




Right ventricular size and function evaluated by various echocardiographic indices in dogs with pulmonary hypertension

Elisabeth K. Feldhütter¹ | Oriol Domenech² | Tommaso Vezzosi^{2,3}  |
Rosalba Tognetti³  | Jenny Eberhard¹ | Jana Friederich¹ | Gerhard Wess¹ 

¹Clinic of Small Animal Medicine, LMU University, Munich, Germany

²Anicura Istituto Veterinario Novara, Novara, Italy

³Department of Veterinary Sciences, University of Pisa, Pisa, Italy

Correspondence

Gerhard Wess, Clinic of Small Animal Medicine, LMU University, Veterinaerstr. 13, 80539 Munich, Germany.
Email: gwess@lmu.de

Abstract

Background: Three-dimensional (3D) echocardiography and 2-dimensional (2D) strain measurements of the right ventricle (RV) are important indices in humans with pulmonary hypertension (PH) and need further evaluation in dogs with PH.

Objectives: To evaluate various RV size and function indices in dogs with PH and to examine differences between pre- and postcapillary PH.

Animals: A total of 311 client-owned dogs: 100 dogs with PH, 31 with postcapillary and 69 with precapillary PH, and 211 healthy control dogs.

Methods: Retro- and prospective, multicenter study. Size and function of the RV was determined using several indices, derived using dedicated RV software, including 3D RV end-diastolic volume (EDVn), end-systolic volume (ESVn), ejection fraction, 2D global and free wall RV longitudinal strain (RVLS), end-diastolic area, end-systolic area, fractional area change, tricuspid annular plane systolic excursion, and tissue Doppler imaging-derived systolic myocardial velocity of the lateral tricuspid annulus ($S'n$).

Results: The EDVn (1.8 vs 2.5 mL/kg^{0.942}, $P < .01$) and ESVn (0.8 vs 1.2 mL/kg^{0.962}, $P < .001$) were significantly larger in the PH group compared to healthy controls. Free wall RVLS was decreased in dogs with severe PH compared to controls (−24% vs −29.6%, $P < .001$). Dogs with precapillary PH had worse RV systolic function than dogs with postcapillary PH.

Conclusion: Three-dimensional echocardiography of the RV is a promising tool to detect RV changes in dogs with PH. Also, 2D strain measurements are able to detect decreased RV function and offer several advantages compared to conventional indices.

KEYWORDS

canine, heart dimensions, postcapillary, precapillary, speckle-tracking echocardiography

Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; ACVIM, American College of Veterinary Internal Medicine; BW, body weight in kg; DTI, Doppler tissue imaging; EDV, RV end-diastolic volume; EF, ejection fraction; ESV, RV end-systolic volume; FAC, fractional area change; HR, heart rate; LA/Ao, left atrium-to-aorta ratio; LHD, left heart disease; LV, left ventricle; ml, milliliters; MMVD, myxomatous mitral valve disease; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PDA, persistent ductus arteriosus; PG, pressure gradient; PH, pulmonary hypertension; RV, right ventricle; RVEDA, RV end-diastolic area; RVESA, RV end-systolic area; RVLS, right ventricular longitudinal strain; STE, speckle-tracking echocardiography; TAPSE, tricuspid annular plane systolic excursion; TDI S' , tissue Doppler imaging-derived systolic myocardial velocity of the lateral tricuspid annulus; TRPG, tricuspid regurgitation pressure gradient; TTE, transthoracic echocardiography; v, velocity; VSD, ventricular septal defect.

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1 | INTRODUCTION

Pulmonary hypertension (PH) is defined by abnormally increased pressure within the pulmonary vasculature.¹ By definition, PH is present when the systolic blood pressure in the pulmonary system exceeds 30 mm Hg.²⁻⁵ In human medicine, there are 5 different types of PH according to its origin, because several underlying diseases can lead to this condition.⁶ Recently, this classification was adapted to veterinary medicine, resulting in 6 groups of PH: Group 1, pulmonary arterial hypertension (PAH); group 2, secondary to left-sided heart disease (LHD); group 3, respiratory disease/hypoxia; group 4, pulmonary thromboembolism; group 5, parasitic disease and group 6, multifactorial disorders or those of unclear mechanism.¹ Furthermore, a simpler classification can be made into postcapillary PH as a result of LHD (group 2) and precapillary PH (all other groups).^{1,5}

Right heart catheterization remains the gold standard to diagnose PH,⁷ but transthoracic echocardiography represents a less invasive and feasible method in humans and dogs.^{5,8} Chronic PH can lead to right ventricular (RV) dilatation as well as RV dysfunction and dyssynchrony.^{9,10} Several indices can be used to evaluate RV function, such as tricuspid annular plane systolic excursion (TAPSE)¹¹ or peak systolic annular velocity (*S'*) determined by tissue Doppler imaging (TDI).¹² Another feasible assessment for systolic function is strain measurement by speckle tracking technique. A recent study in veterinary medicine identified decreased systolic function using strain by speckle tracking and visible dyssynchrony in dogs with precapillary PH.¹³

A previous study showed that with increasing severity of PH there is also an increase in right heart size, measured by RV end-diastolic area (RVEDA) index.¹⁴ Another method to assess RV function as well as RV size is 3D echocardiography, because the RV can be better evaluated without depending on geometric estimates. In human medicine, this method has been increasingly used to examine patients with PH,¹⁵⁻¹⁷ identifying decreased RV ejection fraction (EF) and increased 3D end-diastolic volumes (EDV).^{15,17}

Therefore, an aim of our study was to evaluate RV systolic function in dogs with various causes and severity of PH using the following variables: TAPSE, RV fractional area change (FAC), TDI-derived systolic myocardial velocity of the lateral tricuspid annulus (TDI *S'*), 2D free wall and global RV longitudinal strain (RVLS), RV end-systolic area (RVESA) by 2D echocardiography and RV EF and end-systolic volume (ESV) by 3D echocardiography.

In addition, volume load and size of the RV should be evaluated in dogs with PH. For this purpose, RV EDV by 3D echocardiography and RVEDA by 2D echocardiography were obtained. All mentioned indices should be further compared with recently published reference intervals. Our hypothesis was that systolic function of the RV will be decreased in patients with PH, and volume overload will occur.¹⁸

2 | MATERIALS AND METHODS

Our study was designed as a multicenter and prospective as well as retrospective analysis. Dogs were examined at 3 centers: the

Department of Veterinary Cardiology of the Ludwig-Maximilians-Universität München, Munich, at the Department of Veterinary Sciences of the University of Pisa and at the Anicura Istituto Veterinario Novara. The study protocol was reviewed and approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (permission number 190-05-11-2019).

2.1 | Animals

All dogs underwent complete physical and echocardiographic assessment.

Pulmonary hypertension was defined as a tricuspid regurgitation pressure gradient (TRPG) ≥ 36 mm Hg, without evidence of RV outflow tract obstruction. The pressure gradient (PG) was determined by measuring the peak velocity (*v*) of the tricuspid regurgitation jets using continuous-wave Doppler by aligning the Doppler signal as parallel as possible to the blood flow and using a simplified Bernoulli equation ($PG = 4 \times v^2$).

The severity of PH was determined based on this PG: if TRPG was between 36 and 50 mm Hg it was classified mild, if between 51 and 75 mm Hg it was considered moderate and if TRPG >75 mm Hg it was considered severe PH.^{14,19,20}

Patients with PH furthermore were classified into precapillary and postcapillary PH. Precapillary PH was defined as increased pulmonary artery pressure (PAP) with normal left atrial (LA) size, assuming that normal LA size also represents normal LA pressure. Referring to the recently published American College of Veterinary Internal Medicine (ACVIM) Guidelines for PH in dogs, precapillary PH included PAH (eg, idiopathic, congenital cardiac shunts), PH caused by respiratory disease/hypoxia, thromboembolic PH, PH caused by parasitic disease (*Dirofilaria immitis*, *Angiostrongylus vasorum*) and PH with multifactorial or unclear mechanisms or both.¹

Postcapillary PH was defined as increased PAP with increased LA pressure caused by LHD. Increased LA pressure was determined by unequivocal LA enlargement,¹ which in this case corresponds to a left atrium-to-aorta ratio (LA/Ao) in the short axis of ≥ 1.7 . Treatment with pimobendan was not an exclusion criterion.

The healthy control group consisted of dogs without any cardiac or systemic diseases based on echocardiography, physical examination and medical history.

2.2 | Conventional echocardiographic examination

Echocardiographic examination was performed using an ultrasound unit (Philips Epic 7, Vivid iq, GE Healthcare, Milano, Italy and Aplio 300, Canon Medical Systems Europe, Zoetermeer, Netherlands) by experienced board-certified cardiologists (GW, OD) or residents under their direct supervision (JF, JE, TV). Dogs were gently restrained in right and left lateral recumbency without sedation. The examination was terminated if the dogs showed severe defensive reactions. An ECG was recorded simultaneously and heart rate (HR) was monitored. As described, routine transthoracic 2D, M-

Mode and spectral and color flow Doppler echocardiography was performed.²¹ Afterwards, the same trained cardiologist performed all offline measurements.

2.3 | Right ventricular size and systolic function

To determine the following indices correctly, the left apical 4-chamber view was adapted for optimized imaging of the RV.²² Right ventricular FAC was determined by tracing the endocardial border from the tricuspid annulus along the free wall to the apex and back to the annulus along the interventricular septum at end-diastole (RVEDA) and end-systole (RVESA).²² Because the area variables correlate with body surface area as recently described,¹⁸ they were indexed to body weight (BW) as follows: $RVEDA_n = RVEDA/BW^{0.665}$ and $RVESA_n = RVESA/BW^{0.695}$. The percentage RV FAC was calculated using the following formula: $FAC (\%) = (end-diastolic\ area - end-systolic\ area) \div end-diastolic\ area \times 100$.²²

The TAPSE was measured from an M-mode recording as previously described^{11,18,23,24} (Figure 1) and indexed to BW as $TAPSE_n = TAPSE/BW^{0.285}$.¹⁸

Peak systolic annular velocity (S') was measured using pulsed-wave TVI velocities of longitudinal myocardial motion at the lateral tricuspid annulus^{12,18,23} and also indexed to BW as $TVI\ S'_n = TVI\ S'/BW^{0.186}$.¹⁸

Two-dimensional strain measurements, expressing myocardial deformation, by speckle tracking echocardiography (STE) also were obtained using TomTec software (RV 2D cardiac performance analysis, Image Arena; Munich, Germany).^{9,18} For 2D strain measurement imaging, frame rates from 65 to 181 Hz were used.

The RV was divided into free wall and septal segment and further subdivided into basal, middle and apical segments, respectively. Only strain curves of the endocardial layer were taken into consideration. Global RVLS was calculated by averaging peak longitudinal strain measurements of all 6 segments and free wall RVLS by averaging values of the 3 segments as previously described (Figure 1).¹³

Right ventricular 3D ESV and RV EF also were used as variables for systolic function of the RV, whereas RV 3D EDV represents size and volume load of the RV. Recording of 3D images only was available at 1 center (LMU Munich) because of technical requirements. To generate 3D images, a X5-1 and X7-2 matrix probe was used and ECG was recorded simultaneously. Harmonic imaging technique was used and imaging sector and elevation were kept as narrow as possible to optimize image quality. A single-beat examination was performed with frame rates from 40 to 63 Hz. Loops were recorded and RV volume was generated offline using TomTec software (4D RV-Function 2).

Right ventricular volumes were calculated as previously described.¹⁸ The following anatomical landmarks were identified: LV and RV apex, center of the mitral and tricuspid valves, aortic valve leaflets in the LV outflow tract, and RV in short axis.

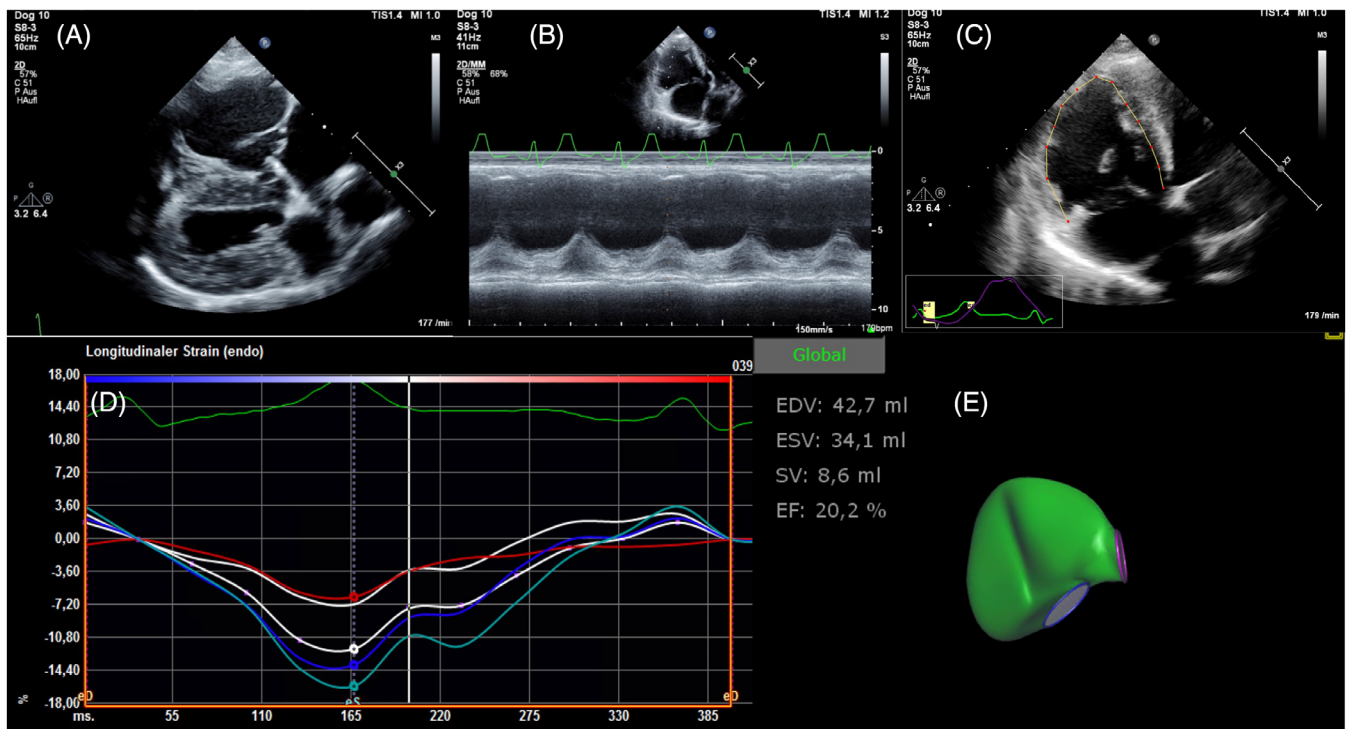


FIGURE 1 Echocardiographic images of an 8-year-old Australian Shepherd suffering from moderate precapillary pulmonary hypertension. (A) Right parasternal long axis 4 chamber view with a severely dilated right heart. (B) Tricuspid annular plane systolic excursion by M-Mode measurements. (C) Tracing of the right ventricular (RV) endocardial border using speckle-tracking echocardiography. (D) The software generates strain curves of all 6 segments, here illustrated free wall RV longitudinal strain displaying a decreased RV function. (E) A 3D dynamic RV model including complete RV volume generated by the software

After automatic tracking of the endocardial borders by the software, a 3D dynamic RV model was generated (Figure 1).

Subsequently, complete RV volume was generated throughout the entire cardiac cycle and EDV, ESV, stroke volume (SV) and EF were determined as recently described.²⁵

Because indexing to BW is also appropriate for volume variables, EDV and ESV were normalized as follows: EDV_n = EDV/BW^{0.942} and ESV_n = ESV/BW^{0.962}.¹⁸

3 | STATISTICAL ANALYSIS

All statistical analyses were performed using commercially available software (MedCalc for Windows, version 19.5.3, MedCalc Software, Ostend, Belgium and IBM SPSS statistics for Mac, version 28.0.1.1). A value of $P < .05$ was considered significant.

A chi-squared test was used to compare categorical data. A Mann-Whitney test was performed to compare all PH-affected dogs with the healthy control group and to compare dogs that received pimobendan with those that did not. Subsequently, a Kruskal-Wallis test was used to compare the echocardiographic indices among the PH groups. If the Kruskal-Wallis test was positive, a Conover post-hoc test for pairwise comparison of subgroups was used.

Subsequently, the numbers of dogs exceeding the reference intervals were calculated.

Simple linear regression was performed to determine the relationship between free wall RVLS and TRPG, HR, sex and age. Multiple regression was used to evaluate independent predictors of free wall RVLS. Data were inspected visually for linearity, homoscedasticity and

multicollinearity to confirm that the conditions for linear regression were met.

To investigate a potential center effect, a random effect was added using a mixed model.²⁶

4 | RESULTS

One-hundred dogs with PH and 211 healthy control dogs were included from October 2014 until July 2020 (Table 1). The group distribution, including the number of dogs at each center, is shown in Figure 2. The data of the healthy control group all was collected prospectively. Of the diseased dogs, 21 animals had been examined retrospectively. With a median age of 139.5 months, the PH group was significantly ($P < .001$) older than the healthy control group, which had a median age of 54.0 months. Dogs with PH had significantly lower BW than the control group (median, 8.5 kg vs 21.6 kg, $P < .001$). No sex differences were found between the control group and the PH group ($P = .12$).

Regarding the severity of PH, 46 dogs suffered from severe PH, 30 from moderate PH and 24 dogs had mild PH. Postcapillary PH was present in 31 dogs, all affected by myxomatous mitral valve disease (MMVD). Sixty-nine dogs had precapillary PH, secondary to various underlying diseases: heartworm disease ($n = 10$), angiostrongylosis ($n = 3$), pulmonary fibrosis ($n = 7$), congenital heart disease ($n = 4$) including ventricular septal defect ($n = 1$) and patent ductus arteriosus ($n = 3$). In 41 dogs, no cause for PH could be found or the owner declined further investigation. A total of 23 dogs received pimobendan, of which 12 had precapillary PH and 11 had postcapillary PH.

TABLE 1 Comparison of clinical and echocardiographic data in all dogs

| | Control | n | Precapillary PH | n | Postcapillary PH | n |
|--|-------------------------------|-----|--------------------------------|----|--------------------------------|----|
| Sex (male/female) | 86/125 | 211 | 30/39 | 69 | 21/10 | 31 |
| Bodyweight (kg) | 21.6 (1.78-64.5) | 211 | 9.4 (1.9-40) ^a | 69 | 8 (2.5-24) ^a | 31 |
| Age (months) | 54 (12-169) | 211 | 141 (3-207) ^a | 69 | 139 (6-225) ^a | 31 |
| Heart rate (bpm) | 93 (40-240) ^{b,c} | 211 | 127 (55-158) ^{a,c} | 69 | 148 (101-205) ^{a,b} | 31 |
| Pimobendan | | 0 | | 12 | | 11 |
| TRPG (mm Hg) | - | - | 73.8 (35-148.8) | 69 | 62.3 (34-100) | 31 |
| RVEDAn (cm ² /kg ^{0.665}) | 1 (0.5-1.8) ^{b,c} | 211 | 1.2 (0.7-2) ^a | 67 | 1.3 (0.6-2) ^a | 30 |
| RVESAn (cm ² /kg ^{0.695}) | 0.5 (0.2-1.2) ^{b,c} | 211 | 0.6 (0.3-1.7) ^a | 67 | 0.6 (0.3-1.3) ^a | 30 |
| FAC (%) | 43.6 (23.2-63) ^c | 211 | 44 (6.3-65.5) ^c | 67 | 51.4 (5.8-72.3) ^{a,b} | 30 |
| TAPSEn (mm/kg ^{0.285}) | 6.2 (2.8-9.7) ^{b,c} | 206 | 5.4 (2.5-11.3) ^{a,c} | 47 | 9.1 (5.6-12.9) ^{a,b} | 18 |
| TVI S'n (cm/s/kg ^{0.186}) | 8.5 (4.1-14.2) | 188 | 7.8 (3.7-17.6) | 40 | 8.8 (6.3-13.8) | 12 |
| Free wall RVLS × -1 (%) | 29.7 (17.5-51.6) ^b | 206 | 23.4 (6.4-38.7) ^{a,c} | 69 | 32.2 (20.9-55.1) ^b | 31 |
| Global RVLS × -1 (%) | 26 (13.1-46.2) ^b | 206 | 20.1 (6.6-33) ^{a,c} | 69 | 26.5 (15.4-51.4) ^b | 31 |

Note: Data are expressed as median (min-max).

Abbreviations: EDV, 3D RV end-diastolic volume; EF, ejection fraction; ESV, 3D end-systolic volume; FAC, fractional area change; free wall RVLS, free wall RV longitudinal strain; global RVLS, global RV longitudinal strain; RVEDA, RV end-diastolic area; RVESA, RV end-systolic area; TAPSE, tricuspid annular plane systolic excursion; TVI S', tissue Doppler imaging-derived systolic myocardial velocity of the lateral tricuspid annulus.

^a $P < .05$ compared to control.

^b $P < .05$ compared to precapillary PH.

^c $P < .05$ compared to postcapillary PH.

When comparing RV size indices between healthy and diseased dogs, EDVn (1.8 vs 2.5 mL/kg^{0.942}, *P* < .01) and RVEDAn (1.0 vs 1.2 cm²/kg^{0.665}, *P* < .001) were significantly larger in the PH group compared to the control group.

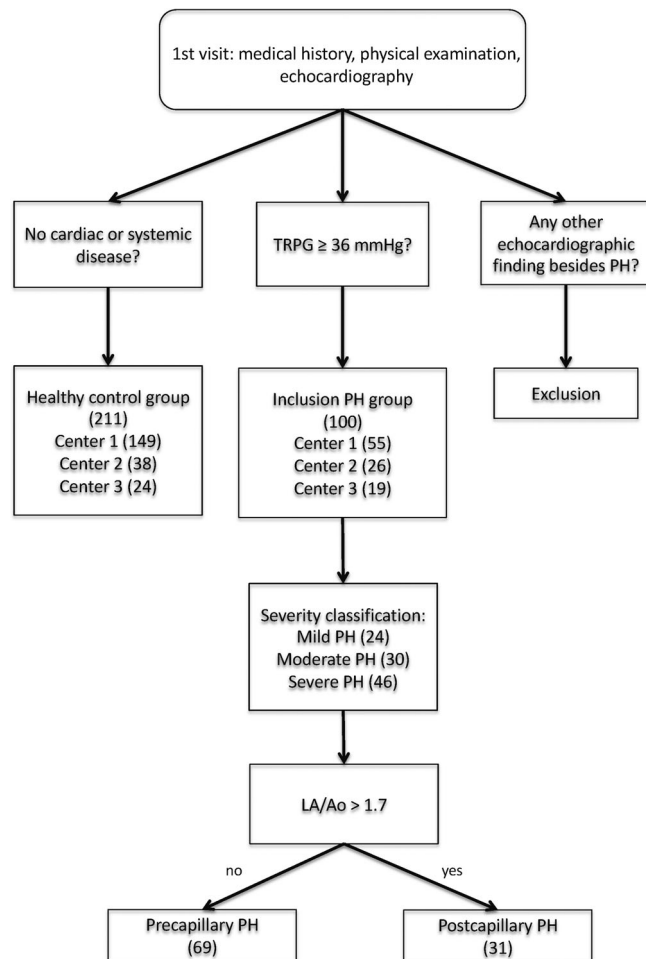


FIGURE 2 Study structure flowchart. The number of dogs is indicated. The severity classification of pulmonary hypertension (PH) was determined based on tricuspid regurgitation pressure gradient (TRPG): 36 to 50 mm Hg mild PH, 51 to 75 mm Hg moderate PH, TRPG >75 mm Hg severe PH

An analysis of the subgroups with different severity stages of PH and between pre- and post-capillary PH was not performed for the 3D variables (EDV, ESV, and EF) because group sizes were too small. When considering the severity of PH for the remaining variables, RVEDAn differed significantly between severe and moderate PH compared to healthy control dogs (*P* < .001, Table 2). No significant differences were found between pre- and post-capillary PH regarding RVEDAn (*P* = .97, Table 1).

Considering RV systolic function, the following variables differed significantly between control group and PH group: ESVn (0.8 vs 1.2 mL/kg^{0.962}, *P* < .001), RVESAn (0.5 vs 0.6 cm²/kg^{0.695}, *P* < .001), free wall RVLS (−29.7 vs −26.8%, *P* < .001) and global RVLS (−26 vs −21.5%, *P* < .001). On the other hand, TAPSEn (6.2 vs 6.1, *P* = .81), TVI S'n (8.5 vs 8.1 cm/s/kg^{0.186}, *P* = .71), EF (50 vs 48.2%, *P* = .05) and FAC (43.6 vs 47.3, *P* = .08) were not significantly different between diseased and healthy controls.

Considering RVESAn, significant differences were found between moderately and severely diseased animals, as well as between healthy and severely diseased animals, respectively (*P* < .001). Free wall RVLS had significantly fewer negative values, which corresponds to poorer systolic function in dogs with severe PH compared to controls (*P* < .001, Figure 3). Global RVLS was decreased in dogs with mild, moderate and severe PH compared to healthy dogs, as well as between moderate and severe PH, respectively (*P* < .001). The remaining variables FAC (*P* = .06), TAPSEn (*P* = .42), and TVI S'n (*P* = .72) were not show significantly different among the individual severity groups (Table 2).

When comparing pre- and post-capillary PH regarding systolic function indices (Table 1), free wall RVLS and global RVLS had significantly fewer negative values (poorer systolic function) in dogs with precapillary PH compared to dogs with postcapillary PH (*P* < .001, respectively).

The TAPSEn also was significantly lower in dogs with precapillary PH compared to postcapillary PH (*P* < .001). When dogs with precapillary PH were considered as a separate group, patients with moderate and severe PH had significantly lower TAPSEn than healthy dogs (*P* = .02).

Results for RVESAn (*P* = .38), FAC (*P* = .06), and TVI S'n (*P* = .18) did not differ significantly between pre- and post-capillary PH.

TABLE 2 Comparison of echocardiographic indices between various severity groups of PH and healthy controls

| | Control | n | Mild PH | n | Moderate PH | n | Severe PH | n |
|--|------------------|-----|-------------------------------|----|----------------------------|----|----------------------------------|----|
| RVEDAn (cm ² /kg ^{0.665}) | 1 (0.5-1.8) | 211 | 1.1 (0.8-1.5) | 23 | 1.2 (0.6-2.0) ^a | 29 | 1.4 (0.8-2) ^a | 45 |
| RVESAn (cm ² /kg ^{0.695}) | 0.5 (0.2-1.2) | 211 | 0.5 (0.3-0.8) | 23 | 0.6 (0.3-1.7) | 29 | 0.7 (0.4-1.5) ^{a,c} | 45 |
| FAC (%) | 43.6 (23.2-63) | 211 | 50.4 (29-72.2) | 23 | 50 (5.8-67.7) | 29 | 49 (6.3-66.2) | 45 |
| TAPSEn (mm/kg ^{0.285}) | 6.2 (2.8-9.7) | 206 | 7.2 (4.7-11.4) | 11 | 6.1 (2.7-12.9) | 21 | 5.8 (2.5-10.8) | 33 |
| TVI S'n (cm/s/kg ^{0.186}) | 8.5 (4.1-14.2) | 188 | 8.2 (6.4-17.9) | 10 | 8.8 (4.5-11.1) | 14 | 7.8 (3.7-14.3) | 27 |
| Free wall RVLS × −1 (%) | 29.7 (17.5-51.6) | 206 | 28.4 (16-55.1) | 24 | 28 (12.2-48.4) | 29 | 24 (6.4-38.7) ^a | 46 |
| Global RVLS × −1 (%) | 26 (13.1-46.2) | 206 | 23.9 (11.4-51.4) ^a | 24 | 23.1 (8-38.1) ^a | 29 | 19.2 (6.6-33.1) ^{a,b,c} | 46 |

^a*P* < .05 compared to control group.

^b*P* < .05 compared to mild PH.

^c*P* < .05 compared to moderate PH.

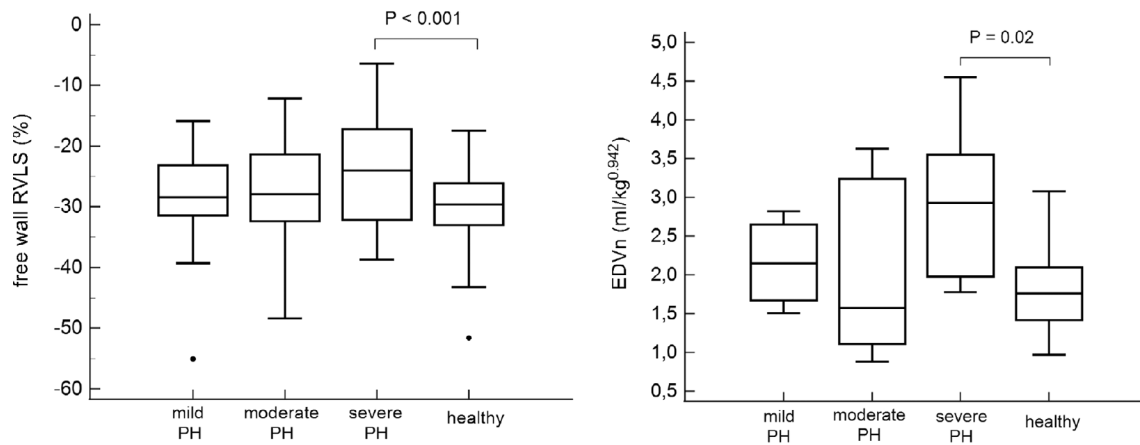


FIGURE 3 Box-and-whisker plots for free wall right ventricular longitudinal strain and end-diastolic volume, comparing different stages of pulmonary hypertension (PH). Significant differences in dogs with severe PH compared to healthy controls

TABLE 3 Comparison between the recently published lower and upper limits for healthy dogs and the diseased dogs from this study

| Lower or upper limits | Number of cases (percentage), precapillary PH/postcapillary PH | Mild PH | Moderate PH | Severe PH |
|---|---|---------|-------------|-----------|
| EDVn > 2.5 mL/kg ^{0.942} | 8 of 16 (50%), 5/3 | 1 | 3 | 4 |
| ESVn > 1.2 mL/kg ^{0.962} | 8 of 16 (50%), 6/2 | 2 | 3 | 3 |
| EF < 42.1% | 5 of 16 (31%), 5/0 | 1 | 3 | 1 |
| RVEDAn > 1.4 cm ² /kg ^{0.665} | 33 of 97 (34%), 24/9 | 1 | 9 | 23 |
| RVESAn > 1.2 cm ² /kg ^{0.695} | 19 of 97 (20%), 17/2 | 0 | 6 | 13 |
| FAC < 30% | 14 of 97 (14%), 12/2 | 1 | 4 | 9 |
| TAPSEn < 4.5 mm/kg ^{0.285} | 9 of 65 (13%), 9/0 | 0 | 3 | 6 |
| TVI S'n (cm/s/kg ^{0.186}) | 5 of 52 (10%), 5/0 | 0 | 1 | 4 |
| Free wall RVLS × -1 > -20.8% | 28 of 100 (28%), 27/0 | 2 | 7 | 18 |
| Global RVLS × -1 > -18.3% | 32 of 100 (32%), 29/3 | 6 | 6 | 20 |

Note: The number of dogs with PH below or above the normal limits and whether they have pre- or postcapillary PH is indicated. Also, the severity of PH is presented. Data are expressed as numbers (percentage).

Results comparing the variables in the PH dogs with the recently published upper and lower limits¹⁸ for healthy dogs are summarized in Table 3. The results emphasize that mainly dogs with precapillary PH exceed the upper or fall below the lower limits and therefore suffer from decreased systolic function (free wall and global RVLS, TAPSE, FAC, TVI S', EF, ESV, and RVESA). The decreased systolic function mainly affects animals with more severe PH.

Visual inspection of model assumptions showed that conditions of linear regression were met. Simple linear regression identified a significant, but weak positive correlation between free wall RVLS and TRPG ($R^2 = 0.1$, $P < .01$) and age ($R^2 = .01$). Heart rate and sex did not correlate with free wall RVLS ($R^2 < .01$, $P = .47$ and $R^2 < .001$, $P = .63$, respectively). In the multiple regression, only TRPG remained as independent predictor of free wall RVLS (regression coefficient $b = 3.3$, $P < .01$). Age ($P = .10$), sex ($P = .94$) and HR ($P = .33$) were not independent predictors of free wall RVLS.

The mixed model showed no notable center effect; only approximately 1.6% of the model variance was associated with the different centers, which indicates a negligible center effect.

Considering the diseased dogs, no significant differences were observed between dogs that received pimobendan and those that did not for any variable (Table 4).

5 | DISCUSSION

Multiple studies have shown that dogs with PH experience enlargement of the RV with increasing severity,^{13,14,27} which is consistent with our findings in which RVEDAn was higher in moderate and severe PH dogs compared to healthy controls. This observation is consistent with the results of a previous study.¹⁴ Additionally, our study showed that end-diastolic 3D RV volume, a relatively new variable in veterinary medicine, also confirms enlargement of the RV in

TABLE 4 Comparison of echocardiographic variables in diseased dogs receiving pimobendan and not receiving pimobendan

| | Pimobendan | No Pimobendan | P |
|--|------------|---------------|-----|
| N cases | 23 | 77 | |
| TRPG (mm Hg) | 64 | 71 | .3 |
| EDVn (mL/kg ^{0.942}) | 3.1 | 2 | .08 |
| ESVn (mL/kg ^{0.962}) | 1.5 | 1.2 | .13 |
| EF (%) | 50.1 | 48 | .95 |
| RVEDAn (cm ² /kg ^{0.665}) | 1.2 | 1.2 | .23 |
| RVESAn (cm ² /kg ^{0.695}) | 0.6 | 0.6 | .28 |
| FAC (%) | 51.6 | 47.2 | .95 |
| TAPSEn (mm/kg ^{0.285}) | 7.2 | 6 | .4 |
| TVI S'n (cm/s/kg ^{0.186}) | 8.1 | 8.1 | .9 |
| Free wall RVLS × -1 (%) | 30.1 | 25.5 | .27 |
| Global RVLS × -1 (%) | 25 | 21.2 | .10 |

Note: Data are expressed as median.

dogs with PH. These results are also consistent with studies of 3D volume in PH in humans.^{17,28} Because of the relatively small number of dogs, no differences between the severity levels of PH for the 3D variables were investigated. Additional studies with a larger number of animals are needed for this purpose.

Systolic function of the RV also decreases in PH-affected dogs and humans, as various studies using several variables have already shown.^{13,27,29,30} Our study identified increased RVESAn in moderately and severely diseased dogs, reflecting worse RV systolic function.

The TAPSEn was only decreased in dogs with precapillary PH, and only in moderately and severely diseased dogs. This result is similar to a previous study, where TAPSE normalized to BW was decreased in dogs with precapillary PH.¹³ Another study found that TAPSEn was decreased in dogs with pre- and post-capillary PH,¹¹ but in this study the 2 groups were not observed separately, and no differentiation was made between pre- and post-capillary PH dogs.

The TVI S'n neither differed between healthy and diseased dogs, nor among severity groups or between pre- and post-capillary hypertension, which is consistent with previous results.¹³ In contrast, another study found decreased peak myocardial velocity in systole with increasing TRPG.³¹ A possible explanation is that TVI S' was not normalized to BW in the previous study,³¹ and dogs with severe PH were significantly smaller than the dogs of the control group. However, various studies showed that TVI S' is weight-dependent and larger values are obtained with increasing BW.^{18,32} Based on our results, we conclude that TVI S' is not a suitable variable to detect decreased RV function in dogs with PH.

We measured 2D strain as another variable for systolic function, using software designed specifically for the RV. Considering free wall and global RVLS, only dogs with precapillary PH had decreased strain values, with the exception of 3 dogs with postcapillary PH, which also had decreased global RVLS values. These results are consistent with a previous study,¹³ in which dogs with precapillary PH also had decreased strain values. The RVLS of the free wall is of particular relevance here, because it reflects RV systolic function more accurately

than does global RVLS.³³ Another study has shown that the transverse strain of the RV, which was not investigated in our study, is also decreased in dogs with PH.³⁴ The main advantage of strain measurement using STE over conventional indices such as TAPSE or TVI S' is angular independence³⁵ and the possibility of evaluating the entire RV in >1 dimension and not only regional segments.¹⁸ This feature may enable changes to be detected at an earlier stage. The only independent predictor of free wall RVLS was TRPG.

By assessing these parameters in clinical practice, any effects of PH on the heart can be determined, and thus cardiac function can be assessed. This information then can be useful when establishing prognoses or making treatment decisions.

The fact that dogs with postcapillary PH, suffering from MMVD, are not affected by systolic dysfunction can be explained as follows: in people with mitral valve prolapse it is known that RV systolic function predominantly depends on LV activity including septal function.³⁶⁻³⁸ Because of ventricular interdependence, the RV free wall is moved toward the left during systole by LV contraction.^{36,39,40} Moreover, animal experiments demonstrated that 20% to 40% of the generated RV systolic pressure and volume outflow result from LV contraction.⁴⁰⁻⁴² And even if the RV free wall is replaced by a noncontractile patch, circulation can be maintained by the septum as long as RV dilatation is not present.^{40,42} Because dogs with MMVD usually have hyperkinetic septal motion,^{36,43} it is reasonable that RV systolic function also can be maintained. This effect is lacking in dogs with systolic dysfunction (eg, dilated cardiomyopathy or precapillary PH). The decreased systolic function in precapillary PH also has a clinical impact on these dogs: decreased TAPSE is associated with shorter survival time in dogs suffering from PH not secondary to left heart disease.²⁷ The question is also whether the decreased systolic function has therapeutic consequences. Pimobendan, for instance, as a phosphodiesterase 3 inhibitor (PDE3i) with positive inotropic and systemic vasodilatory effects, can improve RV systolic function after a single PO dose in healthy dogs.⁴⁴ In contrast, another study showed that in dogs with severe PH (respiratory disease/hypoxia) survival time was not prolonged by the combination of sildenafil and pimobendan compared to treatment with sildenafil alone.⁴⁵ In this retrospective study, no standardized dosing regimen was used, and only dogs with respiratory disease as an underlying cause were included. A more recent study investigated the effect of a single IV dose of pimobendan in 5 beagle dogs with experimentally-induced precapillary PH.⁴⁶ The single dose improved LV and RV function based on various echocardiographic indices, a long-term effect was not investigated however.⁴⁶ The inotropic response to PDE3i may be decreased in the failing canine myocardium, as has been shown in previous studies.^{46,47} Therefore, the efficacy in severe cases of PH still needs to be investigated.

In our study, no significant differences in RV function indices could be found between dogs treated with pimobendan and those that were not treated. We also did not have a standardized treatment regimen because it was not the primary objective of our study. Because there is no clear evidence of a beneficial effect of pimobendan in precapillary PH yet, the recent ACVIM consensus statement does not argue for or against its use.¹ The long-term effect of pimobendan in dogs with other causes of PH should be investigated using a consistent treatment regimen.

Our study had some limitations. First, the number of diseased animals with 3D images is limited. One reason is that the technical requirements for 3D echocardiography were only available at 1 center. Furthermore, 3D studies require excellent image quality and a high degree of patient compliance. Interfering factors such as panting or rapid movements can easily lead to inadequate image quality. Therefore, additional studies with larger numbers of animals with 3D images are needed to verify our results. Second, the number of animals used for the different variables varied considerably. This result can be explained by the fact that some dogs were evaluated retrospectively and not all of the necessary images were always recorded. Also, not all recordings were possible for every animal because of inadequate image quality. Third, because ours was a multicenter study, different investigators generated the images. Although each examiner was a trained cardiologist, small differences in imaging techniques, as well as the use of different echocardiography machines, cannot be excluded. Fourth, 23 dogs received pimobendan. As explained earlier, a long-term beneficial effect on RV systolic function in dogs with PH has not yet been demonstrated. Although we did not find significant differences in measurements between dogs that received and did not receive pimobendan, an effect of the PDE3i cannot be completely excluded. Fifth, the accuracy of using peak TRPG to diagnose PH and classify its severity has limited reliability.⁴⁸⁻⁵¹ Using echocardiography can lead to both under and overestimation of actual PAP, with underestimation being more common.^{48,49,52} The latter occurs especially with inadequate quality of the TR jet flow profile⁴⁸ or when a severe increase in right atrial pressure is present.¹ Because of a lack of validated methods to estimate RA pressure in dogs, it is not recommended to add this variable to the calculated PG.¹ Another reason for possible underestimation is inaccuracy of the simplified Bernoulli equation. This limitation applies to blood flowing through an orifice of constant size with hardly any friction loss.⁴⁸ When considering changes in size throughout the cardiac cycle and severe regurgitation into an enlarged right atrium, the Bernoulli equation can lead to underestimation of true PAP.^{48,52} Additionally, if decreased RV systolic function caused by severe PH is present, the TR velocity may be decreased leading again to an underestimation of the actual PAP.⁴⁸ Because of the uncertainties of indirect pressure determination described above, the ACVIM consensus statement no longer supports grade classification of PH using peak TRPG. Instead, the grading should be done based on clinical signs and outcome data from large longitudinal studies, which are not yet available.¹ For lack of alternatives, we decided to use conventional grading. Catheterization is the gold standard for differentiating between pre- and post-capillary PH.¹ Because of the invasive nature of this method, we relied on estimation by means of echocardiography. Mixed forms of PH thus may have possibly been omitted.

6 | CONCLUSION

Three-dimensional echocardiography of the RV seems to be a promising technique for detecting RV changes in dogs with PH. Also, 2D

strain measurements, especially free wall RVLS, can detect decreased RV function, possibly better than conventional measurements such as TVI S' or FAC, because the described disadvantages of these parameters are avoided. These factors might have consequences concerning treatment and prognosis in dogs with PH, which should be evaluated in future studies.

ACKNOWLEDGMENT

No funding was received for this study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by Ludwig Maximilians University Munich for all centers involved, number: 190-05-11-2019.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Tommaso Vezzosi  <https://orcid.org/0000-0001-8301-6582>

Rosalba Tognetti  <https://orcid.org/0000-0001-8449-9176>

Gerhard Wess  <https://orcid.org/0000-0002-6634-8072>

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How to cite this article: Feldhütter EK, Domenech O, Vezzosi T, et al. Right ventricular size and function evaluated by various echocardiographic indices in dogs with pulmonary hypertension. *J Vet Intern Med.* 2022;1-10. doi:[10.1111/jvim.16496](https://doi.org/10.1111/jvim.16496)