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A loud right-apical systolic murmur is associated with the diagnosis of secondary pulmonary arterial hypertension: Retrospective analysis of data from 201 consecutive client-owned dogs (2006–2007)

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ABSTRACT

Canine pulmonary arterial hypertension (PAH) remains under-recognized and under-treated despite being prevalent. This retrospective study investigated whether selected historical and physical examination findings were associated with the diagnosis of canine PAH, defined as tricuspid regurgitation (TR) with a confirmed systolic pressure gradient $\geqslant$35 mmHg. Two hundred and one client-owned dogs (PAH group, $n = 96$; control group, $n = 105$) were studied. Dogs in the control group had TR with a confirmed systolic gradient <35 mmHg. All dogs underwent a complete physical examination and a complete echocardiographic assessment.

A loud systolic right-apical murmur (RAM) was significantly associated with TR $\geqslant$ 35 mmHg. The proportion of dogs with PAH significantly increased as the RAM grade increased, with odds ratios of 4.4–37.6 for Grades 3/6–5/6 ($P = 0.004$ to <0.001), respectively. A stronger right-than-left apical-murmur had a positive predictive value (PPV) of 83% and was 96% specific for TR $\geqslant$ 35 mmHg, and when combined with syncope, it had a PPV of 92% and was 92% specific. A Grade $\geqslant$4/6 RAM had a PPV of 85% and was 93% specific. Syncope with a Grade $\geqslant$4/6 RAM had a PPV of 94% and was 92% specific. Ascites combined with a Grade $\geqslant$4 or $\geqslant$5/6 RAM had a PPV of 100% and was 100% specific for TR $\geqslant$ 35 mmHg. For each of these three murmur categories (Grades $\geqslant$4/6, $\geqslant$5/6, and a louder-right-than-left murmur), when detected with no concurrent ascites or syncope, the positive likelihood ratio varied from 4.6 to 6.4. A loud systolic RAM in dogs with degenerative valve disease is highly suggestive of concurrent PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a heterogeneous condition that increases pulmonary vascular resistance (Kellihan and Stepien, 2012). Some of the least conservative definitions of PAH have included an elevation of the systolic pulmonary arterial pressure to >25 mmHg at rest (MacDonald and Johnson, 2005; Bach et al., 2006; Martin and Corcoran, 2006). The most studied cause of PAH in veterinary medicine is heartworm disease (Sasaki et al., 1992; Johnson and Hamlin, 2000). Primary idiopathic PAH has only been reported in one dog (Glaus et al., 2004), but secondary PAH is relatively common, affecting 14–74% of dogs with acquired mitral regurgitation (MR; Serres et al., 2006b; Kellihan and Stepien, 2012). Moreover, dogs with MR are perhaps living longer than previously due to more effective pharmacotherapy, and might therefore be considered to be at greater risk of developing secondary PAH. Secondary PAH potentially triggers right-sided congestive heart failure (R-CHF), exercise intolerance, or syncope in 23–38% of cases (Johnson et al., 1999; Pyle et al., 2004; Serres et al., 2006b; Kellihan and Stepien, 2012). Nevertheless, PAH is often clinically silent during most of its course.

Clinical signs associated with PAH often also result from comorbidities and are therefore non-specific. These can include tachypnea, exercise intolerance, cough, dyspnea, lethargy, syncope or collapse, jugular venous distension or pulsation, a gallop rhythm, a split S_2, cardiac murmurs, hepatomegaly, and ascites. Therefore, the index of suspicion for PAH is commonly very low, often delaying the eventual diagnosis. As a corollary, because the prevalence of PAH is frequently underestimated, it is under-diagnosed and consequently under-treated, despite the availability of potent medications (Bach et al., 2006; Serres et al., 2006a; Kellum and Stepien, 2007; Moreno, 2007; Atkinson et al., 2009; Brown et al., 2010).

The noninvasive diagnostic study most commonly used for identification and quantification of PAH is Doppler echocardiography, which often has limited availability and can be cost-prohibitive. The diagnostic limitations of this rather prevalent condition emphasize a need for a tangible, practical preliminary test, so that clinicians can include PAH in their differential diagnosis list and

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can refer appropriate cases for more definitive study. Ideally, such a test should be based on historical and/or physical examination findings rather than on imaging modalities.

In dogs with bilateral systolic apical murmurs related to chronic degenerative valve disease, the right sided murmur can either result directly from tricuspid regurgitation (TR) with a high-velocity jet, or it can be an indirect, secondary audible manifestation of a murmur of MR, radiating from the left to the right hemi-thorax. However, a palpable right apical systolic thrill does not typically radiate from the left to the right and might therefore reflect TR with a high trans-valvular systolic pressure gradient. Nevertheless, palpable precordial TR thrills due to septal leaflet prolapse with an eccentric (lateral) jet or due to tricuspid valve dysplasia (TVD) accompanied by normal pulmonary arterial pressure might be an exception to this general rule.

As right ventricular (RV) afterload is elevated to varying degrees in dogs with PAH, the systolic pressure gradient between the RV and the right atrium (RA) can be extremely high. In theory, if TR is present, its jet velocity can be exacerbated and its murmur grade increased to as high as 5–6/6, i.e. a palpable thrill is present. We hypothesized that a systolic, right apical murmur (RAM) associated with a palpable thrill could raise the index of suspicion for PAH, and that the detection of a right-sided murmur that is louder than a concurrent left-sided murmur would also suggest PAH. We investigated whether selected history and physical examination findings, such as syncope, ascites, and/or a grade $\geqslant$4/6 TR murmur, were associated with the Doppler diagnosis of PAH and its severity.

Materials and methods

Case selection and medical records review

Medical records of 350 client-owned dogs consecutively presented for the first time to the Cardiology Service of a university veterinary teaching hospital between 1st January 2006 and 31st July 2007 were retrospectively reviewed. Medical history, clinical signs and a single examiner's (DGO) physical examination findings, as well as quantitative echocardiographic parameters, were documented and analyzed. The most common diagnosis was degenerative valvular disease, while other diagnoses included cardiomyopathy, often suspected to be induced by tachycardia due to underlying primary chronic atrial fibrillation, typically in giant breed dogs.

The study entry criterion was a diagnosis of quantifiable TR on Doppler echocardiography. An auscultatory diagnosis of TR was not required. Exclusion criteria included incomplete echocardiographic studies, a diagnosis of pulmonic stenosis, septal defect, TVD, or arrhythmogenic RV cardiomyopathy, and lack of a demonstrable and quantifiable jet of TR (as PA pressure status could not be determined). One hundred and forty-nine dogs were excluded on the basis of the exclusion criteria. The remaining 201 dogs included 96 with PAH (TR $\geqslant$ 35 mmHg) and 105 dogs that served as a control group (TR < 35 mmHg). All dogs in the PAH group were further categorized by severity as mild (35–49 mmHg), moderate (50–74 mmHg) or severe ($\geqslant$75 mmHg; Simonneau et al., 2004).

Echocardiography

Echocardiography was performed using a 7S (3.1–8.0 MHz) or a 3S (1.5–3.6 MHz) phased array transducer (Vivid 3, General Electric). Images were obtained using standard bilateral views. Assessment included diastolic and systolic heart chamber dimensions and wall motion. Diastolic and systolic velocities were recorded across all four valves. Doppler interrogation of TR jets was performed during all respiratory cycle phases at random. To avoid underestimation of jet peak flow velocities, each measurement was averaged from at least three non-consecutive cardiac cycles, chosen from those with the highest velocities. Spectral Doppler signals of TR were used to calculate the peak systolic pressure gradient across the valve, using the modified Bernoulli equation. To avoid relying on approximations rather than measurements, no attempt was made to estimate the influence of RA pressure on the calculated trans-valvular systolic pressure gradients and the absolute RV systolic pressure was not calculated (Berger et al., 1985).

Statistical methods

Normality of variables was assessed using the Shapiro–Wilk test. Continuous variables were compared using the two-sample *t* test or the Mann–Whitney *U*-test, based on data distribution. The Pearson chi-squared or Fisher's exact tests were used to compare categorical variables.

A multivariate logistic regression analysis was used to determine the association between murmur grade (0–6/6) and presence or absence of PAH. Dogs without a cardiac murmur were used as a reference category. The risk of PAH in specific breeds was calculated with the most commonly affected breed used as a reference category. The Spearman rank coefficient was used to determine correlations between selected quantitative variables. Sensitivity, specificity, positive and negative predictive values of various diagnostic findings were computed as markers of PAH. When applicable, likelihood ratios were calculated.

All calculations were performed using statistical software (SPSS 17.0 for Windows). A P of $\leqslant$0.05 was considered statistically significant.

Results

Signalment

The proportion of male dogs and the proportion of intact dogs was not statistically different between the PAH group and the control group (55/96 [57.3%] vs. 67/105 [63.8%], and 39/96 [40.6%] vs. 51/105 [48.6%], respectively).

The mean age was significantly higher in the PAH group than in the control group (11 ± 3 years vs. 9.7 ± 4 years, respectively; $P = 0.005$). The proportion of dogs with PAH was higher in dogs in their second decade of life, compared to those <10 years old (55.2% vs. 32.8%; OR, 2.52; 95% confidence intervals [CI_{95}], 1.34–4.66; $P = 0.003$).

The proportions of the Miniature poodle and Pekingese breeds were 2.2 and 8.7 times higher in the PAH group than in the control group, (8.3% vs. 3.8% and 8.3% vs. 0.95%, respectively; Table 1). The proportion of the Pekingese breed in the PAH group was significantly higher than all other breeds combined (OR, 9.45; $CI_{95\%}$ 1.16–77.07; $P = 0.015$).

Clinical signs and physical examination findings

Among the 96 dogs with PAH, there was also evidence of MR (94%) and a MR murmur (78%; Fig. 1). Physical examination findings and clinical signs that were more common in the PAH group than the control group are also shown in Fig. 1. RAM was auscultated in 61% of dogs in the PAH group and 17% of dogs in the control group (Fig. 2). None of the dogs with RAM had a murmur graded <2/6.

Split heart sounds were not documented in any of the studied dogs. Apical murmurs on either side were significantly louder in the PAH group (left: median, 3; range, 0–6, $n = 75$; right: median, 3.5; range, 0–6, $n = 59$) than in the control group (left: median, 0; range, 0–6, $n = 54$; right: median, 2; range, 0–5, $n = 18$; $P < 0.001$ for each side).

Of the 201 dogs studied, 108 did not have ascites or syncope (PAH group, $n = 34$), while 110 had either ascites or syncope

Table 1
Distribution of selected dog breeds in pulmonary arterial hypertension (PAH) and control groups.

Breed	PAH group (*n*)	Control group (*n*)	PAH-to-control group ratio
Golden retriever	1	5	0.20
Dogue de Bordeaux	1	4	0.25
Boxer	1	3	0.33
Labrador retriever	2	4	0.50
Miniature pinscher	4	8	0.50
Miniature poodle	8	4	2.00
Pekingese	8	1	8.00

The difference in proportions across all breeds combined was significant at $P = 0.014$; Purebreds that are not specified in the table included the following: American Staffordshire, Bassett hound, Beagle, Belgian shepherd, Border collie, Bullmastiff, Cane Corso, Chihuahua, Cavalier King Charles Spaniel, Cocker spaniel, Dachshund, Doberman pinscher, English bulldog, French bulldog, Great Dane, Giant Schnauzer, German shepherd, Maltese, Neapolitan Mastiff (Mastino Napoletano), Standard terrier, Viszla, Weimaraner, Whippet, and Yorkshire terrier.