

Tricuspid Annular Plane Systolic Excursion (TAPSE) in Dogs: Reference Values and Impact of Pulmonary Hypertension

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Background: The impact of pulmonary hypertension (PH) on right ventricular systolic function is difficult to assess. Tricuspid annular plane systolic excursion (TAPSE) is an echocardiographic measurement of right ventricular systolic function and a strong predictor of outcome in human PH patients.

Hypothesis/Objectives: Determine a reference range for TAPSE in healthy dogs, and quantify TAPSE in dogs with PH. It is hypothesized that TAPSE is lower in dogs with PH compared with a reference group, and decreases as PH worsens.

Animals: Fifty normal dogs and 30 dogs with PH.

Methods: TAPSE was measured by 2-dimensional echocardiography-guided M-mode from the left apical 4-chamber view. Peak systolic tricuspid valve regurgitation jet velocity was measured by continuous-wave Doppler to estimate right ventricular-to-right atrial pressure gradient. PH was subjectively classified as mild, moderate, and severe.

Results: There was a curvilinear correlation between TAPSE and body weight. The upper and lower limits of the 95% reference interval were determined by quantile regression. Interobserver and intraobserver agreement was adequate with a coefficient of variation <10%. There were significant differences when comparing dogs with PH and the healthy group, as well as between the PH subgroups ($P < .01$), except between dogs with mild and moderate PH ($P = .99$). Only dogs in the severe PH group had TAPSE values that were mostly below the lower limit of the reference interval.

Conclusions and Clinical Importance: TAPSE is easily obtainable with acceptable inter and intraobserver agreement. TAPSE is decreased in PH and below the reference interval in most dogs with severe PH.

Key words: Canine; Echocardiography; Hemodynamics; Monitoring.

In dogs, pulmonary hypertension (PH) is associated with various conditions, such as idiopathic pulmonary arterial hypertension, pulmonary diseases, heart-worm disease, thromboembolic disease, and cardiac disease.^{1–10} Whether it is precapillary (pulmonary arterial hypertension) or postcapillary (pulmonary venous hypertension), PH may impair right ventricular performance as it progresses in severity.^{11,12}

Echocardiography is currently the best noninvasive tool to evaluate cardiac structure and function in the veterinary clinical setting. Although methods are well established for the left cardiac chambers, assessing the function of the right ventricle (RV) is technically challenging because of its complex geometry and contractile properties. The RV is triangular in shape and its cavity is divided into inflow and outflow tracts that cannot be imaged simultaneously. Moreover, experimental studies in dogs demonstrated that longitudinal displacement of the base of the ventricle towards the apex is the major contributor to RV contraction.¹³ Therefore, echocardiographic measurements and algorithms that are extensively used to quantify left ventricular performance in clinical practice cannot be applied to the RV.^{14,15}

Tricuspid annular plane systolic excursion (TAPSE) is an echocardiographic parameter that has been

Abbreviations:

PG	pressure gradient
PH	pulmonary hypertension
RA	right atrium
RV	right ventricle
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging

developed in people to evaluate right ventricular systolic function.^{15,16} It measures the apical displacement of the lateral portion of the tricuspid valve annulus during systole from an M-mode recording.¹⁶ In human adults, TAPSE has been validated against invasive methods as a marker of RV systolic function, with normal values reported between 1.5 and 2 cm, and it has prognostic value regardless of heart rhythm or rate.^{15–21} In patients with PH, TAPSE values below the reference range identify those with decreased right ventricular systolic function and an associated higher mortality risk.²²

The use of TAPSE has not been evaluated in normal dogs or dogs with PH, and a reference range has not been established. Because few methods designed to assess right ventricular performance are applicable to clinical practice, evidence of right ventricular systolic dysfunction typically is inferred from the presence of right-sided congestive heart failure (eg, ascites). Thus, an important application of TAPSE measurement would be the early identification of right-sided cardiac systolic dysfunction in the presence of PH.

The 1st aim of the present study was to generate empirically derived reference limits for TAPSE from a sample population of healthy dogs and determine the intra and interobserver variability of this echocardiographic parameter. Our 2nd objective was to evaluate

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the effects of PH on TAPSE, based on the hypothesis that right ventricular systolic function and TAPSE values decrease as the severity of PH progresses.

Materials and Methods

This study was conducted at the Louisiana State University Veterinary Teaching Hospital over a 15-month period, between February 2010 and May 2011.

Animals

A total of 50 adult dogs deemed free of cardiac or respiratory disease based upon physical examination, thoracic radiography, and standard 2-dimensional/Doppler echocardiogram formed the reference group. The PH group included consecutive dogs diagnosed with echocardiographic evidence of PH. Presence of right ventricular outflow tract obstruction was ruled out by 2-dimensional/Doppler echocardiography. Peak systolic tricuspid valve regurgitation velocity was measured by continuous-wave Doppler from the view that allowed the best alignment with the direction of the jet. Right ventricular-to-right atrial (RA) pressure gradient (PG) was estimated from peak tricuspid regurgitation jet velocity using the simplified Bernoulli equation. Evidence of PH was based on tricuspid valve regurgitation with a velocity >3 m/s (estimated PG above 36 mmHg). Dogs were divided into 3 subgroups: A mild PH group (3–3.5 m/s; estimated PG = 36–50 mmHg), a moderate PH group (3.5–4.3 m/s; estimated PG = 50–75 mmHg), and a severe PH group (>4.3 m/s; estimated PG >75 mmHg).²³ Presence of ascites indicated right-sided congestive heart failure.

Acquisition of TAPSE Measurement

TAPSE was measured from an M-mode recording^a of the lateral aspect of the tricuspid valve annulus seen from an “off-axis” left parasternal apical 4-chamber view that was centered on the RV. To limit the risk of underestimating the measurement, the M-mode cursor was carefully aligned parallel to the longitudinal displacement of the tricuspid valve plane with the right ventricular free wall. TAPSE was measured with electronic calipers between the most basilar position of the tricuspid annulus at end-diastole and its most apical displacement at end-systole using the leading edge method (Fig 1). TAPSE values were averaged from measurements on 3 consecutive beats during sinus rhythm.

Observer Agreement

M-mode recordings from 10 randomly selected^b dogs from the healthy or PH groups were used to determine intra and interobserver variability. Three different observers (C.S., J.V., R.P.) with experience in canine echocardiography repeated measurements on 3 nonconsecutive days.

Statistical Analysis

Simple linear regression analysis was used to consecutively measure the association of TAPSE (dependent variable) with body weight scaled to the $1/3$ power ($\text{weight}^{1/3}$) and the aortic diameter (predictors).²⁴ Assumptions of linearity, normality, homoscedasticity, and independence of the residuals were evaluated with residual plots and quantile plots. The presence of outliers and influential values were assessed with standardized residuals plots and Cook's distance statistics. For reference intervals determination in healthy dogs, the 95% central tendency

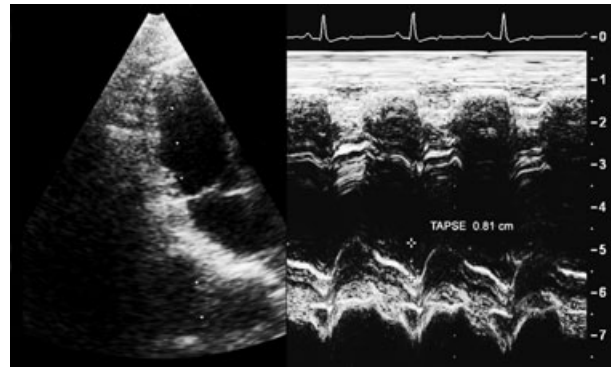


Fig 1. Left apical 4-chamber echocardiographic view with the M-cursor aligned with the lateral segment of the tricuspid annulus (left panel) and M-mode recording of tricuspid annular plane systolic excursion (right panel).

was computed with the 95% confidence intervals of the limits. However, to account for differences that can be expected with the large variation in weight of the dogs, weight-dependent regression-based reference limits were determined using a quantile regression approach. The 95% reference interval was determined by fitting the 2.5% and 97.5% quantiles using polynomial models with body weight as the predictor variable. The simplest polynomial with all significant parameters was chosen as the final model. Model fit was assessed by checking residuals of the quantile regression model for the median (percentile 0.5). Reference interval plots were performed using predicted values along with their confidence bands calculated from the quantile regression models. Differences between disease groups and the normal group controlling for body weight was assessed using analysis of covariance (ANCOVA). Normality and homoscedasticity were checked with Shapiro–Wilk on residuals and residual plots. Posthoc comparisons were performed using Tukey adjustments. In addition, to assess the usefulness of the reference intervals previously determined, the different TAPSE values for the disease groups were plotted along with the regression-based reference lines. Specificity and sensitivity of the reference intervals subsequently were reported.

Intraobserver and interobserver agreement were assessed by a 2-way intraclass correlation coefficient for absolute agreement. Agreement was considered high when the coefficient value was ≥ 0.76 , medium between 0.40 and 0.75, and low when ≤ 0.39 .²⁵ Intraobserver and interobserver variability also were assessed using the average coefficient of variation.

Results are displayed as median and range or mean and standard deviation as appropriate. All statistics were performed using R^b, the R-package “quantreg” for quantile regression and “irr” for agreement.^c An alpha of 0.05 was used for significance.

Results

Animals

The 50 dogs that comprised the reference group had a mean body weight of 16 ± 10.5 kg. Thirty dogs with PH were evaluated during the study period. Based on the measure of peak tricuspid valve regurgitation jet velocity, 13 dogs were included in the mild PH group (range 3–3.5 m/s), 6 in the moderate PH group (range 3.9–4.2 m/s), and 11 in the severe PH group (range 4.7–6.9 m/s). Mean body weight was 14 ± 11 kg in the

mild PH group, 13 ± 9.5 kg in the moderate PH group, and 14 ± 11.5 kg in the severe PH group. Compared with the reference group, echocardiographic changes to the right heart were reported in some dogs with PH, including right ventricular chamber dilatation (mild in 4/30, moderate in 6/30, severe in 6/30), right atrial dilatation (mild 3/30, moderate 3/30, severe 5/30), free wall hypertrophy (13/30), papillary muscle hypertrophy (13/30), and septal flattening (8/30). Eighteen dogs in the PH groups had evidence of left-sided cardiac disease, including atrio-ventricular valve endocardiosis in 17 dogs and dilated cardiomyopathy in 1 dog. Nine dogs were diagnosed with heartworm disease. Four dogs had radiographic and clinical evidence of pulmonary lesions in the absence of left heart disease, including pneumonia (1), suspected pulmonary thromboembolism (1) and suspected pulmonary fibrosis (2). Eight of 11 dogs in the severe PH group also had right-sided congestive heart failure. All dogs were in sinus rhythm at the time of the examination.

TAPSE Values in Healthy Dogs

Tricuspid annulus systolic excursion could be measured in all dogs. There was a curvilinear correlation between TAPSE and weight. However, when weight was scaled to the 1/3 power, a strong linear association with TAPSE became apparent (slope, 0.52; 95% CI, 0.45–0.59; t_{48} , 15.4; $P < .001$; $Y = 0.17 + 0.52X$; r^2 , 0.83). There was also a strong linear association between TAPSE and aortic diameter (slope, 0.62; 95% CI, 0.56–0.69; t_{48} , 18.5; $P < .001$; $Y = 0.30 + 0.62X$; r^2 , 0.82). Because body weight and aorta were strongly collinear with a Pearson correlation coefficient of 0.96 ($P < .001$), the reference range was established according to weight, which avoided the variability associated with aorta diameter measurement. To define the lower and upper limits of the 95% reference interval, quantile regression was performed for the 2.5th and 97.5th percentiles (Table 1 and Fig 2). The confidence bands of the limits also were calculated. Higher order polynomial terms were not significant and did not significantly improve the fit of the models. Model fit was judged to be adequate.

Intra and Interobserver Variability

Interobserver and intraobserver agreements were found to be adequate (Table 2) suggesting that TAPSE

is a reliable measurement. Likewise, the average coefficient of variation was $<10\%$ for both intra- and interobserver measurements.

Effect of PH on TAPSE Value

There was a significant difference in TAPSE values between the healthy group and the PH groups after controlling for weight ($P < .05$). Posthoc multiple comparison procedures identified significant differences between all groups and subgroups (all $P < .01$), except between the mild and moderate PH groups ($P = .99$). Indeed, TAPSE values were lower in the mild and moderate PH groups than in the normal group ($P < .01$) but stayed within the confidence bands (Fig 3a,b). Conversely, TAPSE values in the severe group were below the 2.5th centile (ie, outside of the reference range established with 50 healthy dogs [Fig 3c]). When considering only the reference limits, the sensitivity of the reference interval was 100% for severe PH. When taking the confidence bands into account, the sensitivity was 67% for severe PH. For the normal dogs, the specificity of the reference interval was 100% but the reference intervals were not validated on a new set of normal dogs. Detailed examination of the plots indicated that the 1 dog with the lowest TAPSE value had the highest tricuspid valve regurgitation velocity (6.9 m/s) in association with right-sided congestive heart failure and severe cardiac chamber enlargement. Interestingly, the 1 dog with mild PH that had right-sided congestive heart failure had the lowest TAPSE value of that group of animals, which also fell between the lower reference limit and the confidence band. This dog had severe tricuspid valve regurgitation, which was attributed to chronic atrioventricular valve disease (Fig 3a).

Discussion

This study showed that TAPSE measurement is easily obtainable with a standard echocardiography system, and has adequate intra- and interobserver agreement. When applied to dogs with PH, a disease that can alter right ventricular function, TAPSE values were significantly decreased compared with the reference range established from a sample of healthy dogs. Moreover, TAPSE was typically below the lower limit of this interval in dogs included in the severe PH group.

Alteration in right ventricular function has been identified as an independent negative prognostic indicator in numerous studies evaluating the outcome of human patients with heart failure secondary to dilated or ischemic cardiomyopathy.²⁶ Conversely, little information is available on dogs because the assessment of RV systolic function has been challenging. Among the noninvasive methods that have been validated in dogs, gated radionuclide ventriculography has been shown to accurately assess RV ejection fraction and RV filling and emptying rates when compared with cardiac magnetic resonance imaging, but this technique is

Table 1. Estimated regression coefficients for models of 2.5% and 97.5% quantiles.

	Variable	Coefficient (β)	95% CI
Lower limit (2.5 percentile)	Intercept	-0.12	-0.18 to 0.36
	Weight ^{1/3}	0.51	0.16 to 0.63
Upper limit (97.5 percentile)	Intercept	0.19	0.05 to 0.42
	Weight ^{1/3}	0.60	0.37 to 1.06

CI, confidence interval.

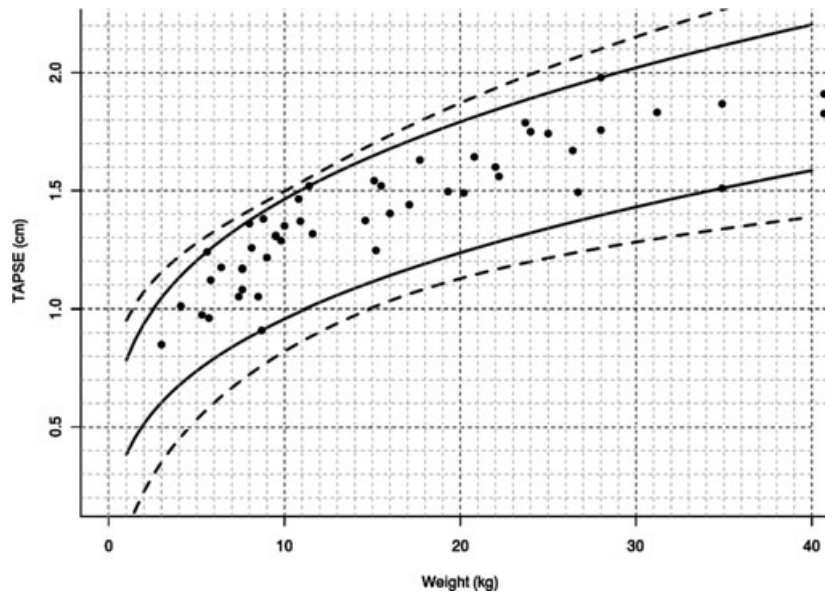


Fig 2. Regression-based reference intervals; scatter plot with 2.5th and 97.5th centiles (solid lines) of tricuspid annular plane systolic excursion (TAPSE) (cm) from the healthy group of dogs against weight (kg). The dashed lines delineate the confidence bands. This graph is available as a supplemental online document to compare measured TAPSE values to the reference range established in this study.

Table 2. Intra- and interobserver agreement analysis.

	ICC	95% CI	<i>P</i>	CV (%)
Intraobserver	0.95	0.91–0.98	<.001	5.3
Interobserver	0.91	0.83–0.95	<.001	7.9

CI, confidence interval; CV, coefficient of variation; ICC, intra-class correlation coefficient; *P*, for null hypothesis that ICC = 0.

expensive and its availability limited.²⁷ As for echocardiography, the challenges for RV performance assessment are linked to the inherently complex RV geometry, a heavily trabeculated inner surface with poor endocardial definition, anatomically separate inflow and outflow which can only be seen from separate views, and the load dependency, in combination with the lower accuracy of most conventional echocardiographic parameters in comparison with invasive measures.²⁸ Tissue Doppler imaging (TDI)-derived right ventricular myocardial motion has been shown to be a satisfactory method to assess the systolic function of the basal segments of the RV, but these measurements are more difficult to obtain than TAPSE, and the technology is only available on a limited number of ultrasound systems.^{29,30} Right ventricular Tei index, an index of myocardial performance, has been evaluated in healthy dogs and in dogs with right heart disease, but the need for 2 different echocardiographic views and therefore 2 different cardiac cycles increases the variability of the measurement.^{31,32} In addition, the use of Tei index is limited by the absence of the isovolumic periods in the normal RV as well as the pseudonormalization of the index when RA pressure is

increased. Indeed, increased RA pressure determines a shortening of the isovolumic relaxation time, which will result in a decreased value of the Tei index.³³

Conversely, TAPSE is easily obtainable. In the present study, there was adequate agreement among observers (Table 2). This finding is comparable to the results of human studies, in which TAPSE was highly repeatable and reproducible.^{16,34,35} In human adults, most studies report that a TAPSE value >1.5 cm is suggestive of normal right ventricular systolic function.^{15,16,36} This use of a single threshold value of TAPSE to distinguish between normal and decreased right ventricular function is in contrast with current recommendations that favor the use of standard deviation or percentile-derived reference ranges.³⁷ In addition, TAPSE is a linear measurement, the value of which increases with body dimensions.³⁵ Therefore, the use of a single reference range applicable to all dogs is not possible. In this study, the use of quantile regression to determine the limits of the reference range allowed modeling the relation of specific percentiles (2.5th and 97.5th percentiles) of the response variable TAPSE with body weight, rather than simply estimating the variations of the mean TAPSE value. This method takes into account that some percentiles of TAPSE may be more affected by changes in body weight than other percentiles. Therefore, it defines with more precision the lower and upper limits of the reference interval and also is more robust against outliers, in particular considering the small size of the reference group.³⁸

TAPSE measures the displacement of the valve annulus from its end-diastolic position toward the cardiac apex in systole. Similar to longitudinal right

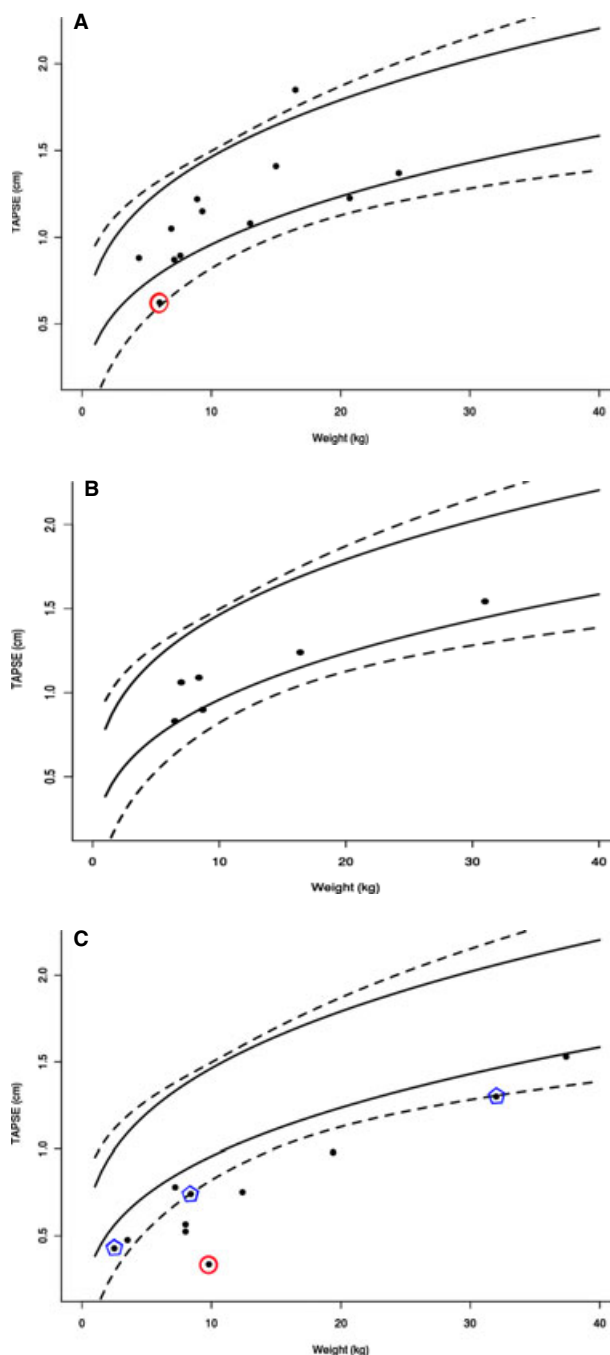


Fig 3. Scatter plots with 2.5th and 97.5th centiles (solid lines) of tricuspid annular plane systolic excursion (TAPSE) (cm) from the dogs included in the mild (a), moderate (b), and severe (c) pulmonary hypertension (PH) groups against weight (kg). The dashed lines delineate the confidence bands. (a) The only animal in the group of dogs with mild PH that presented with congestive heart failure had the lowest TAPSE value (indicated by circle). (c) Only 3 animals in the group of dogs with severe PH were free of signs of congestive heart failure (indicated by pentagon). The dog with the highest tricuspid valve regurgitation velocity (6.9 m/s) had the lowest TAPSE value (indicated by circle).

ventricular myocardial velocities measured by TDI in dogs and people, the amplitude of tricuspid annulus motion along the long axis of the heart has been

shown to be an acceptable index of systolic function.^{30,39,40} It can indeed be correlated with the orientation of the deep muscle layer of the RV wall that is predominantly parallel to the longitudinal axis of the heart.¹⁴ More importantly, TAPSE, as a marker of systolic function, has been identified as a relevant tool in the prognostic stratification of human patients with left and right heart failure.^{17,20,22,26}

Compared with the left ventricle, the adaptation of the RV to increased afterload, as seen with PH, is poor.¹⁴ In the event of an abrupt increase in pulmonary vascular resistance, a linear decrease in stroke volume is observed as pulmonary pressure increases.¹⁴ Right ventricular hypertrophy only occurs with a more progressive increase in afterload, but usually is rapidly followed by a dilatation of the ventricle and ultimately failure.⁴¹ In people with adult-onset PH, TAPSE was a highly sensitive and specific indicator of decreased right ventricular function, as measured by the stroke volume index.²² In the same study, lower TAPSE values were associated with higher pulmonary vascular resistance, increased right atrial size and smaller dimensions of the left cardiac chambers. Moreover, nonsurvivors had the lowest TAPSE values.²² These results support the hypothesis of the current study that the decrease in TAPSE values as PH severity increases, and more importantly when signs of right-sided congestive heart failure are present is a marker of decreased RV systolic function. Based on the dogs evaluated in this study, it is noteworthy that only animals included in the severe PH group had TAPSE values below the reference limits, whereas, based on TAPSE only, the mild and moderate PH groups were indistinguishable from the healthy group. TAPSE values below the lower limit of the reference range in the severe PH group suggest a decrease in right ventricular systolic performance. However, systolic function was not directly measured because of the invasiveness, cost, and lack of availability of these techniques. Therefore, it cannot be ascertained that right ventricular systolic dysfunction was the only contributor to low TAPSE values in animals with high peak tricuspid regurgitation jet velocity. Indeed, there are examples of normal RV systolic function in the presence of severe PH, such as occurs in some human patients with Eisenmenger's physiology. However, this situation does not seem to be the case when PH is acquired.⁴¹

A 2nd limitation of this study is that peak systolic tricuspid regurgitation jet velocity measured by Doppler echocardiography was used to estimate RV-to-RA PG using the simplified Bernoulli equation and subsequently define 3 PH groups. Although echocardiography is recognized as a reliable method to estimate pulmonary artery pressure, cardiac catheterization is preferable but rarely used in veterinary clinical practice.^{42,43} Underestimation of Doppler-derived RV-to-RA PG may result from a weak tricuspid jet signal or an excessive angle between the ultrasound beam and the direction of the flow. In addition, the simplified Bernoulli equation does not take into account the inertial component that is included in the

complete equation. Estimated RA pressure was not used in this study to predict systolic pulmonary pressure, because methods to approximate RA pressures from echocardiographic data have not been validated in dogs.²³

A 3rd limitation is the heterogeneity of the population studied. Most dogs with PH had atrioventricular valve endocardiosis or heartworm disease, but other diseases represented included dilated cardiomyopathy in 1 dog and respiratory disease. The variety of diseases and their chronicity might have impacted the systolic function of the right heart differently. For example, whereas atrioventricular valve endocardiosis and dilated cardiomyopathy are mostly considered left-sided heart diseases, some animals could have had a reduction in right ventricular myocardial contractility. Moreover, because of the physiologic mechanism of ventricular interdependence, TAPSE values may be further decreased when left and right ventricular dysfunction is present concomitantly.¹⁹ In people, TAPSE values may be decreased in the setting of isolated left ventricular systolic dysfunction.³⁶ Therefore, additional studies are needed in dogs to determine the exact contribution of left heart and right heart systolic dysfunction to TAPSE.

The importance of M-mode cursor alignment with the longitudinal motion of the tricuspid valve annulus also should be emphasized when TAPSE is measured. Excessive angulation of the cursor with respect to the displacement of the ventricular base may result in substantial underestimation of TAPSE.²⁸

Finally, the reference interval for TAPSE was established from a small population of healthy dogs. However, this number is comparable to most studies of dogs previously designed to establish normal echocardiographic dimensional data, which typically included an average of 30 dogs.⁴⁴ In addition, the reference range obtained from this group of healthy dogs may not be suitable for accurate quantification of TAPSE in animals with a body weight <3 kg and >42 kg because dogs within these ranges of weight were not included in the reference group. Extrapolation of the lines to quantify TAPSE in smaller and larger dogs may be possible, but is hypothetical. Lastly, it cannot be ruled out that some dogs in the reference group had mild PH if measurable tricuspid regurgitation was absent.

In conclusion, this study provides information on the normal values of TAPSE in dogs for quantification in addition to qualitative evaluation of right ventricular systolic dysfunction in clinical practice (a supplemental online TAPSE reference range chart is provided to plot individual TAPSE measurements). It also describes the effects of PH, as estimated by peak systolic tricuspid regurgitation velocity, on TAPSE values. Additional studies should be performed to confirm the use of TAPSE as a marker of right ventricular systolic function, to test this parameter against already established methods, and to determine its role as a prognostic indicator in dogs with PH and right-sided heart disease.

Footnotes

^a Philips IE33, Philips Healthcare, Andover, Mass

^b R, Version 2.12.1, The R Foundation for Statistical Computing, Vienna, Austria

^c The Comprehensive R Archive Network, <http://cran.r-project.org/>

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Regression-based reference interval for clinical use: to use this reference range, find the weight (kg) of the dog on the horizontal axis and draw a vertical line up from that point. Find the appropriate TAPSE (cm) measurement on the vertical axis. Draw a horizontal line across from that point until it intersects the vertical line. Make a small dot where the 2 lines intersect.

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