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

A. Tidholm, K. Höglund, J. Häggström, and I. Ljungvall

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.

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). 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). Pulmonary venous hypertension in dogs with CHF and MMVD is caused by increased left atrial (LA) and pulmonary venous pressures. 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.

Abbreviations:

| Acronym | Definition |
|---------|------------|
| 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. However, it has been suggested that the addition of estimated RA pressures might lead to the overestimation of PH severity. Noninvasive Doppler estimates of RVSP correlate well with invasively measured SPAP in people. In dogs, there is moderate correlation between invasive and noninvasive values of SPAP. The threshold to diagnose PH in dogs by Doppler-estimated RVSP has varied between 30 and 45 mmHg in different studies. The cutoff value for RVSP to diagnose clinically relevant PH has varied between 45 and 56 mmHg. A TRPG ≥55 mmHg is a negative predictor of survival in dogs with MMVD.

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 mid-systolic closure (“W wave”) in PA flow.

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. The maximum velocity of PA is often unchanged, although less flow, or even flow reversal in late systole, occurs with severe PH. Tricuspid annular plane systolic excursion (TAPSE) has been used to evaluate RV systolic performance in people and in dogs.

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 measurable 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 measurable flow velocity; (3) absence of other heart diseases; (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. 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 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. 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. 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. Left ventricular end-diastolic diameter (LVDD) was normalized for body weight at end-diastole (LVDDn) and at systole (LVDDSn) using the formulas: LVDDn[body weight (kg)]0.704 and LVDDSn[body weight (kg)]0.704, respectively. Right ventricular end-diastolic diameter (RVDD) and TAPSE were normalized for body weight (RVDDn and TAPSEn) using the formulas: RVDDn[body weight (kg)]0.733 and TAPSEn[body weight (kg)]0.733, respectively.

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

**Statistical Analysis**

A computer program was used for all statistical analyses. Data are presented as medians and interquartile ranges (IQR). The non-parametric Wilcoxon signed rank test was used for testing the equality of the medians between the groups dichotomized at TRPG of 36, 36, 36 or 55 mmHg, 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, RV FDD, 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 R² 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, 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 R² 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. 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 sildenailf, 4 dogs digoxin, and 1 dog diltiazem.

Assessment of the variability showed that all CV mean values were below 15%, except for RV FDDn 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, RV FDDn, 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 RV FDDn, 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 RV FDDn (R² = 0.11, P = .0001), HR (R² = 0.03, P = .01), LA/Ao (R² = 0.09, P = .0001) (Figs 1, 2). Quadratic regression described significant parabolic associations between TRPG and RV FDDn (adjusted R² = 0.28, P < .0001), PA AT/DT (adjusted

| 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) |
| RV FDDn | 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; RV FDDn, 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.

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-

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).
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.\textsuperscript{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
these proteins. In our study, the decreased LV chamber myosin and decreased degree of phosphorylation of myocytes with lower cellular content of the contractile protein myosin and decreased degree of phosphorylation of these proteins. 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. 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 than 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. Measurements of AT/DT might be affected by RV systolic function, severity of TR, respiration, and HR, which should be taken into consideration when interpreting results of these measurements.

Right ventricular hypertrophy and dilatation is commonly associated with PH. However, one study reported that only 33% of dogs with PH had RV enlargement, although most dogs in that study had only mild PH. 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 inducing LA dilatation is considered to be a common sequel to increasing LA pressures. The degree of PH in dogs with MMVD was correlated with MR severity and hypertension inducing LA dilatation in a previous study. 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 development of PH. As endothelial, 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 decreased. In the final 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, 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, i.e., 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. 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. The rationale behind the use of TAPSE as an indicator of PH 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. The TAPSE has been shown to decrease in dogs with severe PH, whereas dogs with mild to moderate PH were indistinguishable from normal dogs. 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. In our study, it is likely that TR velocities might have been underestimated in some dogs, as suggested by the comparatively 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 phosphodiesterase 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. 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.

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

### Acknowledgment

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

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

### References

1. Serres F, Chetboul V, Tissier R, et al. Doppler echocardiography-derived evidence of pulmonary arterial hypertension in dogs with degenerative mitral valve disease: 86 cases (2001–2005). J Vet Med Assoc 2006;229:1772–1778.
2. Borgarelli M, Crosara S, Lamb K, et al. Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous degeneration. J Vet Intern Med 2012;26:69–75.
3. Borgarelli M, Zini E, D’Agnold G, et al. Comparison of primary mitral valve disease in German Shepherd dogs and in small breeds. J Vet Cardiol 2004;6:27–34.
4. Kellihan HB, Stepen RL. Pulmonary hypertension in canine degenerative mitral valve disease. J Vet Cardiol 2012;14:149–164.
5. Stepen RL. Pulmonary arterial hypertension secondary to chronic left-sided cardiac dysfunction in dogs. J Small Anim Pract 2009;50:34–43.
6. Levine RA. Right ventricular inflow tract. In: Weyman AE, ed. Principles and Practice of Echocardiography. Philadelphia: Lea and Febiger; 1994:844–845.
7. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657–662.
8. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615–621.
9. Lanzarini L, Fontana A, Luca E, et al. Noninvasive estimation of both systolic and diastolic pulmonary artery pressure from Doppler analysis or tricuspid regurgitant velocity spectrum in patients with chronic heart failure. Am Heart J 2002;144:1087–1094.
10. Currie PJ, Seward JB, Chan KL, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985;6:750–756.
11. Soydan LC, Kellihan HB, Bates ML, et al. Accuracy of Doppler echocardiographic estimates of pulmonary artery pressures in a canine model of pulmonary hypertension. J Vet Cardiol 2015;17:13–24.
12. Johnson L, Boon JA, Orton EC. Clinical characteristics of 53 dogs with Doppler-derived evidence of pulmonary hypertension:1992–1996. J Vet Intern Med 1999;13:440–447.
13. Schober KE, Baade H. Doppler echocardiographic prediction of pulmonary hypertension in West Highland White Terriers with chronic pulmonary disease. J Vet Intern Med 2006;20:912–920.
14. Borgarelli M, Abbot J, Braz-Ruivo L, et al. Prevalence and prognostic significance of pulmonary hypertension in dogs with myxomatous mitral valve degeneration. J Vet Intern Med 2015;29:569–574.
15. Kosturakis D, Goldberg SJ, Allen HD, et al. Doppler echocardiographic prediction of pulmonary arterial hypertension in congenital heart disease. Am J Cardiol 1984;53:1110–1115.
16. Shivkumar K, Ravi K, Henry JW, et al. Right ventricular dilatation, right ventricular wall thickening, and Doppler evidence of pulmonary hypertension in patients with a pure restrictive ventilatory impairment. Chest 1994;106:1649–1653.

17. Burgess MI, Mogulkoc N, Bright-Thomas RJ, et al. Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. J Am Soc Echocardiogr 2002;15:633–639.

18. Serres F, Chetboul V, Gouni V, et al. Diagnostic value of echo-doppler and tissue doppler imaging in dogs with pulmonary hypertension. J Vet Intern Med 2007;21:1280–1289.

19. Pariaut R, Saelinger C, Strickland KN, et al. Tricuspid annular plane systolic excursion (TAPSE) in dogs: reference values and impact of pulmonary hypertension. J Vet Intern Med 2012;26:1148–1154.

20. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 2006;174:1034–1041.

21. Boon JA. Congenital heart disease. In: Boon JA, ed. Manual of Veterinary Echocardiography. Baltimore: Williams & Wilkins; 1998:383–445.

22. Boon JA. Acquired heart disease. In: Boon JA, ed, Manual of Veterinary Echocardiography. Baltimore: Williams and Wilkins; 1998:261–382.

23. Atkins CE, Bonagura JD, Ettinger SJ, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. J Vet Intern Med 2009;23:1142–1150.

24. Atkins CE, Hägström J. Pharmacological management of myxomatous mitral valve disease in dogs. J Vet Cardiol 2012;14:165–184.

25. Hanson K, Hägström J, Kvart C, et al. Left atrial to aortic root indices using two-dimensional and M-mode echocardiography in Cavalier King Charles spaniels with and without left atrial enlargement. Vet Radiol Ultrasound 2002;43:568–575.

26. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

27. Pinedo M, Villacorta E, Tapia C, et al. Inter-and intra-observer variability in the echocardiographic evaluation of right ventricular function. Rev Esp Cardiol 2010;63:801–809.

28. 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.

29. Boon JA. The M-mode and Doppler examination. In: Boon JA, ed. Veterinary Echocardiography, 2nd ed. Chichester: Wiley-Blackwell; 2011:129.

30. Petrie A, Watson P. Statistics for Veterinary and Animal Science. Oxford: Blackwell Science; 1999.

31. Bland M. Multifactorial methods. In: Bland M, ed. An Introduction to Medical Statistics, 2nd ed. Oxford: Oxford University Press; 1995:322–323.

32. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.

33. Lazar JM, Flores AR, Grandis DJ, et al. Effect of chronic right ventricular pressure overload on left ventricular diastolic function. Am J Cardiol 1993;72:1179–1182.

34. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 2002;39:1214–1219.

35. Brinker JA, Weiss JL, Lappe DL, et al. Leftward septal displacement during right ventricular loading in man. Circulation 1980;61:626–633.

36. Stool EW, Mullins CB, Leshin SJ, et al. Dimensional changes of the left ventricle during acute pulmonary arterial hypertension in dogs. Am J Cardiol 1974;33:868–875.

37. Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. Circulation 1997;96:517–525.

38. Perhonen MA, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. J Appl Physiol 2001;91:645–653.

39. Smith BM, Prince MR, Blüenke DA, et al. Impaired left ventricular filling in COPD and emphysema: is it the heart or the lungs? The multi-ethnic study of atherosclerosis COPD study. Chest 2013;144:1143–1151.

40. Meyer M. Left ventricular atrophy in pulmonary arterial hypertension. A sinister dexter conundrum. J Am Coll Cardiol 2014;64:38–40.

41. Guglielmini C, Civitella C, Diana A, et al. Serum cardiac troponin I concentration in dogs with precapillary and post-capillary pulmonary hypertension. J Vet Intern Med 2010;24:145–152.

42. Kellihan HB, MacKie BA, Stepieen RL. NT-proBNP, NT-proANP, and cTnI concentrations in dogs with precapillary pulmonary hypertension. J Vet Cardiol 2011;13:171–182.

43. Zeineh NS, Champion HC. Utility of tricuspid plane systolic excursion in the assessment of right ventricular function. PVRI Rev 2010;2:17–21.

44. Ghiyo S, Recusani F, Klersy C, et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol 2000;85:837–842.

45. Kjaergaard J, Petersen C, Kjaer A, et al. Evaluation of right ventricular volume and function by 2D and 3D echocardiography compared to MRI. Eur J Echocardiogr 2006;7:430–438.

46. Ruocco G, Cerkorja B, Rottoli P, et al. Role of BNP and echo measurement for pulmonary hypertension recognition in patients with interstitial lung disease: an algorithm application model. Respir Med 2015;109:406–415.

47. Schuuring MJ, van Riel AC, Vis JC, et al. New predictors of mortality in adults with congenital heart disease and pulmonary hypertension: midterm outcome of a prospective study. Int J Cardiol 2014;178:270–276.

48. Bano M, Kanaan UB, Ehrlich AC, et al. Improvement in tricuspid annular plane systolic excursion with pulmonary hypertension therapy in pediatric patients. Echocardiography 2015;32:1228–1232.

49. Hsiao SH, Lin SK, Wang WC, et al. Severe tricuspid regurgitation shows significant impact in the relationship among peak systolic tricuspid annular velocity, tricuspid annular plane systolic excursion, and right ventricular ejection fraction. J Am Soc Echocardiogr 2006;19:902–910.

50. Friedberg MK, Redington AN. Challenges and opportunities in pediatric heart failure and transplantation. Right versus left ventricular failure: differences, similarities, and interactions. Circulation 2014;129:1033–1044.