



## RETROSPECTIVE INVESTIGATION ON THE PREVALENCE OF PULMONARY HYPERTENSION IN DOGS WITH BRONCHIAL AND UPPER RESPIRATORY DISEASES

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### ABSTRACT

Bronchial and upper respiratory diseases have been associated with hypoxia and subsequent development of pulmonary arterial hypertension (PAH). However, there are no known studies assessing the prevalence of PAH in dogs with these conditions. The aim of this study was to assess the frequency of PAH in dogs with bronchial and upper respiratory diseases. Medical records of dogs with confirmed diagnosis (by endoscopic examination) of bronchial and/or upper respiratory diseases referred for cardiovascular investigation (January 2009 - May 2013) were retrospectively reviewed. Diagnosis of PAH was made by echocardiography (tricuspid regurgitation  $> 2.8$  m/s and/or pulmonic regurgitation  $> 2.2$  m/s); possible PAH was diagnosed when two or more specific echocardiographic findings were present. 52 dogs (30 with upper respiratory diseases, 17 with bronchial disease and 5 with both) were included. Diagnosis of PAH was performed in 3 dogs (5.7%). Two dogs were considered as probably affected by PAH; a total of 5 dogs (9.4%) resulted in being affected or probably affected by PAH. Our study shows that the prevalence of PAH in dogs with bronchial and/or upper respiratory diseases is low; PAH seems to occur mostly in older dogs and/or with very advanced disease: echocardiography may therefore be a useful tool in this category of patients.

**Key words:** dogs, pulmonary arterial hypertension, respiratory disease, tricuspid regurgitation

### INTRODUCTION

In veterinary medicine, pulmonary arterial hypertension (PAH) is defined as pulmonary arterial systolic pressure greater than 25 mmHg (1). Right-heart catheterization is considered the “gold standard” in order to diagnose PAH (2, 3, 4). However it is rarely performed in veterinary medicine (1, 3, 4). In the absence of right ventricular (RV) outflow tract obstruction (e.g. pulmonary stenosis) or significant right-sided volume overload (e.g. tricuspid valve dysplasia), pulmonary arterial pressure can be inferred non-invasively with Doppler echocardiography, either by calculation of

the maximal velocity of the regurgitant flow across the tricuspid (systolic pulmonary arterial pressure) or across the pulmonary valve (diastolic pulmonary arterial pressure) using the modified Bernoulli equation (4, 5, 6).

The severity of PAH is classified as mild, moderate, and severe based on the estimated pulmonary arterial pressure, with slight variations in cut off values among reports, in dogs affected by cardiovascular diseases (6, 7, 8).

PAH may occur through three mechanisms: increased left atrial pressure, increased pulmonary blood flow, and increased pulmonary vascular resistance. The pathophysiology of PAH is multifactorial and results from an imbalance of endogenous and exogenous pulmonary artery vasodilators and vasoconstrictors; this disequilibrium causes vasoconstriction, vascular smooth muscle cell proliferation and thrombosis, leading to an increased pulmonary vascular resistance in PAH (9, 10).

In people, chronic obstructive airway disease is one of the most common pulmonary causes of PAH (11). Chronic obstructive airway disease may

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decrease the partial pressure of alveolar oxygen, which can result in hypoxia. In contrast to the systemic vasculature, which responds to hypoxia with vasodilatation to better perfuse hypoxic tissue, the pulmonary vasculature responds to hypoxia by pulmonic arterial vasoconstriction, which subsequently increases the pulmonary pressure (6). Few data is available on the PAH prevalence in dogs, except for selected conditions such as canine heartworm disease, left-sided heart failure and *Angiostrongylus vasorum* infection (12, 13, 14, 15, 16, 17)

Recently, some authors evidenced an association of pulmonary hypertension and increase serum CRP (C-reactive protein) concentrations in dogs affected by heartworm disease (12). Interestingly, the CRP concentration relates to the severity of endothelial arteritis, and not as a result of heartworm disease itself (12). The CRP concentration was still high even following adulticide treatment, and this underlined the possibility that CRP may be used as an early biomarker of pulmonary hypertension (12).

In veterinary medicine, lung disease, such as chronic pneumonia and lung fibrosis, chronic bronchitis, bronchiectasis, and upper respiratory disease such as tracheal collapse and laryngeal paralysis, have been associated with sustained or intermittent hypoxia and subsequent PAH development (10). PAH in dogs occurs mostly in patients with very advanced disease or those with predisposing conditions (9, 10). However, there are no known studies assessing the prevalence of PAH in dogs with bronchial and/or upper respiratory disease. The aim of this study was to assess the prevalence of PAH in dogs with bronchial and/or upper respiratory disease.

## MATERIAL AND METHODS

The medical records of 1,063 dogs referred for cardiovascular investigation at the Cardiology Unit of the Department of Veterinary Science and Public Health between January 2009 and May 2013 were retrospectively reviewed. Only first visit cases were included in the study.

Inclusion criteria were: complete clinical records, radiographic, echocardiographic, a confirmed diagnosis by endoscopic examination of bronchial and/or upper respiratory disease and negative *Dirofilaria immitis* antigen test.

Exclusion criteria were: any cardiac and/or systemic disease that may cause PAH, except for mild mitral valve disease; diagnosis of *Angiostrongylus vasorum*, achieved using a Baermann faecal test performed at a veterinary diagnostic laboratory, or by detection of L1 larvae on a direct faecal smear or

bronchoalveolar lavage sample by a trained operator. The signalment, clinical history, and clinical signs (cough, dyspnoea, syncope, asthenia, weight loss, snoring, and reverse sneezing) were recorded.

Echocardiography was performed using an ultrasound system (MyLab 50, ESAOTE, Florence, Italy) equipped with a phased array transducer (7.5–10 MHz for small dogs, 5–7.5 MHz for medium dogs, and 2.5–3 MHz for large dogs and Doppler studies). Examinations were performed in awake dogs in left and right lateral recumbency, as recommended by the American Society of Echocardiography (18).

### *Echocardiographic and Doppler Examinations*

The following echocardiographic parameters were evaluated:

#### *B- and M- modes*

1. Presence/absence of RV hypertrophy and/or dilation in the right parasternal long axis 4-chamber and short axis views at the level of the papillary muscle. The RV wall thickness was considered increased (RV hypertrophy) if it was greater than half the thickness of the left ventricular free wall (1). The RV chamber size was considered normal if it was smaller than or equal to one-half of the left ventricular thickness, mildly enlarged if greater than or equal to one-half the left ventricular thickness, or severely enlarged if greater than the left ventricle (5).

2. Presence/absence of flat or paradoxical interventricular septal motion in the right parasternal short axis and/or in M-mode at the level of the papillary muscle (10).

3. Presence/absence of main pulmonary artery enlargement based on the ratio between the diameters of the main pulmonary artery and the aorta (PA:AO ratio): a ratio greater than 0.98 was considered enlarged (1).

#### *Doppler*

1. Presence/absence of tricuspid regurgitation (TR): the TR systolic peak velocity (m/s) and peak systolic gradient (mmHg) were measured when present.

2. Presence/absence of pulmonic insufficiency (PI): the PI diastolic peak velocity (m/s) and peak diastolic gradient (mmHg) were measured when present. The presence and severity of PI were assessed through colour flow mapping, and the extension of the regurgitation jet and its width at the origin were evaluated (20).

3. Pulmonary artery systolic flow profiles: Type I (normal) was defined as a symmetric profile and

a rounded systolic peak; type II (mild and moderate PAH) as a peak velocity occurring during early systole and a long deceleration phase (asymmetric profile); and type III (severe PAH) was defined as having a notch in the deceleration phase (1).

4. Systolic time intervals: The acceleration time (AT), defined as the time to peak pulmonary artery flow velocity; RV ejection time (ET); and AT:ET ratio were assessed (21).

Doppler flow interrogations of the TR and PI jets were used to estimate the systolic and diastolic pulmonary arterial pressure respectively, allowing diagnosis and quantification of PAH (10). PAH was diagnosed when the TR systolic peak velocity (m/s) was greater than 2.8 m/s; the TR systolic peak velocity (m/s) and peak systolic gradient (mmHg) were used to classify the PAH severity (Table 1) (1, 4). The presence of PI with a velocity >2.2 m/s was considered suggestive of diastolic PAH (1, 4).

### Statistical analysis

The Shapiro–Wilk test was used to verify normal distribution. Normally distributed data were expressed as the mean  $\pm$  standard deviation. For data not normally distributed, the median and interquartile (IQR (25<sup>th</sup> to 75<sup>th</sup> percentile)) were calculated. Data were analyzed using statistical software (JMP version 7, JMP Headquarters, SAS Institute, Cary, NC, USA 27513).

## RESULTS

Fifty-two clinical records fulfilled the inclusion criteria (35 males and 17 females), and represented 4.9 % of the total referral patients seen at the Cardiology Unit of the Department of Veterinary Science and Public Health between January 2009 and May 2013. Fourteen breeds were represented: 10 English Bulldogs (19%) resulted the prevalent,

**Table 1.** Classification of pulmonary hypertension based on TR (tricuspid regurgitation) peak systolic velocity and TR gradient <sup>(1)</sup>. (TR: tricuspid regurgitation)

	Mild	Moderate	Severe
TR peak systolic velocity (m/s)	> 2.8 to < 3.5	3.5 - 4.3	> 4.3
TR systolic gradient (mmHg)	> 31.4 a < 50	50 - 75	> 75

If TR/PI were absent, then PAH was considered possible when two or more of the following echocardiographic findings were recorded:

1. Presence of RV hypertrophy and/or dilation (5, 19)
2. Presence of main pulmonary artery enlargement (PA:AO ratio > 0.98) (1)
3. Presence of type II or III pulmonary artery systolic flow profile (1)
4. AT:ET < 0.31 and/or AT < 58 ms (21)

### Endoscopic examination

Endoscopy was performed using either a rigid instrument equipped with a 18-cm optical length, 2.7-mm thickness (Karl Storz Hopkins II, Dr. Karl-Storz-Straße 34 Tuttlingen, Germany), 1-ccd camera (Wolf Endocam 551, Pforzheimer-Straße 32, 75438 Knittlingen, Germany), and xenon light source (Storz Xenon Nova 20131520, Dr. Karl-Storz-Straße 34 Tuttlingen, Germany) for examination of the nasal cavity, or a flexible video endoscope (4.9-mm diameter and 2-mm channel size, Fujinon Videobronchoscope EB-270 S7-3, Akasaka 9-chome, Minato-ku, Tokyo 107-0052, Japan) for examination of other respiratory airways.

7 males (70%) and 3 females (3%), followed by 8 crossbreeds dogs (15%), 5 males (62.5%) and 3 females (37.5%), 8 French Bulldogs (15%), 7 males (87.5%) and 1 female (12.5%) and 6 Yorkshire Terriers (11%), 2 males (33.3%) and 4 females (66.6%). The age ranged from 0.8 to 16 years (median 7 years; IQR: 3–12.25 years) and the weight from 2 to 40 kg (median 12 kg; IQR: 7.35–18 kg). All dogs showed at least one clinical sign: cough (50.1%), dyspnoea (50.1%), snoring (30.1%), exercise intolerance (15%), weight loss (9.4%), reverse sneeze (5.2%), and syncope (5.6%). Twenty-eight dogs (54%) showed more than one clinical sign simultaneously. The most common associations of symptoms were cough, dyspnoea and exercise intolerance (10.7%), cough and dyspnoea (21.4%), dyspnoea and snoring (10.7%).

### Endoscopic examination

Seventeen dogs (33%; 8 females and 9 males) were diagnosed with bronchial disease (9 chronic bronchitis, 6 chronic bronchitis and bronchial collapse, 2 bronchial collapse). The prevalence on the total population referred was 1.6 %. Crossbreed dogs were the most represented (39%); the age

**Table 2.** Signalment, clinical signs, echocardiographic and Doppler data, PAH severity and endoscopic diagnosis of 5 dogs affected by PAH. (F: female; M: male; TR: tricuspid regurgitation)

	Breed	Sex	Age (years)	Clinical signs	TR peak velocity (m/s)	TR Gradient (mmHg)	Right ventricular hypertrophy/dilation	Pulmonary artery profiles	PAH	Bronchial Upper Respiratory Diseases	Endoscopic diagnosis
1	Poodle	M	11	Dyspnea	3.76	56.60	-	Normal	Moderate	Upper Respiratory Diseases	Laryngeal collapse and paralysis
2	Crossbreed	F	11	Cough and dyspnea	4.02	64.60	Mild	Normal	Moderate	Upper Respiratory Diseases	Tracheal collapse
3	French Bulldog	M	7	Weight loss	2.99	35.7	Mild	Normal	Mild	Upper Respiratory Diseases	Palatal disease
4	Yorkshire Terrier	F	5	Cough	-	-	Mild	Type II	Possible	Upper Respiratory Diseases	Tracheal collapse
5	Poodle	F	12	Cough	-	-	Mild	Type II	Possible	Bronchial Diseases	Chronic bronchitis

ranged from 1 to 15 years (median 12 years ; IQR: 11–13 years) and the weight from 3 to 16 kg (median 8 kg; IQR: 4–13.25 kg).

Thirty dogs (56.6%; 8 females and 22 males) were diagnosed with upper respiratory disease. Twenty-one of them resulted affected by brachycephalic airway obstructive syndrome (BAOS) (70 %; 5 female and 16 male), 3 by laryngeal paralysis, 2 by tracheal collapse, and 1 by laryngeal collapse; 3 dogs exhibited multiple upper respiratory disease simultaneously. The prevalence on the total population referred was 2.8 %. The most represented breeds were English and French Bulldogs (57%). The age ranged from 0.8 to 16 years (median 3.5 years; IQR: 3–10.25 years), and the weight ranged from 2 to 40 kg (median 13.85 kg; IQR: 10–21 kg). In the BAOS group specifically, the age ranged from 0.11 to 12 years (median 3 years; IQR: 2–4 years) and the weight from 8 to 26 kg (median 14 kg; IQR: 12–21 kg). Five dogs (9.5%; 1 female and 4 males), exhibited upper respiratory disease and bronchial disease simultaneously, 0.5 % the prevalence of this group on the total population referred to the Cardiology Unit during the study time.

#### *Echocardiographic data*

Mild RV enlargement was found in 4 dogs (7.5%) and mild RV hypertrophy in 2 dogs (3.8%).

One dog (1.9%) exhibited both RV hypertrophy and dilation simultaneously. No dog presented flat or paradoxical interventricular septal motion or main pulmonary artery enlargement.

TR was observed in 15 dogs (29%). The TR peak systolic velocity ranged from 1.51 m/s to 4.02 m/s (mean  $2.62 \pm 0.71$  m/s), and the TR systolic gradient ranged from 9.10 mmHg to 64.60 mmHg (median 23.90 mmHg; IQR: 17.88–30.15 mmHg).

No dog showed pulmonary insufficiency. Type II pulmonary artery systolic flow profile was found in 2 dogs (3.8%) and was associated with mild RV hypertrophy in both. No dog presented an AT: ET ratio equal to or less than 0.31, and none exhibited an AT equal to or less than 58 ms. The mean AT: ET ratio was  $0.48 \pm 0.04$ , and the mean AT was  $83.08 \pm 14.24$  ms.

PAH was diagnosed in 3 dogs (5.7%) based on a TR peak systolic velocity  $>2.8$  m/s. All three dogs were diagnosed with upper respiratory disease; therefore, the prevalence of PAH in this subgroup was 10%. Two dogs (one with bronchial disease and one with upper respiratory pathology) were considered likely to have PAH based on the presence of secondary specific echocardiographic findings. A total of 5 dogs (9.4%) had confirmed or probable PAH (Table 2), the prevalence in the overall referral population being 0.5 % and 1 % of dogs with valvular disease.

## DISCUSSION

PAH is a well-recognized clinical condition in humans. Conversely, few data are available in dogs, except for PAH secondary to canine heartworm disease, mitral valve disease and *Angiostrongylus vasorum* infection (1, 6, 8, 9, 14, 15,16, 17, 22, 23, 24). The degree of hypoxia that can cause PAH likely exists in a large number of dogs with both upper and lower airway obstructive diseases (9). In particular, lung disease, such as chronic pneumonia, lung fibrosis, chronic bronchitis, bronchiectasis, and upper respiratory pathologies, such as tracheal collapse and laryngeal paralysis, have been associated with sustained or intermittent hypoxia and have been thought as theoretically causing PAH (5, 9, 10). Nevertheless, there are no known studies assessing the prevalence of PAH in dogs with respiratory disease, except for one study of West Highland White terriers, in which PAH occurred in more than 49% of dogs diagnosed with chronic interstitial pulmonary disease (19).

In humans, the prevalence of PAH in patients with at least one previous hospitalization for exacerbation of respiratory failure is 20%, and in patients with advanced respiratory disease, the prevalence is higher (>50%), although the severity is usually mild (2). In our population, the prevalence of PAH in dogs with bronchial and/or upper respiratory diseases associated with potential hypoxia was low (5 dogs, 9.4%), even when both confirmed and possible PAH cases were considered, or very low (3 dogs, 5.7%) when only PAH diagnosed by TR velocity was considered. All 3 dogs with confirmed PAH were diagnosed with upper respiratory disease; therefore, the occurrence of PAH in this disease category was slightly high (3/30, 10%). Only mild and moderate PAH was identified.

In dogs with upper respiratory disease, PAH or possible PAH was diagnosed in 2 dogs with tracheal collapse, 1 dog with laryngeal collapse and paralysis, and 1 dog with BAOS (Table 2). Three of four dogs were older than the median age for the group (3.5 years); the only young dog showed echocardiographic signs of possible PAH and was diagnosed with very severe cervical tracheal collapse (Table 2). The occurrence of PAH in dogs with BAOS was also very low (1/21), though most of the dogs included in the study were young (median age 3 years). Interestingly, the only dog with BAOS (Table 2) diagnosed with PAH was older (7 years) than the rest of dogs with BAOS included in this study. Based on these results, we speculate that early surgical correction may be protective from PAH, but further studies are needed to confirm this hypothesis.

In our cases series, only one dog with bronchial disease presented echocardiographic signs suggesting possible PAH, and no dog with bronchial disease exhibited PAH. We found these data relatively surprising because chronic hypoxemia and increased airway resistance have been described as common findings in patients with advanced chronic bronchitis, and cor pulmonale is considered a possible consequence (25). The low occurrence of PAH in dogs with bronchial disease and in all dogs in our study may be due to the relatively poor vasoconstrictive response to hypoxia exhibited by dogs compared with other species (9, 10). Canine PAH seems to occur mostly during very advanced respiratory disease, as described in West Highland White terriers and suggested by several reports (9, 21).

Based on our results, we recommend an echocardiographic investigation only in older dogs with bronchial and/or upper respiratory disease or in dogs with advanced disease regardless of age. Echocardiographic and spectral Doppler assessments of tricuspid and pulmonic regurgitation are useful tool in this group of patients especially when utilized as a part of comprehensive assessment of PAH, and may supplement the methods traditionally used to investigate the respiratory system in canine patients (3, 26).

Diagnosis of PAH was based only on echocardiographic data: a TR systolic peak velocity greater than 2.8 m/s, a PI diastolic peak velocity greater than 2.2 m/s, the presence of a type II or III pulmonary artery systolic flow profile, and the presence of RV hypertrophy/dilation (4). Pulmonary hypertension was then classified as mild, moderate, and severe based on the tricuspid regurgitation peak systolic velocity and gradient. None of the dogs exhibited severe PAH; two dogs had moderate PAH, one mild, and two possible PAH. Potentially, some cases of PAH in our study population may have been undetectable using echocardiography (3). Cardiac catheterization is the “gold standard” to diagnose PAH, but in veterinary medicine, right heart catheterization is often considered unacceptably invasive by the clinician in a compromised patient, therefore the echocardiographic and spectral Doppler approach remains very common in clinical practice (3). When available however, catheterization enables measurement of multiple hemodynamic parameters that assist in the diagnosis and etiologic classification of PAH (1).

None of the dogs exhibited flat or paradoxical interventricular septal motion, main pulmonary artery enlargement, an AT: ET  $\leq$  0.31, or an AT  $\leq$  58 ms. These findings may be because very few dogs were diagnosed with PAH, and when present, PAH was

mild or moderate, with no cases of severe PAH diagnosed. A median AT:ET of 0.48 and a median AT of 83 ms suggested a normal pulmonary pressure in the population and agree with previously reported values in healthy West Highland White terriers, which had a median AT:ET of 0.40 and a median AT of 73 ms (21).

None of the dogs with PAH presented syncope or exercise intolerance. The dogs with PAH included in our study only showed respiratory signs, with cough and dyspnoea as the most common clinical signs. These particular clinical signs likely reflect the underlying bronchial and/or upper respiratory disease causing PAH.

The epidemiological characteristics of our population agree with those previously reported, namely young English and French Bulldogs with BAOS, older large breed dogs (Labrador and Setter) with laryngeal paralysis, Yorkshire Terrier, typically middle-aged, with tracheal collapse, and older small breed dogs with chronic bronchitis (5, 27, 28, 29, 30).

This study has a number of limitations as a result of its retrospective nature. We only used non-invasive diagnostic approaches, and cardiac catheterization was not performed. PAH was diagnosed based only on certain echocardiographic and Doppler parameters (TR systolic peak velocity greater than 2.8 m/s, PI diastolic peak velocity greater than 2.2 m/s, presence of a type II or III pulmonary artery systolic flow profile, and presence of RV hypertrophy/dilation), and several parameters were not measured, including the TEI index and TAPSE (tricuspid annular plane systolic excursion). Moreover the lack of arterial blood-gas data could be an additional weakness in this study. Only cases with endoscopic diagnosis of bronchial and/or upper respiratory diseases were included; no parenchymal diseases, nor pleural diseases were included in our study.

Finally, most of the dogs diagnosed with BAOS were young and West Highland White terriers, a breed predisposed to PAH secondary to severe lung disease, was not included in the study (21). In conclusion, our study shows that the occurrence of PAH in dogs with bronchial and/or upper respiratory disease is low; PAH seems to occur mostly in older dogs or those with very advanced disease. The echocardiographic and spectral Doppler assessments of tricuspid and pulmonic regurgitation are useful tool in these classes of patients. Nevertheless, further prospective studies including different subsets of pathologies, clinical settings (acute vs chronic), disease severity (mild/moderate/severe) and the evaluation of clinical biomarkers (i.e. C-reactive protein) are needed to confirm these results.

### *Ethical approval*

All applicable international, national, and institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted. For this type of study, formal consent was not required.

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