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 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 indictors 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 cardiomyopathy[8], and ischemic heart disease[9,10] is a powerful independent predictor of cardiovascular morbidity and mortality. A number of

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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

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[a] equipped with a 3–7 MHz phased array sector probe[b] in all dogs. Dogs were unsedated 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)]$^{0.294}$ 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 (E_m) 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 TR^2 + 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 $P < .05$
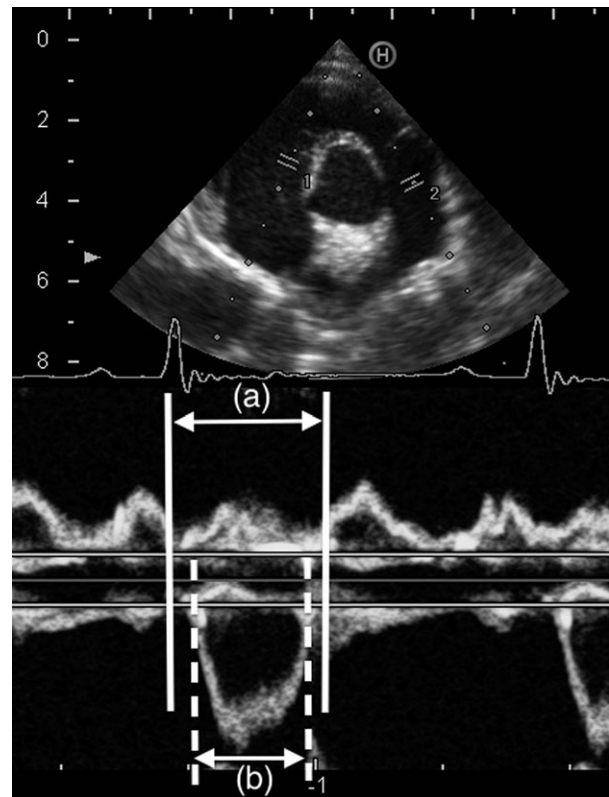

Fig 1. Measurement of RTX by dual pulsed-wave Doppler. The upper waveform is tricuspid inflow and lower waveform is pulmonary artery flow. RTX = (a − b)/b.

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.[c,d] 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 ($R^2 = 0.358$,

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

	Group A	n	Group B	n	P
Age (years)	11 (10–13) [5–15]	19	12 (11–13) [9–15]	11	.36
Sex (female/male)	4/15	19	3/8	11	.86
Body weight (kg)	5.5 (4.2–7.8) [1.7–12]	19	6.1 (4.5–8.1) [1.7–12]	11	.65
Heart rate (bpm)	144 (124–162) [92–180]	19	138 (126–186) [114–204]	11	.68
ACVIM class*					<.001
B1	8 (42.1%)		0 (0%)		
B2	10 (52.6%)		3 (27.3%)		
C	1 (5.3%)		5 (45.4%)		
D	0 (0%)		3 (27.3%)		
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]	19	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
Left heart variables					
LA/Ao*	1.7 (1.5–1.9) [1.09–2.2]	19	2.63 (2.15–3.2) [1.8–3.41]	11	<.001
nLVIDd*	1.60 (1.45–1.78) [1.19–2.29]	18	2.0 (1.93–2.31) [1.23–2.38]	11	.002
nLVIDs	0.85 (0.70–0.98) [0.49–1.14]	18	1.05 (0.76–1.12) [0.58–1.22]	11	.13
FS	47.1 (41.5–54.5) [19.5–57.9]	18	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]	18	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]	19	0.78 (0.61–0.89) [0.4–0.91]	11	.34
E/A*	1.0 (0.80–1.2) [0.7–4.3]	19	2.0 (1.2–2.8) [0.8–4.7]	11	.005
E_m (cm/s)*	6.2 (5.3–8.0) [5.1–10.7]	19	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]	19	6.4 (5.7–7.3) [5.1–9.7]	11	.089
S_m	8.0 (7.4–9.6) [5.3–12.1]	19	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]	19	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]	15	3.5 (3.3–4.05) [3.0–4.4]	9	.012
sPAP (mmHg)*	43.0 (35.0–51.7) [25.0–66.0]	15	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]	19	0.31 (0.25–0.36) [0.2–0.58]	11	.047
RVTX*	0.36 (0.24–0.41) [0.18–0.6]	19	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 ($P < .05$).

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

	RVTX		sPAP	
	P value	R^2	P value	R^2
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	
nLVIDd	<.001	0.44	.064	
E_m	<.001	0.36	.14	
E/A	<.001	0.34	.077	
PA AT/ET	.0093	0.22	.19	

A, late diastolic mitral inflow velocity; E, peak early diastolic mitral inflow velocity; E_m, 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 to ejection time; RVTX, right ventricular Tei-index; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

$P = .0005$), and E/A ($R^2 = 0.344$, $P = .0007$). sPAP had a significant but weak correlation with LA/Ao ($R^2 = 0.217$, $P = .0216$). RVTX was significantly correlated with other right heart variables, including sPAP ($R^2 = 0.614$, $P < .0001$), TR velocity ($R^2 = 0.595$, $P < .0001$), and PA AT/ET ($R^2 = 0.218$, $P < .0093$).

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

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

	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_m	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; E_m, 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.

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) [5–658] 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.

In humans, RV dysfunction in MR is attributable to both the upstream and downstream consequences of volume overload.[19] 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

Table 4. Binary logistic regression analysis of cardiac-related death within 1 year.

	Univariate analysis			Multivariate analysis
Variables	OR	95% CI	P value	P value
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	.039

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.
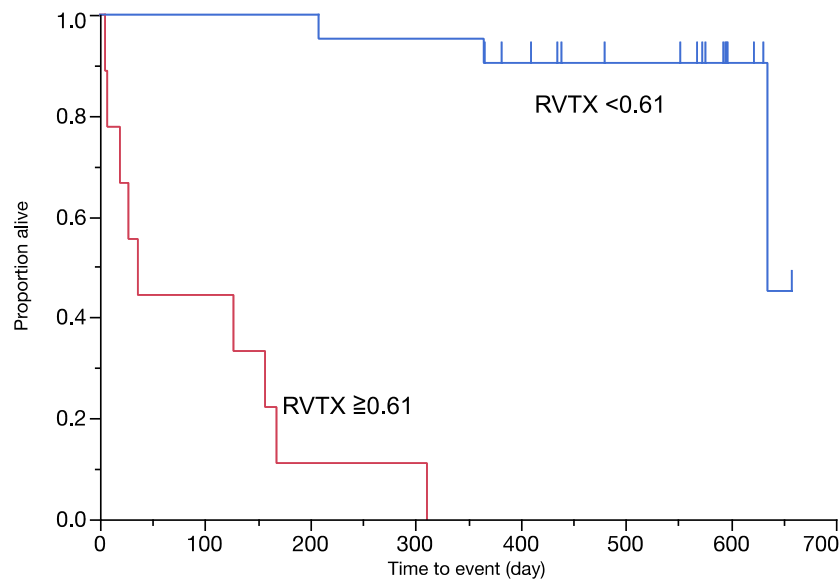
Fig 2. Survival curves obtained by Kaplan–Meier analysis. Dogs with increased right ventricular Tei-index (RVTX) (≥0.61) had significantly shorter survival than dogs with preserved RVTX (<0.61). Vertical lines represent the censored dogs. RVTX, right ventricular Tei index.

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%.[23–26] Two studies indicate that the prevalence and severity of PH are associated with the severity of CHF in dogs with MMVD.[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.[28] However, another study indicated that Doppler estimates of sPAP are not related to survival in dogs with MMVD.[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.[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.[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.[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.[9,33] In dogs with CHF related to severe MR, LV enlargement compresses and flattens the RV.[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).[35] Another study demonstrated that LV enlargement, LV septal function, and sPAP are independent contributors to RV systolic function in human patients with MR.[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.[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[18] and dogs.[17] 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

Acknowledgments

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