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Diagnostic Value of Selected Echocardiographic Variables to Identify Pulmonary Hypertension in Dogs with Myxomatous Mitral Valve Disease

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Background: Pulmonary hypertension (PH) is commonly associated with myxomatous mitral valve disease (MMVD). Because dogs with PH present without measureable tricuspid regurgitation (TR), it would be useful to investigate echocardiographic variables that can identify PH.

Aim: To investigate associations between estimated systolic TR pressure gradient (TRPG) and dog characteristics and selected echocardiographic variables.

Animals: 156 privately owned dogs.

Materials and Methods: Prospective observational study comparing the estimations of TRPG with dog characteristics and selected echocardiographic variables in dogs with MMVD and measureable TR.

Results: Tricuspid regurgitation pressure gradient was significantly ($P < .05$) associated with body weight corrected right (RVIDDn) and left (LVIDDn) ventricular end-diastolic and systolic (LVIDSn) internal diameters, pulmonary arterial (PA) acceleration to deceleration time ratio (AT/DT), heart rate, left atrial to aortic root ratio (LA/Ao), and the presence of congestive heart failure. Four variables remained significant in the multiple regression analysis with TRPG as a dependent variable: modeled as linear variables LA/Ao ($P < .0001$) and RVIDDn ($P = .041$), modeled as second order polynomial variables: AT/DT ($P = .0039$) and LVIDDn ($P < .0001$) The adjusted R^2-value for the final model was 0.45 and receiver operating characteristic curve analysis suggested the model's performance to predict PH, defined as 36, 45, and 55 mmHg as fair (area under the curve [AUC] = 0.80), good (AUC = 0.86), and excellent (AUC = 0.92), respectively.

Conclusion and Clinical Importance: In dogs with MMVD, the presence of PH might be suspected with the combination of decreased PA AT/DT, increased RVIDDn and LA/Ao, and a small or great LVIDDn.

Key words: Pulmonary artery velocity profile; Tricuspid annular plane systolic excursion; Tricuspid regurgitation.

Pulmonary hypertension (PH) is common in dogs with myxomatous mitral valve disease (MMVD).[1–3] Increased pulmonary arterial and venous pressures might be present simultaneously. Presumably, the increased pulmonary arterial pressures are caused by local hypoxia induced by left sided congestive heart failure (CHF).[4] Pulmonary venous hypertension in dogs with CHF and MMVD is caused by increased left atrial (LA) and pulmonary venous pressures.[5] The gold standard for diagnosing PH is via right ventricular catheterization directly measuring right ventricular (RV) systolic pressure (RVSP). In the clinical setting, tricuspid regurgitation (TR) interrogated and measured by Doppler echocardiography is commonly used to estimate TR pressure

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Abbreviations:

Ao	aorta
AT	acceleration time
AUC	area under the curve
CHF	congestive heart failure
CV	coefficient of variation
DT	deceleration time
EF	ejection fraction
ET	ejection time
HR	heart rate
IQR	interquartile range
LA/Ao	left atrial to aortic diameter ratio
LA	left atrium
LVIDDn	left ventricular end-diastolic internal diameter corrected for body weight
LVIDSn	left ventricular end-systolic internal diameter corrected for body weight
LV	left ventricle
MMVD	myxomatous mitral valve disease
MR	mitral regurgitation
PA	pulmonary artery
PH	pulmonary hypertension
ROC	receiver operating characteristic
RVEF	right ventricular ejection fraction
RVIDDn	right ventricular end-diastolic internal diameter corrected for body weight
RV	right ventricle
RVSP	right ventricular systolic pressure
SPAP	systolic pulmonary artery pressure
TAPSEn	tricuspid annular plane systolic excursion corrected for body weight
TRPG	tricuspid regurgitation pressure gradient
TR	tricuspid regurgitation
TV	tricuspid valve

gradient (TRPG). By adding the estimated right atrial (RA) pressure, RVSP can be calculated, reflecting systolic pulmonary artery (PA) pressure (SPAP) in the absence of pulmonic stenosis.[6,7] However, it has been suggested that the addition of estimated RA pressures might lead to the overestimation of PH severity.[8] Noninvasive Doppler estimates of RVSP correlate well with invasively measured SPAP in people.[9,10] In dogs, there is moderate correlation between invasive and noninvasive values of SPAP.[11] The threshold to diagnose PH in dogs by Doppler-estimated RVSP has varied between 30 and 45 mmHg in different studies.[1,5,12,13] The cutoff value for RVSP to diagnose clinically relevant PH has varied between 45 and 56 mmHg.[1,13] A TRPG >55 mmHg is a negative predictor of survival in dogs with MMVD.[14] Additional echocardiographic and Doppler findings indicating PH include RV hypertrophy and dilatation, PA dilatation, flattening or paradoxical motion of the interventricular septum, and loss of presystolic "a wave" and possible presence of midsystolic closure ("W wave") in PA flow.[15–17]

There are several limitations associated with estimating RVSP using Doppler measurements of TR. The velocity of the TR jet might be affected by the degree of TR present, the position of the jet in relation to the Doppler cursor, and to dog compliance. Also, TR might not be present or not possible to accurately measure, thus precluding the diagnosis of PH. It is therefore of interest to investigate easily accessible conventional echocardiographic and Doppler variables possibly associated with PH in dogs.

Pulmonary artery velocity profile, ie, acceleration time to ejection time ratio (AT/ET) or AT to deceleration time ratio (AT/DT), has previously been shown to be altered with a decreased AT/ET and AT/DT in dogs with PH.[1,5,18] The maximum velocity of PA is often unchanged, although less flow, or even flow reversal in late systole, occurs with severe PH.[13] Tricuspid annular plane systolic excursion (TAPSE) has been used to evaluate RV systolic performance in people and in dogs.[19] The TAPSE decreases in people with PH[20] and in dogs with severe PH.[19]

The aim of the study was to investigate associations between estimates of TRPG and dog characteristics as well as selected echocardiographic variables in dogs with MMVD and measureable TR with and without CHF.

Materials and Methods

Dogs

A total of 156 privately owned dogs presented at Albano Animal Hospital, Stockholm, Sweden were included in the study. All dogs were examined using the same equipment and the same protocol. The dogs were included in the study based on the following criteria;

(1) echocardiographic evidence of MMVD defined as thickened or prolapsing mitral valve leaflets and mitral regurgitation (MR) detected on color flow Doppler; (2) TR detected on color flow Doppler with measureable flow velocity; (3) absence of other heart diseases;[21,22] (4) absence of clinical signs of systemic disease. Dogs were classified with and without CHF according to the ACVIM classification of myxomatous mitral valve disease.[23,24] All examinations were performed and evaluated by one veterinary specialist in cardiology AT. The study was approved by the Ethical Committee for Animal welfare in Stockholm.

Conventional Echocardiography

Two-dimensional echocardiographic examinations were performed with an ultrasound unit[a] equipped with 3.0–8.5 MHz phased-array transducers in all dogs. Dogs were unsedated and gently restrained in right and then left lateral recumbency during the examination. Left atrial to aortic (Ao) diameter ratio (LA/Ao) was measured as described previously.[25] Left ventricular (LV) and RV measurements were obtained from the right parasternal location short axis view during 2D-guided M-mode echocardiography according to the recommendations of the American Society of Echocardiography.[26] The TAPSE was measured from M-mode recordings obtained from the left apical 4 chamber-view as the maximal systolic longitudinal displacement of the lateral tricuspid valve (TV) annulus toward the RV apex. Care was taken to align the M-mode cursor as parallel as possible with the longitudinal movement of the TV plane.[27] Left ventricular internal diameter (LVIDD) was normalized for body weight at end-diastole (LVIDDn) and at systole (LVIDSn) using the formulas: LVIDD/[body weight (kg)]$^{0.294}$ and LVIDS/[body weight (kg)]$^{0.294}$, respectively. Right ventricular internal end-diastolic diameter (RVIDD) and TAPSE were normalized for body weight (RVIDDn and TAPSEn) using the formulas: RVIDD/[body weight (kg)]$^{0.33}$ and TAPSE/[body weight (kg)]$^{0.33}$, respectively.[28]

Doppler examinations of all valves were performed and peak velocities were recorded. The modified Bernoulli equation was used to calculate the TRPG between the right atrium (RA) and RV. The PA flow velocity profile was recorded from the right parasternal short-axis view using pulsed wave Doppler and peak velocity, and AT and DT were measured. The AT of the pulmonary outflow was measured from the onset of the flow profile to the peak velocity, and the DT was measured from the peak velocity to the end of the velocity profile. Care was taken not to inadvertently include Ao flow when measuring PA flow.[29] For the statistical analyses including univariate and multiple regression analyses, dogs were dichotomized at TRPG of 36 mmHg, which is commonly used as the cutoff value to diagnose PH,[1,5,12,13] or 45 and 55 mmHg, both of which have been suggested to indicate clinically significant PH.[1,13,14] For the receiver operating characteristic (ROC) curve analysis, the same cutoffs for TRPG; ≥36 mmHg, ≥45 mmHg, and ≥55 mmHg were used to calculate area under the curve (AUC) for each ROC curve.

Measurements were made directly on the monitor freeze-frame image in the same order in each dog with measurement of TR velocity at the end of each examination. Therefore, the examiner was not aware of the estimated TRPG when measuring all other echocardiographic variables. Three consecutive measurements were averaged for each variable, except for the velocities where the highest recorded measurement was used.

Assessment of Variability

Within-day variability was assessed using 5 dogs with MMVD (2 Class B1, 2 B2, and 1 C2) according to the ACVIM classification.[23,24] Each dog was examined 6 times on a given day. Six variables were measured on each of the 6 acquisitions for each dog and the resulting mean values and standard deviations (SD) were used to determine the coefficient of variation (CV), where SD is expressed as a percentage of the mean.[30] The following cutoff

values were used; <5% excellent, <10% good, <15% acceptable variability.

Statistical Analysis

A computer program[b] was used for all statistical analyses. Data are presented as medians and interquartile ranges (IQR). The nonparametric Wilcoxon signed rank test was used for testing the equality of the medians between the groups dichotomized at TRPG of 36[1,5,12,13] or 55 mmHg,[14] respectively. Univariate and multiple regression analyses were used to evaluate associations between TRPG, and dog characteristics (age, sex, and body weight), heart rate (HR) obtained from the echocardiogram, and the echocardiographic measurements LA/Ao, PA AT/DT, PA velocity, RVIDDn, TAPSEn, LVIDDn, LVIDSn, and the presence of CHF. In case of nominal data (sex and presence of CHF), associations were evaluated by the Wilcoxon test. Associations between continuous variables and TRPG were investigated by both linear and quadratic regression. For each of these variables, the type of modeling (linear or quadratic) obtaining the lowest P value and highest adjusted R^2 was used in the multiple regression analysis, which included only variables with $P < .2$ in the univariate analysis. Analyses were performed in a backward stepwise manner,[31] starting with all variables included in the model and then removing the variable with the highest P value until all the remaining variables had a value of $P < .05$. All variables were assessed only as main effects; no interaction terms were considered in the model. The adjusted R^2 is defined as the percentage of the total sum of squares that can be explained by the regression and it also considers the degrees of freedom for the variables added.

The diagnostic efficacy of the model obtained from the multiple regression analysis to predict the presence of PH was further evaluated by the use of ROC curves at 3 different cutoffs for TRPG, 36 mmHg, 45 mmHg, and 55 mmHg. The ROC curves were evaluated using AUC and calculating 95% confidence intervals (CI), and differences were tested using the method by Hanley and McNeil.[32] Level of significance was set at $P < .05$.

Results

Base-line Variables

A total of 156 dogs of 62 breeds were included in the study; Cavalier King Charles spaniel (27), mixed breed (18), Dachshund (15), Miniature Schnauzer (9), Norfolk terrier (7), Chinese Crested (6), Shetland Sheepdog (6), Chihuahua (5), and <5 dogs of 54 other breeds. There were 91 (58%) males and 65 (42%) females. Age at presentation ranged from 4.5 to 16 years, median 10.6 years (IQR 8.8–12 years). Body weight ranged from 1.2 to 45.5 kg, median 9.7 kg, (IQR 6.7–14.3 kg). According to the ACVIM classification, 106 dogs (90 B1 and 16 dogs B2) were classified without CHF, and 50 dogs (6 C1 and 44 C2) were classified with left-sided CHF. None of the dogs presented with right-sided CHF. The TRPG ranged from 9 to 90 mmHg with a median of 30 (IQR, 21–41) mmHg. All dogs were in sinus rhythm, and HR ranged from 74 to 256 beats/min, median 136 (IQR, 111–152) beats/min. At the time of physical and echocardiographic examinations, a total of 80 dogs underwent medical treatment where 72 dogs received pimobendan, 50 dogs furosemide, 48 dogs benazepril, 5 dogs spironolactone, 4 dogs sildenafil, 4 dogs digoxin, and 1 dog diltiazem.

Assessment of the variability showed that all CV mean values were below 15%, except for RVIDDn and PA DT which were below 19% (Table 1).

Comparisons Between Groups Dichotomized at 36 mmHg

Dogs were dichotomized in 2 groups; (1) TR maximum velocity <3 m/s corresponding to TRPG <36 mmHg (n = 104) and (2) TR maximum velocity ≥3 m/s corresponding to TRPG ≥36 mmHg (n = 52). There were no significant differences between the groups regarding age, sex, LVIDDn, and LVIDSn, respectively. Heart rate, LA/Ao, and the presence of CHF were significantly higher, and PA AT/DT and body weight were significantly lower in dogs with TRPG ≥36 mmHg. No differences between groups were found regarding TAPSEn, RVIDDn and PA velocity (Table 2).

Comparisons Between Groups Dichotomized at 55 mmHg

Dogs were dichotomized in 2 groups; (1) TR maximum velocity <3.7 m/s corresponding to TRPG <55 mmHg (n = 139) and (2) TR maximum velocity ≥3.7 m/s corresponding to TRPG ≥55 mmHg (n = 17). There were no significant differences between the groups concerning age, sex, body weight, HR, LVIDDn, LVIDSn, LA/Ao or the presence of CHF. Significant differences between the groups were found regarding PA AT/DT and RVIDDn, whereas no differences were found between the groups regarding TAPSEn and PA maximum velocity (Table 3).

Univariate Regression Analysis

The TRPG was linearly positively associated with increasing RVIDDn ($R^2 = 0.11$, $P < .0001$), HR ($R^2 = 0.03$, $P = .01$), LA/Ao ($R^2 = 0.09$, $P < .0001$) (Figs 1, 2). Quadratic regression described significant parabolic associations between TRPG and LVIDDn (adjusted $R^2 = 0.28$, $P < .0001$), PA AT/DT (adjusted

Table 1. Within-day variability in 6 measurements of selected echocardiographic variables in 5 dogs with myxomatous mitral valve disease examined 6 times on a given day.

Variable	Mean (SD)	CV% and Range
PA velocity (m/s)	0.63 (0.028)	4.4 (2.3–7)
PA acceleration time (AT) (ms)	70 (8.7)	12.3 (4.5–23.6)
PA deceleration time (DT) (ms)	77 (12.9)	16.7 (11–26.3)
PA AT/DT	0.94 (0.09)	9.6 (5–14)
RVIDDn	0.32 (0.06)	18.8 (7–29)
TAPSEn	0.47 (0.05)	10.7 (6.5–17)

PA, pulmonary artery; AT/DT, PA acceleration time to deceleration time ratio; RVIDDn, right ventricular end-diastolic internal diameter corrected for body weight; TAPSEn, tricuspid annular plane systolic excursion corrected for body weight.

Table 2. Clinical and echocardiographic data in 156 dogs with myxomatous mitral valve disease with and without pulmonary hypertension dichotomized at pressure gradient 36 mmHg between the right atrium and ventricle. Continuous data are presented as median and interquartile range (IQR).

Variable	Pressure Gradient <36 mmHg (n = 104)	Pressure Gradient ≥36 mmHg (n = 52)	*P* Value
Sex (male/female)	62/42	29/23	.71
Age (years)	10.5 (8.3–12.1)	10.8 (9.4–12.5)	.24
Body weight (kg)	9.9 (7.0–14.4)	8.1 (6.4–12.7)	.007
Heart rate (beats/min)	129 (104–149)	144 (122–161)	.0017
LA/Ao	1.2 (1.1–1.4)	1.6 (1.3–1.9)	.0002
LVIDDn	1.87 (1.6–2.1)	2.08 (1.6–2.3)	.12
LVIDSn	1.02 (0.87–1.25)	0.97 (0.87–1.3)	.15
Presence of CHF (yes/no)	20/84	30/22	<.0001
PA AT/DT	0.85 (0.75–1.0)	0.77 (0.63–0.88)	.0027
PA velocity (m/s)	0.77 (0.61–0.88)	0.71 (0.6–0.86)	.97
RVIDDn	0.24 (0.18–0.33)	0.27 (0.2–0.43)	.06
TAPSEn	0.66 (0.56–0.83)	0.67 (0.52–0.84)	.99

LA/Ao, left atrial to aorta diameter; LVIDDn, left ventricular end-diastolic internal diameter corrected for body weight; LVIDSn, left ventricular end-systolic internal diameter corrected for body weight; CHF, congestive heart failure; AT/DT, acceleration time to deceleration time ratio; PA, pulmonary artery; RVIDDn, right ventricular end-diastolic internal diameter corrected for body weight; TAPSEn, tricuspid annular plane systolic excursion corrected for body weight.

Table 3. Clinical and echocardiographic data in 156 dogs with myxomatous mitral valve disease with and without pulmonary hypertension dichotomized at pressure gradient 55 mmHg between the right atrium and ventricle. Continuous data are presented as median and interquartile range (IQR).

Variable	Pressure Gradient <55 mmHg (n = 139)	Pressure Gradient ≥55 mmHg (n = 17)	*P* Value
Sex (male/female)	82/56	8/9	.58
Age (years)	10.6 (8.3–12.3)	10.8 (9.1–12.4)	.74
Body weight (kg)	9.8 (6.7–14.3)	9 (6.8–16.1)	.74
Heart rate (beats/min)	136 (113–151)	140 (109–162)	.72
LA/Ao	1.29 (1.1–1.7)	1.29 (1.1–2.2)	.17
LVIDDn	1.9 (1.65–2.16)	1.9 (0.97–2.2)	.17
LVIDSn	1.01 (0.88–1.25)	0.97 (0.51–1.44)	.75
Presence of CHF (yes/no)	42/97	8/9	.18
PA AT/DT	0.84 (0.76–0.97)	0.59 (0.47–0.67)	<.0001
PA velocity (m/s)	0.72 (0.6–0.86)	0.77 (0.6–0.86)	.82
RVIDDn	0.24 (0.18–0.33)	0.35 (0.27–0.81)	.0004
TAPSEn	0.67 (0.56–0.84)	0.55 (0.49–0.71)	.41

LA/Ao, left atrial to aorta diameter; LVIDDn, left ventricular end-diastolic internal diameter corrected for body weight; LVIDSn, left ventricular end-systolic internal diameter corrected for body weight; CHF, congestive heart failure; AT/DT, acceleration time to deceleration time ratio; PA, pulmonary artery; RVIDDn, right ventricular end-diastolic internal diameter corrected for body weight; TAPSEn, tricuspid annular plane systolic excursion corrected for body weight.

$R^2 = 0.23$, $P < .0001$) (Figs 3, 4), and LVIDSn (adjusted $R^2 = 0.07$, $P = .0012$). The presence of CHF was associated with higher TRPG ($P < .0001$). There was no association between TRPG and age, sex, body weight, PA velocity, or TAPSEn.

Multiple Regression Analysis

Of the 11 included variables, 4 remained significant in the multiple regression analysis with TRPG as dependent variable: Modeled as linear variables LA/Ao ($P < .0001$) and RVIDDn ($P = .041$). Modeled as second order polynomial variables: PA AT/DT ($P = .0039$) and LVIDDn ($P < .0001$) The adjusted R^2-value for the final model was 0.45 (Figs 3, 4).

Receiver Operating Characteristic Curve Analysis

The model obtained from the multiple regression analysis was tested as a possible diagnostic tool for predicting PH defined at 3 different levels: TRPG ≥36 mmHg, ≥45 mmHg, and ≥55 mmHg by calculating the AUC for each ROC curve (Fig 5). The AUC was 0.80 (95% CI 0.72–0.86) at 36 mmHg which corresponded to a sensitivity of 0.67 and a specificity of 0.78, 0.86 (95% CI 0.79–0.91) at 45 mmHg, with a sensitivity of 0.80 and a specificity of 0.88, and 0.92 (95% CI 0.86–0.96) at 55 mmHg, with a sensitivity of 0.88 and specificity of 0.93, indicating fair, good and excellent test performance, respectively. Statistical difference was obtained comparing the AUC at the cut-

off of ≥36 mmHg and ≥55 mmHg (P = .003), but not in any of the other comparisons.

Discussion

Our study shows that PH should be suspected in dogs with MMVD if the combination of decreased pulmonary arterial AT/DT, increased RVIDDn and LA/Ao, and a small or great LVIDDn is present. The best predictor of PH, using this combination of findings, was obtained for TRPG ≥55 mmHg.

The parabolic curve describing the association between TRPG and LVIDDn in our study (Fig 3) indicates that in a subset of dogs with PH, the diameter of the LV is reduced in diastole. The reduction in the LV size in patients with PH might be explained by increased RV pressures causing higher trans-septal pressures, which, because of the shared space within the pericardial sac, causes leftward bowing of the interventricular septum, and thereby decreased LV filling.[33,34] In human patients with severe precapillary PH, the LV end-diastolic volume, stroke volume, and ejection fraction are reduced. Reduced LV compliance has been

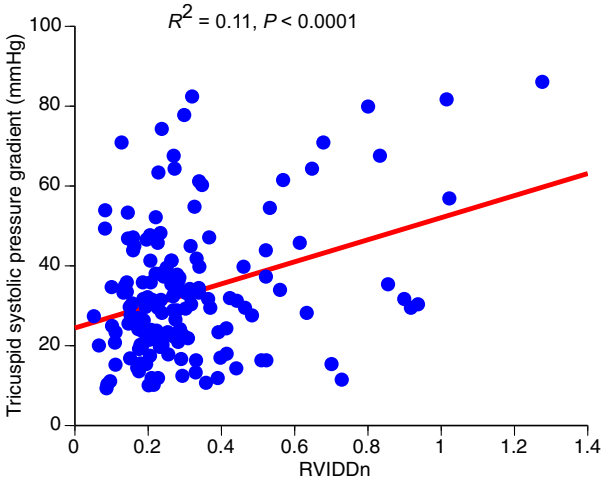

Fig 1. Linear association between tricuspid regurgitation pressure gradient (TRPG) and right ventricular internal diameter in diastole corrected for body weight (RVIDDn) in 156 dogs with myxomatous mitral valve disease with and without pulmonary hypertension.

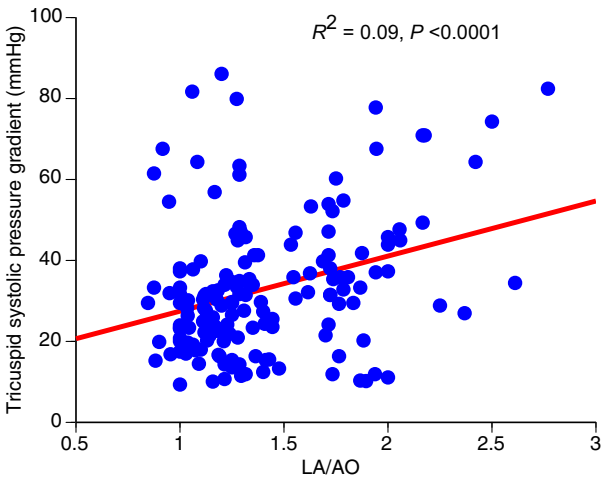

Fig 2. Linear association between tricuspid regurgitation pressure gradient (TRPG) and left atrial to aortic diameter ratio (LA/Ao) in 156 dogs with myxomatous mitral valve disease with and without pulmonary hypertension.

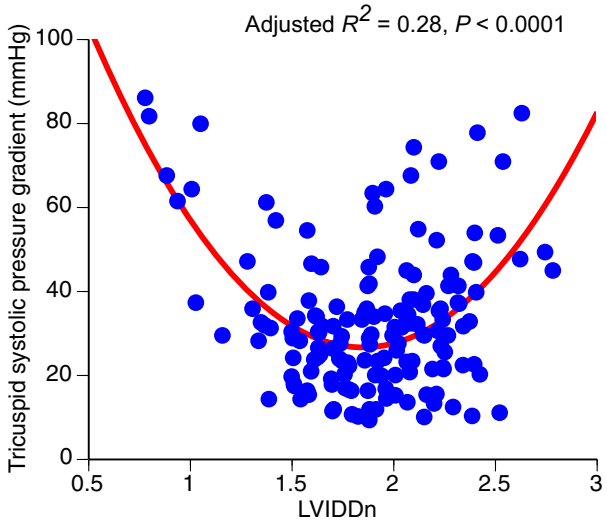

Fig 3. Parabolic curve describing the association between tricuspid regurgitation pressure gradient (TRPG) and left ventricular internal diameter in diastole corrected for body weight (LVIDDn) in 156 dogs with myxomatous mitral valve disease with and without pulmonary hypertension.

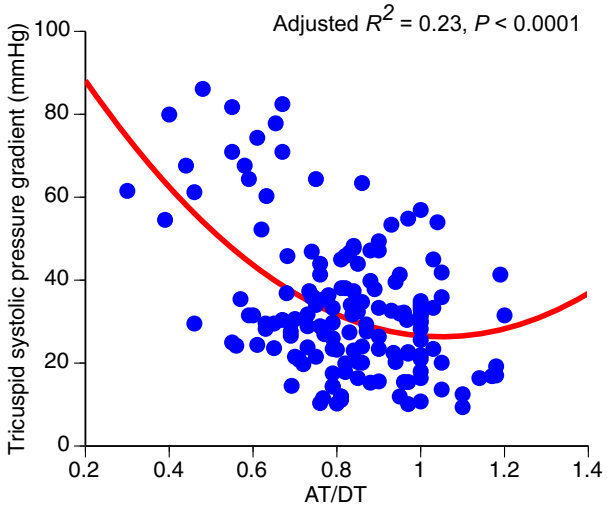

Fig 4. Parabolic curve describing the association between tricuspid regurgitation pressure gradient (TRPG) and pulmonary artery acceleration time (AT) and deceleration time (DT) ratio in 156 dogs with myxomatous mitral valve disease with and without pulmonary hypertension.

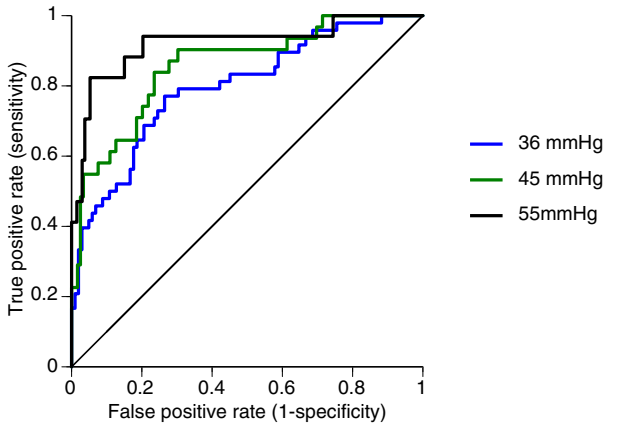

Fig 5. The ROC curves obtained by use of multivariate analysis assessing the diagnostic efficacy of predicted values for separating groups of dogs with different degrees of pulmonary hypertension (PH), ie, tricuspid regurgitation pressure gradient (TRPG) of 36, 45, and 55 mmHg, respectively. The best predictor of PH using left atrial to aortic ratio, right and left ventricular diastolic internal diameter corrected for body weight, and pulmonary artery flow acceleration time to deceleration time ratio was obtained for TRPG ≥55 mmHg (AUC 0.92, 95% CI 0.86–0.96).

associated with alterations in septal configuration,[33,35,36] and reduced LV chamber volume and mass have been demonstrated in people within days to weeks of forced extreme physical inactivity or zero-gravity conditions.[37,38] People with chronic obstructive pulmonary disease have comparatively smaller pulmonary veins and reduced LV filling.[39] The reduction in LV filling caused by PH has been shown to cause atrophied myocytes with lower cellular content of the contractile protein myosin and decreased degree of phosphorylation of these proteins.[40] In our study, the decreased LV chamber size was only observed in some of the dogs with severe PH, which might be explained by different mechanisms behind the development of PH.

In our study, estimations of TRPG were positively associated with decreasing pulmonary arterial AT/DT ratio both in the univariate and the multiple regression analysis, which is in accordance with previous studies.[1,5,13,18] A low AT/DT might suggest, whereas a normal AT/DT does not preclude, the presence of PH in dogs with MMVD. In healthy dogs, Doppler flow profiles of Ao and PA flow differ in peak velocity and AT/DT because of differences in afterload, where Ao flow has a higher velocity and a lower AT/DT compared to PA flow. In the presence of PH, PA flow profile becomes more similar to the Ao flow signal because LV and RV afterload become more similar. Measurements of AT/DT are sensitive to the sample location and care should be taken not to inadvertently include Ao flow when measuring PA flow.[29] Measurements of AT/DT might be affected by RV systolic function, severity of TR, respiration, and HR,[13] which should be taken into consideration when interpreting results of these measurements.

Right ventricular hypertrophy and dilatation is commonly associated with PH.[16,17,41] However, one study reported that only 33% of dogs with PH had RV enlargement, although most dogs in that study had only mild PH.[1] Increasing RVIDDn was positively associated with increasing TRPG both in the univariate and in the multiple regression analysis in our study. The association between increasing RVIDDn and increasing TRPG might, however, be related to increased TR volume, and might thus not be applicable to dogs without TR.

Increasing LA/Ao ratio was positively associated with increasing TRPG both in the univariate and in the multiple regression analysis in this study. This finding is in agreement with previous studies, and pulmonary venous hypertension is considered to be a common sequel to increasing LA pressures.[1,5,42] The degree of PH in dogs with MMVD was correlated with MR severity and LA hypertension inducing LA dilatation in a previous study.[1] Increased activity of neurohormones associated with increased LA pressure and dilatation results in decreased sensitivity to endogenous vasodilators in the pulmonary vasculature, adding to the resulting PH.[5] As expected, increased HR and presence of left-sided CHF was positively associated with increasing TRPG.

The model obtained from the multiple regression analysis was used to predict TRPG values, which, in turn was used to predict PH at 3 different levels: ≥36 mmHg, ≥45 mmHg, and ≥55 mmHg. The AUC increased with increasing value of the cutoff for PH, indicating that the test was more effective at higher pressures. This is not surprising as the majority of dogs clustered at TRPG between approximately 20–40 mmHg (median 30 (IQR 21–41) mmHg), which is a comparably narrow range. However, as the cutoff for the presence of PH was set higher, the model's ability to predict the presence of PH increased. Indeed, the model could predict the presence of PH defined as TRPG ≥55 mmHg with an AUC of 0.92, which is considered an excellent test performance. In a recent report, 55 mmHg was shown to be an independent predictor of survival in dogs with MMVD,[14] and the present study showed that some echocardiographic variables other than TR jet velocity, might predict its presence.

The RV base-to-apex shortening during systole, ie, TAPSE, is considered to be one of the most reliable and reproducible echocardiographic variables evaluating RV systolic performance in a variety of pathologic conditions in humans, with an excellent correlation with RV ejection fraction (RVEF) calculated using MRI and radionuclide ventriculography.[27,43–45] Tricuspid annular plane systolic excursion has been used to reliably detect PH, and has been shown to correlate well with RVEF and with mortality in human patients with PH.[46–48] The rationale behind the use of TAPSE as an indicator of RV systolic performance stems from the fact that RV contraction is characterized by predominant longitudinal shortening. However, severe TR might cause underestimation of the degree of RV dysfunction and correlation with RVEF.[49] The TAPSE has been shown to decrease in dogs with severe PH, whereas dogs with mild to moderate PH were indistinguishable from normal dogs.[19] In our study, TAPSEn was not associated

with TRPG in the univariate (or the multiple) regression analysis. Thus, TAPSE does not seem to be a sensitive variable in predicting PH in MMVD dogs.

Repeatability of measurements was acceptable, ie, below 15%, for most variables. Although both RVIDDn and PA deceleration time showed a comparatively greater variability, CV was below 19% for these variables.

There are several limitations of the study. As the study only included MMVD dogs with measurable TR, the studied population might not represent the total population of dogs with MMVD and PH, and this might have biased the results. Replacing the gold standard for measuring TRPG with calculations based on noninvasive measurement of TR has limitations and might not be accurate. The accuracy of Doppler assessment of TR was found to be only moderately correlated with invasive measurements in a recent experimental study of dogs with pulmonary hypertension.[11] In our study, it is likely that TR velocities might have been underestimated in some dogs, as suggested by the relatively low estimated TRPG in these dogs. For accurate measurements of TR velocities, perfect alignment with the TR flow is needed, which might not be possible when the TR jet is small and eccentric, or if the dog is uncooperative. Another limitation is the lack of measurement of RA pressure. As mentioned above, RVIDDn might also be influenced by the volume of TR, and might therefore not be valid in dogs without TR. The TR velocities are considered to vary with respiration, but no attempts were made to synchronize measurements with the phases of the respiratory cycle in our study. All dogs were imaged at rest and TRPG might be different during exercise. The TRPG might have been underestimated because of the concurrent treatment with diuretics, angiotensin enzyme inhibitor, inodilators and phosphodiaesterase inhibitors in some dogs. Linear measurements such as TAPSE and RVIDD need to be corrected for body size in order to allow comparisons between individuals of different body size. In the absence of studies describing the exact nature of the association between TAPSE, RVIDD, and body weight, we choose to raise these measurements to the power of 1/3 as most linear measurements relate to body mass close to this power.[28] As for all studies, statistical significance is strongly driven by sample size. Some of the statistically significant associations found in this study had comparably low R^2-values, indicating comparably weak (and possibly clinically insignificant) associations. However, the aim of this study was to find the optimal combination of selected clinical and echocardiographic variables for predicting the presence of PH in dogs with MMVD, and the final model had an adjusted R^2 of 0.47, which, in our opinion, is acceptable for a clinical test. Lastly, the interdependence between RV and LV function was not addressed in this study.[50]

In conclusion, in dogs with MMVD, the presence of PH might be suspected if the combination of decreased pulmonary arterial AT/DT, increased RVIDDn and LA/Ao, and a small or great LVIDDn is present.

Footnotes

[a] iE33, Philips Ultrasound, Bothell, WA
[b] JMP, v. 11.0, SAS Institute Inc, Cary, NC

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

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

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