Prognostic Value of Right Ventricular Tei Index in Dogs with Myxomatous Mitral Valvular Heart Disease

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Background: The right ventricular (RV) Tei index (TX) has a significant correlation with the severity of pulmonary hypertension. However, the role of RV dysfunction in dogs with myxomatous mitral valvular heart disease (MMVD) has not been addressed.

Objectives: To investigate the correlation between right ventricular Tei-index (RVTX) and the prognosis for dogs with MMVD.

Animals: Thirty client-owned dogs with MMVD.

Methods: Clinical cohort study. Dogs were divided into two groups on the basis of the onset of cardiac-related death within 1 year of the first echocardiographic examination. Physical examination and echocardiographic variables were compared between the groups. Receiver operating characteristic (ROC) curves and multivariate logistic analysis were used to assess the comparative accuracy when identifying dogs with cardiac-related death.

Results: The highest accuracy was obtained for RVTX with an area under the ROC curve (AUC) of 0.95 (95% confidence interval [CI] 0.81–0.99) followed by the left atrial to aortic root ratio with an AUC of 0.91 (95% CI 0.74–0.98), peak early diastolic mitral inflow velocity with an AUC of 0.84 (95% CI 0.64–0.94), and Doppler estimates of systolic pulmonary artery pressure with an AUC of 0.84 (95% CI 0.61–0.95). According to the multivariate logistic regression analysis, RVTX was the only independent correlate of cardiac-related death within 1 year.

Conclusions and Clinical Importance: Right ventricular Tei-index has a strong correlation with the prognosis for dogs with MMVD. The most significant independent predictor of death was RVTX in this study.

Key words: Echocardiography; Myocardial performance index; Pulmonary hypertension; Right heart function.

In dogs with myxomatous mitral valvular heart disease (MMVD), the onset of left heart failure depends on the severity of volume overload in the left heart. In fact, echocardiographic variables representing the degree of volume overload in the left atrium, such as the left atrial to aortic root ratio (LA/Ao) and peak early diastolic mitral inflow velocity (E), have been demonstrated to be good prognostic indicators for dogs with MMVD.¹⁻⁴ Moreover, LA function, particularly the booster pump function, could be a better prognostic indicator for MMVD.⁵

Right ventricular (RV) systolic dysfunction in human patients with left heart failure because of mitral regurgitation (MR),⁶⁻⁷ dilated cardiomyopathy⁸, and ischemic heart disease⁹,¹⁰ is a powerful independent predictor of cardiovascular morbidity and mortality. A number of

Abbreviations:

A
late diastolic mitral inflow velocity

A_m
late diastolic velocity of the septal mitral annulus

AT/ET
acceleration time to ejection time

AUC
area under the receiver operating characteristic curve

BW
body weight

CHF
congestive heart failure

CI
confidence interval

E
peak early diastolic mitral inflow velocity

E_m
early diastolic velocity of the septal mitral annulus

EF
ejection fraction

ET
ejection time

FS
fractional shortening

HR
heart rate

ICT
isovolumic contraction time

IRT
isovolumic relaxation time

LA
left atrial

LA/Ao
left atrial to aortic root ratio

LV
left ventricular

LVIDd
left ventricular diameter in diastole

LVIDs
left ventricular diameter in systole

MMVD
myxomatous mitral valvular heart disease

MR
mitral regurgitation

nLVIDd
normalized LVIDd

nLVIDs
normalized LVIDs

PA
pulmonary artery

PAH
pulmonary arterial hypertension

PAP
pulmonary artery pressure

PH
pulmonary hypertension

PVR
pulmonary vascular resistance

ROC
receiver operating characteristic

RV
right ventricular

sPAP
systolic pulmonary artery pressure

TR
tricuspid regurgitation

TX
Tei-index

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studies have provided evidence that indicators of the RV systolic function, including ejection fraction (EF) and tricuspid annular plane systolic excursion, are independent prognostic factors in human patients with MR.6,7

The Tei index (TX), also known as the myocardial performance index, is an index of global myocardial function, including systolic and diastolic performance.11 TX has been used to evaluate the RV function in dogs with right heart disease, including tricuspid regurgitation (TR) and pulmonary hypertension (PH).12,13 To the best of our knowledge, no previous study has investigated the relationship between the prognosis and right ventricular Tei-index (RVTX) in dogs with MMVD. Thus, in this study, we investigated the correlation between RVTX and survival in dogs with MMVD.

Materials and Methods

Animals

Thirty client-owned dogs were included in this study. Dogs were consecutively selected between July 2013 and December 2014 on the basis of an echocardiographic diagnosis of MMVD at the Hokkaido University Veterinary Teaching Hospital. All of the dogs included in this study had undergone physical examination, blood tests, thoracic radiographs, and echocardiography. Dogs with atrial flutter or fibrillation and other concurrent cardiac diseases, such as cardiomyopathy or infective endocarditis, or congenital cardiac diseases, were excluded.

Dogs were divided into two groups for statistical analysis based on whether they survived for more than 1 year after the first echocardiographic examination (Group A, “survivors”) or whether they experienced cardiac-related death within 1 year of the first echocardiographic examination (Group B, “nonsurvivors”). Cardiac-related death was defined as death occurring because of the progression of clinical signs of congestive heart failure (CHF) without any other identifiable cause of death.

Echocardiography

Echocardiography was performed by an experienced veterinarian (KN) with an ultrasound unit equipped with a 3–7 MHz phased array-sector probe in all dogs. Dogs were sedated and restrained gently in left and right lateral recumbency during the examinations. Measurements were obtained by the two-dimensional (2D)-guided M-mode with concomitant electrocardiogram registration for the ventricles, according to the guidelines of the American Society of Echocardiography.14

For the left heart variables, LA/Ao was obtained from the right parasternal short-axis 2D view, as previously described.15 The left ventricular (LV) diameter in diastole (LVIDd) and LV diameter in systole (LVIDs) were measured from the M-mode echocardiogram in the right parasternal short-axis 2D view. M-mode values were used to derive the fractional shortening and the normalized dimension. The normalized dimensions were calculated according to the following equations: normalized LVIDd (nLVIDd) = LVIDd/ [body weight (BW)]0.315 and normalized LVIDs (nLVIDs) = LVIDs/(BW)0.315.16 From the left apical four-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 (Em) and late diastolic velocity of the septal mitral annulus.

For the right heart variables, the ratio of the pulmonary artery (PA) acceleration time to the ejection time (AT/ET) was measured by the pulsed-wave Doppler from the left parasternal short-axis 2D view. The peak TR velocity was measured from the echocardiographic view that provided the highest velocity. Systolic pulmonary artery pressure (sPAP) was estimated by calculating the peak TR gradient by the simplified Bernoulli equation: sPAP = 4 × peak TR2 + right atrial (RA) pressure. The RA pressure was estimated as 5 mmHg when there was no evidence of RA dilatation, 10 mmHg when RA dilatation was present without right-sided CHF, and 15 mmHg with right-sided CHF. The RVTX was calculated by dual pulsed-wave Doppler, where it was defined as the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ET. This method was proved to have high reproducibility in normal dogs.17 Each TX was calculated after image acquisition. The tricuspid inflow and PA flow were measured simultaneously by dual-phased Doppler with a left parasternal short-axis view, and ICT + IRT was derived by subtracting ET based on the time from the cessation of the tricuspid valve A-wave until the onset of the tricuspid valve E-wave in one image (Fig 1).17,18 ET was measured from the start until the beginning of the PA spectrum.

Statistical analysis

The measurements were expressed as the median (interquartile range) [range]. Variables were compared by Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for categorical variables. The relationships between different variables were assessed by Spearman’s rank correlation coefficient analysis. To assess the comparative accuracy of different echocardiography variables for identifying dogs with cardiac-related death, receiver operating characteristic (ROC) curves and the respective area under the ROC curve (AUC) were calculated for the variables significant at $P < .05$.
in Wilcoxon rank-sum test. Predictors of cardiac-related death within 1 year were assessed by binary logistic regression analysis. Echocardiographic variables with $P < .05$ in univariate analyses were included in the multivariate analysis, which was performed by the backward elimination method (likelihood ratio). Kaplan–Meier curves for survival were constructed to explore differences in the survival time for different dog subgroups stratified according to RVTX, by the previously mentioned ROC curve based on a cutoff value. Dogs that were alive when the study ended were categorized as the censored case. The difference in survival was tested by log-rank statistics. All of the statistical analyses were performed with commercially available statistical software.$^a$ A two-sided $P$ value $< 0.05$ was considered significant.

## Results

Among 30 dogs included in this study, 19 dogs were classified in group A and 11 dogs in group B. Table 1 shows the demographic data, physical examination results, and radiographic and echocardiographic characteristics of the study population.

The results for the echocardiographic variables are also shown in Table 1. For the left heart variables, there were significant differences in LA/Ao, nLVIDd, $E$, $E/A$, and $E_m$ between the two groups. TR velocity, sPAP, PA AT/ET, the PH variables, and RVTX were significantly higher in nonsurvivors. TR velocity and sPAP could not be measured in 4 of 19 dogs in Group A and 2 of 11 dogs in Group B because of the absence of TR.

RVTX and sPAP were significantly correlated with some of the left heart variables (Table 2). There were significant correlations between RVTX and LA/Ao ($R^2 = 0.694$, $P < .0001$), $E$ ($R^2 = 0.448$, $P < .0001$), nLVIDd ($R^2 = 0.438$, $P < .0001$), $E_m$ ($R^2 = 0.358$, $P < .0001$), and nLVIDs ($R^2 = 0.438$, $P < .0001$).

### Table 1. Clinical and echocardiographic characteristics of dogs in Groups A and B.

| Group A | Group B |
|---------|---------|
| Age (years) | 11 (10–13) [5–15] | 12 (11–13) [9–15] | 11 | .36 |
| Sex (female/male) | 4/15 | 3/8 | 11 | .86 |
| Body weight (kg) | 5.5 (4.2–7.8) [1.7–12] | 6.1 (4.5–8.1) [1.7–12] | 11 | .65 |
| Heart rate (bpm) | 144 (124–162) [92–180] | 138 (126–186) [114–204] | 11 | .68 |
| ACVIM class* | B1 | 8 (42.1%) | 0 (0%) | <.001 |
| Pulmonary edema* | 0 (0%) | 3 (27.3%) | .041 |
| Ascites* | 0 (0%) | 4 (36.4%) | .012 |
| VHS | 10.3 (9.5–11.1) [9–11.8] | 13 (11.8–13.3) [9.8–13.5] | <.001 |
| Medication | ACE inhibitor | 8 (42.1%) | 9 (81.8%) | .058 |
| Pimobendan* | 2 (10.5%) | 6 (54.6%) | .028 |
| Diuretics* | 0 (0%) | 4 (36.4%) | .012 |
| LA/Ao* | 1.7 (1.5–1.9) [1.09–2.2] | 2.63 (2.15–3.2) [1.8–3.4] | 11 | <.001 |
| nLVIDd* | 1.60 (1.45–1.78) [1.19–2.29] | 2.0 (1.93–2.31) [1.23–2.38] | 11 | .002 |
| nLVIDs | 0.85 (0.70–0.98) [0.49–1.14] | 1.05 (0.76–1.12) [0.58–1.22] | 11 | .13 |
| FS | 47.1 (41.5–54.5) [19.5–57.9] | 50.4 (43.9–59.6) [31.9–62.9] | 11 | .45 |
| $E$ (m/s)* | 0.76 (0.63–1.09) [0.4–1.64] | 1.28 (1.06–1.82) [0.69–2.25] | 11 | .002 |
| $A$ (m/s) | 0.83 (0.64–0.94) [0.38–1.07] | 0.78 (0.61–0.89) [0.4–0.91] | 11 | .34 |
| $E/A$* | 1.0 (0.80–1.2) [0.7–4.3] | 2.0 (1.2–2.8) [0.8–4.7] | 11 | .005 |
| $E_m$ (cm/s)* | 6.3 (5.8–8.0) [5.1–10.7] | 8.6 (6.4–11.1) [4.9–22.9] | 11 | .019 |
| $A_m$ (cm/s) | 7.5 (6.4–8.5) [4.7–11.5] | 6.4 (5.7–7.3) [5.1–9.7] | 11 | .089 |
| $S_m$ | 8.0 (7.4–9.6) [5.3–12.1] | 9.5 (8.1–11.0) [6.4–12.2] | 11 | .175 |
| $E/E_m$ | 11.9 (10.4–15.3) [7.8–20.5] | 15.9 (12.6–19.1) [7.2–23.5] | 11 | .061 |
| Right heart variables | TR velocity (m/s)* | 3.1 (2.8–3.4) [2.2–3.9] | 3.5 (3.3–4.0) [3.0–4.4] | 9 | .012 |
| sPAP (mmHg)* | 43.0 (35.0–51.7) [25.0–66.0] | 56.9 (48.0–79.7) [41.0–89.5] | 9 | .007 |
| PA AT/ET* | 0.41 (0.33–0.46) [0.19–0.49] | 0.31 (0.25–0.36) [0.2–0.58] | 11 | .047 |
| RVTX* | 0.36 (0.24–0.41) [0.18–0.6] | 0.89 (0.61–1.04) [0.4–1.11] | 11 | <.001 |

$A$, late diastolic mitral inflow velocity; ACE, angiotensin-converting enzyme; ACVIM, American College of Veterinary Internal Medicine; $A_m$, late diastolic velocity of the septal mitral annulus; $E$, peak early diastolic mitral inflow velocity; $E_m$, early diastolic velocity of the septal mitral annulus; FS, fractional shortening; LA/Ao, left atrial to aortic root ratio; nLVIDd, normalized left ventricular diameter in diastole; nLVIDs, normalized left ventricular diameter in systole; PA AT/ET, pulmonary artery acceleration time relative to ejection time; RVTX, right ventricular Tei-index; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; VHS, Vertebral Heart Score.

Group A included dogs that survived for more than 1 year after echocardiographic examination. Group B included dogs that experienced cardiac-related death within 1 year.

Data are expressed as the median (interquartile range) [range] or number (percentage).

*Values between Groups A and B differed significantly ($P < .05$).
The results of the present study indicate that RVTX is strongly correlated with early death in dogs with MMVD. Although several echocardiographic variables were significantly different between the two groups, we found that RVTX, a variable that corresponds to the RV function, was the most significant independent predictor of mortality. This study demonstrates that RV function analysis may be the most reliable prognostic indicator for dogs with MMVD.

In humans, RV dysfunction in MR is attributable to both the upstream and downstream consequences of volume overload.9 Upstream, MR elicits increases in LA and pulmonary capillary wedge pressure, thereby resulting in PH. In this situation, pulmonary vascular resistance (PVR) is not increased, and there is no pressure gradient between PAP and pulmonary wedge pressure. However, in some human patients, the increased PAP is out of proportion to that expected from the increases in the LA pressure, and PVR is increased abnormally, which leads to severe PH with the same magnitude as that seen in pulmonary arterial hypertension.20 Although the diagnosis of PH should be confirmed based on direct measurements of PAP and PVR, the results of our study indicate that RVTX is strongly correlated with early death in dogs with MMVD.

Table 2. Correlates of echocardiographic variables of dogs in Groups A and B.

| Variables | RVTX | sPAP |
|-----------|------|------|
| P value   | R²   | P value | R² |
| RVTX      | –    | –     | <.001 | 0.61 |
| LA/Ao     | <.001 | 0.69 | .022 | 0.22 |
| sPAP      | <.001 | 0.61 | –   | –   |
| TR        | <.001 | 0.60 | <.001 | 0.95 |
| E         | <.001 | 0.45 | .073 | .001 |
| nLVIDd    | <.001 | 0.44 | .064 | .001 |
| E/A       | <.001 | 0.34 | .077 | .001 |
| PA AT/ET  | .0093 | 0.22 | .19 | .001 |

P = .0005, and E/A (R² = 0.344, P = .0007). sPAP had a significant but weak correlation with LA/Ao (R² = 0.217, P = .0216). RVTX was significantly correlated with other right heart variables, including sPAP (R² = 0.614, P < .0001), TR velocity (R² = 0.595, P < .0001), and PA AT/ET (R² = 0.218, P < .0003).

The ROC curves and the corresponding AUC were calculated to facilitate a comparative assessment of the accuracy of the echocardiographic variables in identifying the dogs with short survival times. As shown in Table 3, the highest accuracy was obtained for RVTX, which had an AUC of 0.95 (95% CI 0.81–0.99), a sensitivity of 100%, and a specificity of 82%, followed by LA/Ao, which had an AUC of 0.91 (95% CI 0.74–0.98), a sensitivity of 84%, and a specificity of 82%. It was found that E, sPAP, and nLVIDd had the same AUC of 0.84 (95% CI 0.64–0.94, 0.61–0.95, 0.59–0.95), but they differed in terms of sensitivity (74, 73, and 89% respectively) and specificity (82, 89, and 82%, respectively).

Univariate logistic regression analysis showed that LA/Ao, E, sPAP, and RVTX were significantly related to cardiac-related death within 1 year. Subsequently, multivariate logistic regression analysis identified RVTX as the only independent correlate (P = .039, odds ratio 4.625 [95% CI 1.084–19.724], Hosmer–Lemeshow P = .309) (Table 4).

After a median follow-up period of 437 (178–576) days, cardiac-related death occurred in all nine dogs with increased RVTX (>0.61) and 3 of 21 dogs with preserved RVTX (<0.61). Remaining 18 dogs with preserved RVTX were alive when the study ended. The Kaplan–Meier survival analysis showed that dogs with increased RVTX had significantly shorter survival times than dogs with preserved RVTX (P < .0001; Fig 2).

**Discussion**

The results of the present study indicate that RVTX is strongly correlated with early death in dogs with MMVD. Although several echocardiographic variables were significantly different between the two groups, we found that RVTX, a variable that corresponds to the RV function, was the most significant independent predictor of mortality. This study demonstrates that RV function analysis may be the most reliable prognostic indicator for dogs with MMVD.

Table 3. Area under the receiver operating characteristic curve and optimal diagnostic cutoffs between Groups A and B.

| Variables | Cutoff | AUC [95% CI] | Sensitivity | Specificity |
|-----------|--------|--------------|-------------|-------------|
| RVTX      | 0.61   | 0.95 [0.81–0.99] | 1.00 | 0.82 |
| LA/Ao     | 1.95   | 0.91 [0.74–0.98] | 0.84 | 0.82 |
| E         | 1.04   | 0.84 [0.64–0.94] | 0.74 | 0.82 |
| sPAP      | 46.0   | 0.84 [0.61–0.95] | 0.73 | 0.89 |
| nLVIDd    | 1.86   | 0.84 [0.59–0.95] | 0.89 | 0.82 |
| TR velocity | 3.2   | 0.81 [0.58–0.93] | 0.73 | 0.89 |
| E/A       | 1.9    | 0.81 [0.58–0.93] | 0.94 | 0.64 |
| E/Em      | 8.0    | 0.76 [0.52–0.91] | 0.79 | 0.73 |
| PA AT/ET  | 0.39   | 0.72 [0.48–0.88] | 0.68 | 0.82 |

A, late diastolic mitral inflow velocity; AUC, area under the receiver operating characteristic curve; CI, confidence interval; E, peak early diastolic mitral inflow velocity; Emax, early diastolic velocity of the septal mitral annulus; LA/Ao, left atrial to aortic root ratio; nLVIDd, normalized left ventricular diameter in diastole; PA AT/ET, pulmonary artery acceleration time relative to ejection time; RVTX, right ventricular Tei-index; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

| Variables | OR   | 95% CI | P value |
|-----------|------|--------|---------|
| Univariate analysis | Multivariate analysis |
| LA/Ao     | 1.429 | 1.081–1.890 | .012   |
| E         | 1.341 | 1.064–1.689 | .013   |
| sPAP      | 1.118 | 1.010–1.238 | .031   |
| RVTX      | 2.138 | 1.250–3.657 | .006   |

CI, confidence interval; E, peak early diastolic mitral inflow velocity; LA/Ao, left atrial relative to aortic root ratio; OR, odds ratio; RVTX, right ventricular Tei-index; sPAP, systolic pulmonary artery pressure.
PVR by cardiac catheterization, PH is usually diagnosed by Doppler echocardiography because of its low invasiveness. In fact, Doppler estimates of sPAP have been shown to be a prognostic indicator in patients with left heart disease in humans.\(^21,22\)

Pulmonary hypertension is also a major concern in dogs with MMVD, and the diagnosis is generally made based on Doppler echocardiography. Although the true prevalence of PH in dogs with MMVD is unknown, its reported prevalence ranges from 14 to 53%.\(^\text{23–26}\) Two studies indicate that the prevalence and severity of PH are associated with the severity of CHF in dogs with MMVD.\(^\text{26,27}\) The results of the present study demonstrate that there is a significant relationship between the Doppler estimates of sPAP and the prognosis for dogs with MMVD. This result agrees with a recent study, which demonstrated that moderate-to-severe PH worsens the outcome in dogs with MMVD.\(^\text{28}\) However, another study indicated that Doppler estimates of sPAP are not related to survival in dogs with MMVD.\(^\text{29}\) Thus, it is still unclear whether the presence of PH is a negative prognostic factor or not.

The technical limitations of Doppler estimates of sPAP can reduce its value as a prognostic indicator. sPAP cannot be measured in some dogs because of the absence of TR. TR cannot be obtained in 31% of human PH patients confirmed by cardiac catheterization.\(^\text{30}\) In the present study, 22% of all dogs and 18% of nonsurvivor dogs lacked TR. By contrast, RVTX is available for all dogs when obtaining the RV inflow and outflow images. In human patients with PH, RVTX is a severity indicator as well as a prognostic predictor of adverse outcome in human patients with primary PH.\(^\text{31,32}\) However, RVTX is associated with the severity of PH in dogs in a previous study, although the value of RVTX as a prognostic indicator was not investigated.\(^\text{12}\) The correlation between RVTX and Doppler estimates of sPAP ($R^2 = 0.2789$) was much weaker in this previous study compared with that in the present study ($R^2 = 0.614$), which may be because of differences in the Doppler method employed (dual pulsed-wave Doppler in the present study but conventional pulsed-wave Doppler in the previous study). The present study is the first to demonstrate a strong correlation between RVTX and the severity of PH, as well as the prognostic value of RVTX for dogs with cardiac disease.

The downstream effects are also crucial for right heart dysfunction in human patients with left heart disease. Thus, MR elicits downstream remodeling of the LV and septal shift toward the RV, thereby resulting in a reduced RV preload and function in humans.\(^\text{9,33}\) In dogs with CHF related to severe MR, LV enlargement compresses and flattens the RV.\(^\text{34}\) MR triggers eccentric hypertrophy with geometric changes in the LV cavity, which increases the constraint on and the interaction with the RV. It has been suggested that RV afterload is not a major cause of RV systolic dysfunction in human patients with MR because the estimated sPAP correlates very weakly with the RV ejection fraction (RVEF).\(^\text{35}\) Another study demonstrated that LV enlargement, LV septal function, and sPAP are independent contributors to RV systolic function in human patients with MR.\(^\text{33}\) Moreover, RV dysfunction estimated based on the RV fractional area change, but not TR velocity, is significantly associated with mortality in human patients with previous left heart valve procedure.\(^\text{36}\) In the present study, RVTX was associated with both of the indicators of PH (sPAP) and LV enlargement (nLVIDd), but RVTX was the only independent predictor of 1-year mortality in dogs with MMVD.

Some limitations of this study must be considered. First, cardiac catheterization, the gold standard of PAP and PVR, was not performed. Second, the number of dogs studied was small, and thus, the study had less...
power for detecting differences between groups. Third, RVTX was measured by dual pulsed-wave Doppler, which is not available on broad echocardiographic systems, and previous study demonstrated that the RVTX values derived from different methods (conventional pulsed-wave Doppler and tissue Doppler imaging) are not interchangeable in humans and dogs. Fourth, the lack of any validation showing that RVTX correlates RV function in dogs. Finally, it is possible that medication use influenced the echocardiographic variables and survival time. The use of angiotensin-converting enzyme inhibitors, pimobendan, and diuretics was significantly higher in the nonsurvivors; however, this study included dogs in various clinical stages, so it was impossible to standardize the treatment.

In conclusion, RVTX, an indicator of RV systolic and diastolic function, is strongly correlated with the prognosis for dogs with MMVD. Assessing the RV function can provide further insights into the prognosis for dogs with MMVD.

Footnotes

* HI VISION Preirus, Hitachi Medical Corp., Chiba, Japan
* EUP-S52, Hitachi Medical Corp., Chiba, Japan
* JMP Pro, 12.0.1, SAS institute Inc., Cary, NC
* IBM® SPSS® Statistics, version 21, IBM Corp., Chicago, IL

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