpowered to detect differences between groups. Fourth, dogs in stages C and D were united into I group because of the small sample size, making it impossible to analyze differences between refractory and non-refractory dogs. Fifth, the blood pressure was not evaluated in all dogs. Sixth, strain measurements in the present study were obtained using the software originally designed for LV. Measurements obtained by other ultrasound system or software might be incomparable with those of the present study. Last, it is possible that medication use influenced the echocardiographic indices.

In conclusion, the results of the present study indicate that LA longitudinal strain was significantly lower in dogs in the advanced stages of MMVD. LA longitudinal strain during atrial contraction was the best predictor of the presence or history of CHF. LA strain assessed on conventional echocardiography and radiography could add meaningful information to confirm the presence of CHF in the clinical setting. Further studies are needed to determine the clinical implications of these findings for treatment decisions and/or prognosis determination.

Footnotes

a Artida, Toshiba Medical Systems Corp, Tochigi, Japan
b PST-50BT, Toshiba Medical Systems Corp
c UltraExtend V3.10, Toshiba Medical Systems Corp
d JMP Pro, 11.2.0, SAS Institute Inc, Cary, NC
e IBM® SPSS® Statistics, version 21; IBM Corp, Chicago, IL

Acknowledgments

Grant support: This study was partially supported by a Grant-in-Aid for Scientific Research (No. 25850203) from the Japanese Society for the Promotion of Science (K.N.).

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Fuji K, Ozaki M, Yamagishi T, et al. Effect of left ventricular contractile performance on passive left atrial filling-clinical study using radionuclide angiography. Clin Cardiol 1994;17:258–262.
2. Castello R, Pearson AC, Lenzen P, Labovitz AJ. Evaluation of pulmonary venous flow by transesophageal echocardiography in subjects with a normal heart: Comparison with transthoracic echocardiography. J Am Coll Cardiol 1991;18:65–71.
3. Appleton CP. Hemodynamic determinants of Doppler pulmonary venous flow velocity components: New insights from studies in lightly sedated normal dogs. J Am Coll Cardiol 1997;30:1562–1574.

4. Suga H. Importance of atrial compliance in cardiac performance. Circ Res 1974;35:39–43.

5. Hoit BD, Shao Y, Gabel M, Walsh RA. In vivo assessment of left atrial contractile performance in normal and pathological conditions using a time-varying elastance model. Circulation 1994;89:1829–1838.

6. Rosca M, Lancellotti P, Popescu BA, Pierard LA. Left atrial function: Pathophysiology, echocardiographic assessment, and clinical applications. Heart 2011;97:1982–1989.

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

8. Serres F, Chetboul V, Tissier R, et al. Comparison of 3 ultrasound methods for quantifying left ventricular systolic function: Correlation with disease severity and prognostic value in dogs with mitral valve disease. J Vet Intern Med 2008;22:566–577.

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

10. Nakamura K, Osuga T, Morishita K, et al. Prognostic value of left atrial function in dogs with chronic mitral valvular heart disease. J Vet Intern Med 2014;28:1746–1752.

11. Osuga T, Nakamura K, Morita T, et al. Vitamin D status in different stages of disease severity in dogs with chronic valvular heart disease. J Vet Intern Med 2015;29:1518–1523.

12. Cameli M, Caputo M, Mondillo S, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. Cardiovasc Ultrasound 2009;7:6.

13. Ren B, de Groot-de Laat LE, Geleijnse ML. Left atrial function in patients with mitral valve regurgitation. Am J Physiol Heart Circ Physiol 2014;307:H1430–H1437.

14. Yang L, Liu Y, Shih J, et al. Predictive value of left atrial deformation on prognosis in severe primary mitral regurgitation. J Am Soc Echocardiogr 2015;28:1309–1317.e4.

15. Cameli M, Lisi M, Giacomin E, et al. Chronic mitral regurgitation: Left atrial deformation analysis by two-dimensional speckle tracking echocardiography. Echocardiography 2011;28:327–334.

16. Baron Tealdo M, Guglielmini C, Diana A, et al. Feasibility and reproducibility of echocardiographic assessment of regional left atrial deformation and synchrony by tissue Doppler ultrasonographic imaging in healthy dogs. Am J Vet Res 2014;75:59–66.

17. Caivano D, Rishniw M, Patata V, et al. Left atrial deformation and phasic function determined by 2-dimensional speckle tracking echocardiography in healthy dogs. J Vet Cardiol 2016;18:146–155.

18. Rishniw M, Erb HN. Evaluation of four 2-dimensional echocardiographic methods of assessing left atrial size in dogs. J Vet Intern Med 2000;14:429–435.

19. Dickson D, Caivano D, Patteson M, Rishniw M. The times they are a-changin’: Two-dimensional aortic valve measurements differ throughout diastole. J Vet Cardiol 2016;18:15–25.

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

21. Osuga T, Nakamura K, Lim SY, et al. Repeatability and reproducibility of measurements obtained via two-dimensional speckle tracking echocardiography of the left atrium and time-left atrial area curve analysis in healthy dogs. Am J Vet Res 2013;74:864–869.
42. Diwan A, McCulloch M, Lawrie GM, et al. Doppler estimation of left ventricular filling pressures in patients with mitral valve disease. Circulation 2005;111:3281–3289.

43. Kim JH, Park HM. Usefulness of conventional and tissue doppler echocardiography to predict congestive heart failure in dogs with myxomatous mitral valve disease. J Vet Intern Med 2015;29:132–140.

44. Yang L-T, Shih J-Y, Liu Y-W, et al. Effects of left atrial strain on functional capacity in chronic severe mitral regurgitation. Int J Cardiol 2013;168:e151–e153.