

Standard Article

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Echocardiographic Evaluation of the Right Atrial Area Index in Dogs with Pulmonary Hypertension

T. Vezzosi , O. Domenech, M. Iacona, F. Marchesotti, E. Zini , L. Venco, and R. Tognetti

Background: Right atrial area (RAA) is a prognostic factor in human patients with pulmonary arterial hypertension (PAH). Reference intervals for RAA have been described in healthy dogs.

Objectives: To evaluate RAA indexed to the body surface area in dogs with PAH as an indicator of right atrial size, PAH severity and right-sided congestive heart failure (R-CHF).

Animals: A total of 119 client-owned dogs, 48 dogs with PAH and 71 control dogs.

Methods: Prospective observational study. Pulmonary arterial hypertension was classified according to the tricuspid regurgitation pressure gradient (TRPG) as mild (36–50 mmHg), moderate (51–75 mmHg), or severe (>75 mmHg). The RAA index was calculated as the RAA divided by body surface area.

Results: The RAA index was higher in dogs with moderate PAH (13.3 cm²/m²; range, 3.4–24.7 cm²/m²) and severe PAH (12.1 cm²/m²; range, 5.4–21.8 cm²/m²) than in those with mild PAH (6.7 cm²/m²; range, 4.8–10.7 cm²/m²) or in controls (7.3 cm²/m²; range, 4.2–10.2 cm²/m²; $P < 0.001$). The RAA index was higher ($P < 0.0001$) in dogs with R-CHF (17.5 cm²/m²; range, 12.7–24.7 cm²/m²) compared to those without R-CHF (7.6 cm²/m²; range, 4.4–19.4 cm²/m²). The most accurate cutoff value of the RAA index to identify R-CHF was >12.3 cm²/m² (sensitivity, 100%; specificity, 89.5%). In dogs with PAH, severity of tricuspid regurgitation (TR) was the only independent predictor of RAA index based on multivariate analysis ($P < 0.02$).

Conclusions and Clinical Importance: The RAA index can be used to evaluate right atrial size in dogs and may be more effective than TRPG in predicting R-CHF in dogs with PAH. The severity of TR is the main determinant of the RAA index in dogs with PAH.

Key words: canine; congestive heart failure; right atrial enlargement; right atrial size; tricuspid regurgitation.

Pulmonary arterial hypertension (PAH) is a pathologic condition characterized by abnormally high pressure in the pulmonary arterial circulation. In dogs, PAH occurs as a primary or secondary condition, associated with cardiac, pulmonary, parasitic, thromboembolic, and neoplastic diseases.¹ Right heart catheterization is the gold standard technique for PAH diagnosis, but it is invasive. However, echocardiography

Abbreviations:

BSA	body surface area
PAH	pulmonary arterial hypertension
RAA	right atrial area
RA	right atrium
R-CHF	right-sided congestive heart failure
TRPG	tricuspid regurgitation pressure gradient
TR	tricuspid regurgitation

From the Department of Veterinary Sciences, University of Pisa, Pisa, Italy (Vezzosi, Iacona, Tognetti); Istituto Veterinario di Novara, Novara, Italy (Domenech, Marchesotti, Zini); Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland (Zini); Department of Animal Medicine, Production and Health, University of Padova, Padova, Italy (Zini); Clinica Veterinaria Lago Maggiore, Novara, Italy (Venco).

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Corresponding author: T. Vezzosi, Department of Veterinary Sciences, University of Pisa, via Livornese lato monte, 56122 San Piero a Grado, Pisa, Italy; e-mail: tommaso.vezzosi@vet.unipi.it

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is the most commonly used screening test for PAH both in humans and dogs because it is noninvasive.^{1,2}

Chronic PAH causes various adaptive changes in right heart geometry that can result in progressive right ventricular hypertrophy and dilatation, dysfunction, right atrial (RA) enlargement, and right-sided congestive heart failure (R-CHF).^{3–5} In human medicine, RA enlargement has been identified as a predictor of poor outcome in patients with PAH^{6–10} and is commonly evaluated by echocardiographic assessment of the RA diameter and area.^{11,12} It also has been shown in humans that right atrial area (RAA) better represents right ventricular diastolic dysfunction than does RA diameter.^{11–13} Thus, in light of the different body weights of human patients, RAA indexed to the body surface area (BSA) has also been proposed.^{9,14–16}

In veterinary medicine, RA enlargement generally is evaluated subjectively.^{17,18} One study has provided reference values for RA size in healthy dogs, according to allometric scales.¹⁹ In light of the limited information on the echocardiographic assessment of the right heart during PAH, we evaluated the RAA index in dogs with PAH as an indicator of RA size, PAH severity, and R-CHF.

Materials and Methods

Animals

Privately owned dogs that had undergone complete cardiac examination as part of a clinical evaluation or for pre-anesthetic assessment were included, with owners giving their signed consent. The investigation lasted 1 year. Permission for this prospective cross sectional study was granted by the Institutional Welfare and Ethics Committee of the University of Pisa (authorization number: 38/15). Ours was a prospective, multicenter, cross sectional study including dogs with PAH and healthy control dogs. Dogs were considered healthy based on the absence of clinical signs according to history, physical examination, cardiovascular assessment, and transthoracic echocardiogram.

Pulmonary arterial hypertension was identified if a tricuspid regurgitation pressure gradient (TRPG) ≥ 36 mmHg based on echo-Doppler assessment was observed.^{20–22} The TRPG was derived from the peak systolic tricuspid regurgitation jet velocity using the simplified Bernoulli equation (pressure gradient = 4 multiply by velocity²). Peak systolic tricuspid regurgitation jet velocity obtained by 2-dimensional (2D)/color Doppler-guided continuous wave Doppler was measured with the echocardiographic view that provided the clearest jet profile and best alignment with the jet.

Dogs with PAH were divided into 3 groups based on the TRPG: mild PAH if TRPG was 36–50 mmHg, moderate PAH if TRPG was 51–75 mmHg, and severe PAH if TRPG was >75 mmHg. Right-sided congestive heart failure (R-CHF) was diagnosed if the presence of ascites was associated with jugular venous distension, hepatomegaly, and a subjectively dilated caudal vena cava. Dogs were not included in the study if they had congenital heart disease, atrial fibrillation, or belonged to breeds typically prone to arrhythmogenic right ventricular cardiomyopathy (e.g boxers and bulldogs). In addition, all dogs receiving sildenafil or pimobendan were excluded from the study, because of the potential influence of these drugs on TRPG.

Echocardiography

All examinations were performed by 3 experienced operators (TV, LV, and OD). Unsedated dogs were restrained in right and

left lateral recumbency on an echocardiographic scanning table. Each dog underwent a complete echocardiographic examination, which included transthoracic 2D, M-mode, and Doppler imaging.²³ Tricuspid regurgitation (TR) severity was evaluated qualitatively, using color Doppler and continuous wave Doppler.²⁴ Briefly, mild TR was considered when a small, central TR jet on the color Doppler and a faint parabolic TR jet signal were present on the continuous wave Doppler. Moderate TR was considered when an intermediate TR jet on the color Doppler and a dense parabolic TR jet signal on the continuous wave Doppler were present. Severe TR was considered when there was a very large central jet or an eccentric jet impinging on the wall on the color Doppler and a dense triangular with early peaking TR jet signal was seen on the continuous wave Doppler.

Echocardiographic examination of the RA was performed from the left apical 4-chamber view optimized for the right heart. The RAA was measured by planimetry at the end of the ventricular systole tracing from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus, following the RA endocardium, and excluding the caudal vena cava, cranial vena cava, and RA appendage (Fig 1).¹¹ The RAA index was calculated as RAA divided by body surface area (BSA). The BSA was calculated as: $0.101 \times \text{body weight (kg)}^{2/3}$, as previously described.²⁵ All measurements were performed offline by the same operator (TV) evaluating 3–5 cardiac cycles, and mean values were calculated.

Statistical analysis

Statistical analysis was performed using commercially available statistical software.^{a,b}

Descriptive statistics were generated. The normality of data distribution was tested by the Shapiro-Wilk test, and parametric or nonparametric tests were used according to the Gaussian distribution. Data are reported as median and range (minimum–maximum), unless otherwise stated.

In the control group, linear regression was used to evaluate relationships between echocardiographic variables and BSA. Pearson chi-squared or Fisher's exact tests were used to compare categorical variables. Continuous variables were compared by an unpaired *t*-test or Mann–Whitney *U*-test, based on data

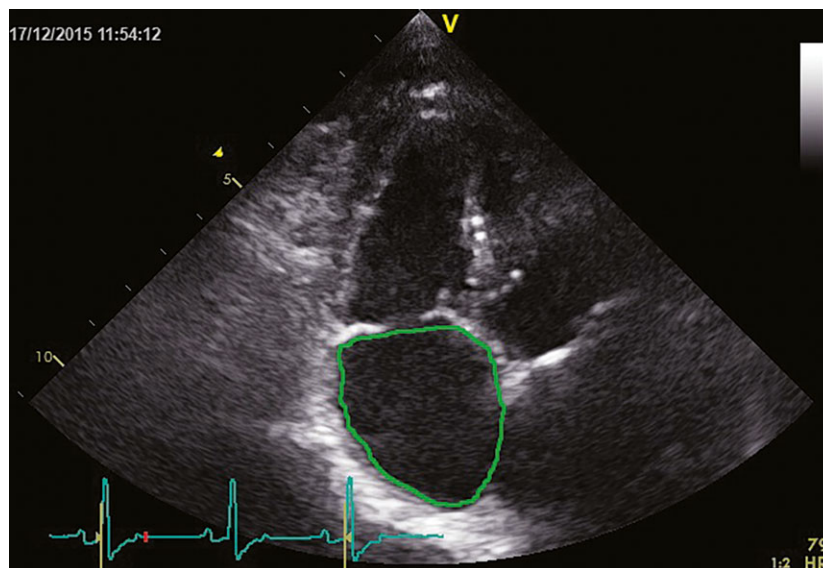


Fig 1. Left apical 4-chamber view optimized for the right heart. The right atrial area (RAA) was measured by planimetry at the end of ventricular systole.

distribution. Differences in echocardiographic continuous data among PAH groups were determined by 1-way analysis of variance with subsequent pairwise comparisons by Tukey's multiple comparisons test (for normally distributed data) or by the Kruskal–Wallis test with subsequent pairwise comparisons by the Dunn test (for non-normally distributed data). Receiver operating characteristic curve analysis was used to identify the optimal diagnostic RAA index cutoff to identify R-CHF, and the optimal combination of sensitivity and specificity (Youden Index $J = [\text{Sensitivity} + \text{Specificity}] - 100$) was determined.

In dogs with PAH, simple (univariate) linear regression analyses were performed to determine the strength of association of selected clinical (age, sex, and heart rate) and echocardiographic variables (TRPG and TR severity) with the RAA index. Multiple linear regression analysis was used to identify significant independent predictors of the RAA index. The variables were entered into a multiple linear regression model in a backward stepwise manner if P was <0.2 based on univariate linear regression analysis. For all linear regression models, assumptions of linearity, homoscedasticity, normality of residuals, and little or no multicollinearity (for multiple linear regression) were met.

Finally, to verify the suitability of the RAA index in a clinical setting, intra- and interobserver measurement variability were determined with the coefficient of variation (CV). For intra-observer variability, 1 operator (TV) calculated the RAA index from 6 randomly selected echocardiographic studies on 2 different occasions separated by 30 days. The interobserver variability was carried out by 2 operators (TV and OD) measuring the RAA index from 6 randomly selected blinded echocardiographic studies.

A value of $P < 0.05$ was considered statistically significant.

Results

The study sample consisted of 119 dogs, including of 71 control dogs and 48 dogs with PAH. Table 1 summarizes the clinical and echocardiographic data for all dogs. In 48 dogs with PAH, the causes were heartworm disease ($n = 19$), myxomatous mitral valve disease ($n = 10$), chronic pulmonary disease ($n = 10$), angiostrongylosis ($n = 6$), and heart base tumors ($n = 3$). Dogs with PAH were significantly older than controls (median, 11 years; range, 0.8–18 years vs. median, 3 years; range, 1–14; $P < 0.0001$) and had lower body weight (median, 28 kg; range, 2.1–46 kg vs. median, 12.6 kg; range, 3.4–38 kg; $P < 0.0001$). Regarding sex, no differences were found between dogs with PAH and controls (male and female: 31 and 40 vs. 28 and 20;

$P = 0.1372$). In the PAH group, based on TRPG, 15 dogs had mild PAH (median, 40 mmHg; range, 36–49 mmHg), 10 had moderate PAH (median, 61 mmHg; range, 52–74 mmHg), and 23 had severe PAH (median, 103 mmHg; range, 77–149 mmHg). Ten of 48 (20.8%) dogs with PAH had R-CHF.

In healthy dogs, the RAA showed a strong positive correlation with BSA ($r = 0.90$; $P < 0.0001$; Fig 2). In dogs with PAH, no differences in RAA index were found between dogs with mild PAH and controls ($6.7 \text{ cm}^2/\text{m}^2$; range, 4.8–10.7 cm^2/m^2 vs. $7.3 \text{ cm}^2/\text{m}^2$; range, 4.2–10.2 cm^2/m^2 ; $P = 0.284$). Conversely, the RAA index was significantly higher in dogs with moderate ($13.3 \text{ cm}^2/\text{m}^2$; range, 3.4–24.7 cm^2/m^2) and severe PAH ($12.1 \text{ cm}^2/\text{m}^2$; range, 5.4–21.8 cm^2/m^2) in comparison with dogs with mild PAH and the control group ($P < 0.001$; Fig 3).

The RAA index was significantly higher ($P < 0.0001$) in dogs with R-CHF (median, $17.5 \text{ cm}^2/\text{m}^2$; range, 12.7–24.7 cm^2/m^2) in comparison with dogs without R-CHF (median, $7.6 \text{ cm}^2/\text{m}^2$; range, 4.4–19.4 cm^2/m^2 ; Fig 4). On the other hand, no difference in TRPG was found between dogs with R-CHF (86 mmHg; range, 52–135 mmHg) and without R-CHF (62 mmHg; range, 39–149 mmHg). The most accurate cut off value of the RAA index to identify R-CHF was $>12.3 \text{ cm}^2/\text{m}^2$ (sensitivity, 100%; specificity, 89.5%; Table 2).

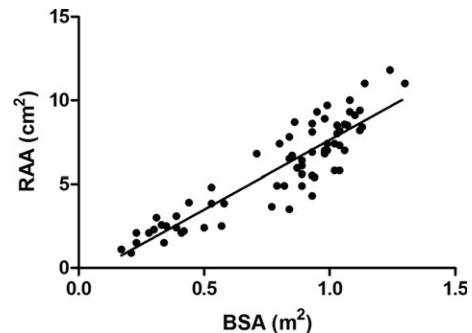


Fig 2. Correlation between right atrial area (RAA) and body surface area (BSA) in control dogs. The RAA showed a strong positive correlation with BSA in healthy dogs ($r = 0.90$; $P < 0.0001$).

Table 1. Clinical and echocardiographic data of all study dogs ($n = 119$).

	Healthy	Mild PAH	Moderate PAH	Severe PAH
N° cases	71	15	10	23
Male/female	31/40	8/7	8/2	12/11
Age (years)	3.0 (1–14)	11 (5–14)*	9 (1–13)*	12 (0.8–18)*
Weight (kg)	28 (2.1–46)	16 (5.8–32.0)	19 (7.9–34.0)	8.5 (3.4–38.0)*
TRPG (mmHg)	0 (0–25)	40 (36–49)*	61 (52–74)*	103 (77–149)***
Severe TR	0 (0%)	0 (0%)	3 (30%)*	10 (43.5%)*
RAA index (cm^2/m^2)	7.3 (4.2–10.2)	6.7 (4.8–10.7)	13.3 (3.4–24.7)***	12.1 (5.4–21.8)***
R-CHF	0 (0%)	0 (0%)	3/10 (30%)*	7/23 (30.4%)*

Data represent median (min–max) unless otherwise stated. PAH, pulmonary arterial hypertension; TRPG, tricuspid regurgitation systolic pressure gradient; TR, tricuspid regurgitation; RAA, right atrial area; R-CHF, right-sided congestive heart failure.

* $P < 0.001$ compared to control group.

** $P < 0.001$ compared to mild PAH group.

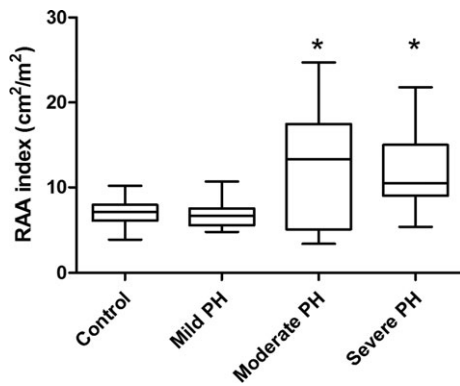


Fig 3. Box and whiskers plot for right atrial area (RAA) index in control dogs in comparison with dogs with different degree of pulmonary arterial hypertension (PAH). The RAA index was significantly higher in dogs with moderate and severe PAH in comparison with dogs with mild PAH and the control group ($P < 0.001$).

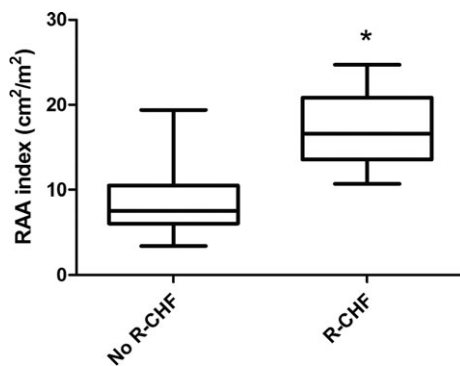


Fig 4. Box and whiskers plot for right atrial area (RAA) index in dogs with and without right-sided congestive heart failure (R-CHF). The RAA index was significantly higher in dogs with R-CHF in comparison with dogs without R-CHF ($P < 0.0001$).

Regarding severity of TR, dogs with mild TR had a lower RAA index (median, $6.6 \text{ cm}^2/\text{m}^2$; range, $3.4\text{--}11.8 \text{ cm}^2/\text{m}^2$) in comparison with dogs with moderate (median, $10.5 \text{ cm}^2/\text{m}^2$; range, $6.4\text{--}15.4 \text{ cm}^2/\text{m}^2$) and severe TR (median, $17.5 \text{ cm}^2/\text{m}^2$; range, $7.5\text{--}24.7 \text{ cm}^2/\text{m}^2$; $P < 0.001$; Fig 5). Thirteen of 48 (27.1%) dogs with PAH had severe TR. Severe TR was found in 0 of 15 (0%) dogs with mild PAH, 3 of 10 (30%) dogs with moderate PAH, and in 10 of 23 (43.5%) dogs with severe PAH. Severe TR was higher ($P < 0.0001$) in dogs

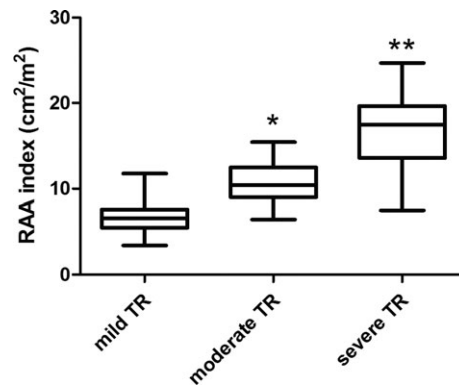


Fig 5. Box and whiskers plot for right atrial area (RAA) index in dogs with pulmonary hypertension and different severity of tricuspid regurgitation (TR). Dogs with mild TR presented a lower RAA index in comparison with dogs with moderate and severe TR ($P < 0.001$).

with R-CHF (9/10, 90.0%) in comparison with dogs without R-CHF (4/38, 10.5%).

In the univariate analysis, among the clinical and echocardiographic variables, TRPG ($P = 0.013$) and TR severity ($P < 0.001$) showed a positive association with RAA index. However, only TR severity maintained a significant ($P < 0.02$) and independent association with increased RAA index based on multivariate analysis (Table 3).

Intra-observer and interobserver measurement variability for RAA yielded average CVs of 7.4% and 9.1%, respectively.

Discussion

We showed that RAA strongly correlates with BSA in healthy dogs. A similar result was found in humans where a linear correlation between RAA and BSA was documented and normalization of RAA to BSA was recommended to account for the different body weights of patients.⁹ In dogs, a recent study reported a strong positive correlation between RAA and body weight.¹⁹ In that study, normal reference values for RA diameters and area were described using body weight-dependent allometric scales. Logic dictates that cardiac volumes should correlate positively with body weight (volume), whereas cross sectional areas within the heart should correlate positively with BSA (proportional to body weight^{2/3}) and cardiac linear dimensions with body length (proportional to body weight^{1/3}).²⁶ In line with

Table 2. Sensitivity and specificity of different cutoff points of right atrial area index for the prediction of right-sided congestive heart failure in 48 dogs with pulmonary arterial hypertension.

	AUC	95% CI	P-value	Cutoff	Se (%)	Sp (%)	Youden index
RAA index	0.97	0.92–1.01	<0.0001	12.3*	100.0	89.5	89.5
				19.7	30.0	100.0	

AUC, area under receiver operating characteristic curve; CI, confidence interval; Se, sensitivity; Sp, specificity; RAA, right atrial area. The value with the asterisk (*) represents the clinically significant cutoff, with the least amount of overlap between groups (optimal combination of sensitivity and specificity and highest Youden index).

Table 3. Multivariate analysis of echocardiographic variables used to predict right atrial area index in dogs with PAH.

Dependent variable	Independent variables	B coefficient	95% CI	P-value
RAA index (cm ² /m ²)	TRPG	-0.019	(-0.073, 0.036)	0.491
	TR severity	2.579	(0.732, 4.425)	0.007

CI, confidence interval RAA, right atrial area; TRPG, tricuspid regurgitation systolic pressure gradient; TR, tricuspid regurgitation.

this concept, in our investigation, RAA correlated positively with BSA and, therefore, RAA indexed to BSA could be successfully used to objectively evaluate RA size in dogs. The normal reference interval for the RAA index was between 4.2 and 10.2 cm²/m².

There was no difference in RAA index between dogs with mild PAH and healthy dogs, whereas it increased in those with moderate and severe PAH. As observed in dogs with experimentally induced PAH, chronic pressure overload may impair right ventricular function and lead to RA enlargement.^{3,4} Similar to dogs, in humans with chronic PAH, enlargement of the RA is not commonly present if the PAH is mild, whereas it is frequent if the PAH is moderate or severe.²⁷ Multivariate analysis showed that the severity of TR was the only independent factor influencing the RAA index. In our study, many dogs with approximately the same TRPG values had different RA sizes. Our results thus suggest that RA size mainly depends on TR severity (volume overload) rather than on TRPG (pressure overload) in dogs with PAH. This conclusion is in line with the medical literature on humans, where RA size in patients with PAH has been shown to depend on TR severity^{7,28} and not on pulmonary arterial systolic pressure as measured by echocardiography.²⁷

Regarding congestive heart failure, the RAA index was significantly higher in dogs with R-CHF compared to those without R-CHF, and an RAA index >12.3 cm²/m² best predicted R-CHF. The RA size has been found to represent an important prognostic factor in humans with PAH.^{2,6-10} The RAA index thus also may represent a prognostic factor in dogs. In our study, prevalence of severe TR was higher in dogs with R-CHF than in dogs without R-CHF. However, there was no difference in TRPG between dogs with and without R-CHF. In the light of our findings, it would seem that R-CHF, as well as RA size, mainly depend on TR severity (volume overload) and not on TRPG (pressure overload).

In line with a previous study,²² our results indicate that dogs with moderate PAH may have R-CHF. A possible explanation might be that these cases were incorrectly classified because of limitations of the TRPG in estimating the actual severity of PAH. The estimation of PAH severity in dogs primarily is based on an assessment of the TRPG.^{1,20-22} However, many studies

in humans have reported inaccuracies when pulmonary artery systolic pressure with TRPG is assessed by Doppler echocardiography rather than right heart catheterization, reporting both underestimation and overestimation.^{12,17,29,30} In addition, severe TR may affect the estimation of pulmonary artery systolic pressure by Doppler echocardiography.³¹

Similar to a previous investigation,¹⁹ it is worth highlighting that the measurement variability in RAA in dogs also was clinically acceptable in our study, thus suggesting that the RAA index can be used reliably during echocardiographic examination in this species.

Our study had some limitations. First, PAH was classified according to TRPG and not by invasive measurements of pulmonary artery systolic pressures (i.e right heart catheterization), which represents the gold standard. However, quantification of the TRPG currently is used by most cardiologists to estimate pulmonary artery systolic pressure in small animals.¹ Second, a TRPG cutoff value of 36 mmHg was used to diagnose PAH in line with the literature,²⁰⁻²² but no consensus exists regarding the best cutoff to diagnose PAH in dogs. Thus, it cannot be ruled out that if a different TRPG cutoff had been used, our results may have been different. Third, our control group was not weight- and age-matched with the PAH group. However, the range of ages and body weights of the control group were very large. Lastly, we did not include an evaluation of right ventricular systolic function, which might influence RA size. However, recent studies in dogs did not show a significant decrease in right ventricular systolic function in dogs with different degrees of PAH.^{32,33}

In conclusion, the RAA index can be used to evaluate RA size in dogs, and the severity of TR is the main determinant of the RAA index in dogs with PAH. In addition, the RAA index might be more effective than the TRPG in predicting R-CHF in dogs with PAH. Further studies are required to verify whether the RAA index represents a prognostic factor in dogs with PAH.

Footnotes

^a GraphPad Prism version 5.0 for Windows, GraphPad Software, San Diego, CA

^b Minitab version 18 for Windows, Minitab Inc, Pennsylvania, PA

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Conflict of Interest Declaration: Eric Zini serves as Associate Editor for the Journal of Veterinary Internal Medicine. He was not involved in review of this manuscript.

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

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