

Pulmonary Hypertension in Dogs: Diagnosis and Therapy

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KEYWORDS

- Sildenafil • Pulmonary disease • Syncope • Heart disease
- Echocardiographic • Right heart catheterization

*“You see only what you look for. You recognize only what you know.”
—Merril C. Sosman*

In the veterinary literature, pulmonary hypertension (PH) has been echocardiographically defined as pulmonary arterial systolic pressure greater than approximately 30 mm Hg.^{1–6} PH is a complex syndrome that has historically resulted in a poor prognosis. Pulmonary arterial pressure (PAP) is influenced by pulmonary blood flow, pulmonary vascular resistance (PVR), and pulmonary venous pressure. The elevated PAP of the syndrome of PH may be caused by pulmonary vascular abnormalities associated with increased blood flow (ie, “hyperkinetic” PH secondary to a patent ductus arteriosus), changes affecting resistance to flow (precapillary pulmonary arterial hypertension, PAH) or caused by increased “downstream” resistance (post-capillary pulmonary venous hypertension, PVH). Pulmonary arterial hypertension has a multifactorial pathophysiology that results from the imbalance of endogenous and exogenous pulmonary artery (PA) vasodilators and vasoconstrictors, ultimately resulting in vasoconstriction, vascular smooth-muscle-cell proliferation, and thrombosis. Diagnosis of PH requires diagnostic testing that quantifies the degree of elevation of PAP, determines the underlying disease process if possible, and identifies the degree of hemodynamic impairment. Significant advances in therapy that target the derangements of the PH pathophysiology have been made in animals and people, providing an improved prognosis for survival and better quality of life.

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CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension can be classified as pre- or postcapillary PH, or can be classified based on the disease process causing PH. The categories include pulmonary arterial hypertension, pulmonary venous hypertension, hypoxic PH, PH secondary to respiratory disease, PH secondary to thromboembolic disease, and PH secondary to miscellaneous etiologies (**Table 1**).^{1–36} The etiology of PH may affect therapeutic choices, as some causes of PH can be rectified (eg, patent ductus arteriosus occlusion), thereby eliminating the PH.

There have been a limited number of published studies that evaluated naturally occurring PH in dogs. Previous investigators have described PH in specific canine hospital populations (**Table 2**).^{1,3,4,6,13} Left-sided heart disease is a common cause of PH in dogs in these studies. Pulmonary hypertension secondary to left-sided heart disease occurs from elevated left atrial pressure (pulmonary venous hypertension) and may be compounded by reactive PA vasoconstriction occurring in response to hypoxia from pulmonary edema if severe left heart failure is present. In contrast to the systemic vasculature that responds to hypoxia with vasodilation to better perfuse

Table 1

Classification of pulmonary hypertension with mechanisms indicated

1. Pulmonary Arterial Hypertension
 - Heartworm disease (↑PVRI)
 - Congenital systemic-to-pulmonary shunts (↑PA blood flow)
 - Atrial septal defect (ASD)
 - Ventricular septal defect (VSD)
 - Patent ductus arteriosus (PDA)
 - Idiopathic
 - Necrotising vasculitis/arteritis

2. Pulmonary Hypertension with Left Heart Disease (↑pulmonary venous pressure)
 - Mitral valve disease
 - Myocardial disease
 - Miscellaneous left-sided heart diseases

3. Pulmonary Hypertension with Pulmonary Disease or Hypoxia (↑PVRI)
 - Chronic obstructive pulmonary disease
 - Interstitial pulmonary fibrosis
 - Neoplasia
 - High-altitude disease
 - Reactive pulmonary artery vasoconstriction (eg, hypoxia owing to pulmonary edema)

4. Pulmonary Hypertension owing to Thrombotic and/or Embolic Disease (↑PVRI)
 - Thromboembolism
 - Immune-mediated hemolytic anemia
 - Neoplasia
 - Cardiac disease
 - Protein-losing disease (nephropathy or enteropathy)
 - Hyperadrenocorticism
 - Disseminated intravascular coagulation
 - Sepsis
 - Trauma
 - Recent surgery
 - Heartworm disease

5. Miscellaneous
 - Compressive mass lesions (neoplasia, granuloma)

Abbreviations: PA, pulmonary artery; PVRI, pulmonary vascular resistance index.

Table 2
Diseases associated with canine pulmonary hypertension in clinical canine populations (references noted)

	Johnson 1999 ³ N = 53	Pyle 2004 ⁵ N = 54	Bach 2006 ⁴ N = 13	Kellum 2007 ¹ N = 22	Serres 2007 ¹³ N = 60
Left-sided heart disease	23 (43%)	24 (44%)	1 (8%)	9 (41%)	51 (85%)
Pulmonary disease	12 (23%)	22 (41%)	5 (38%)	11 (50%)	7 (12%)
Pulmonary overcirculation (ie, left to right cardiovascular shunts)	2 (4%)	1 (2%)	1 (8%)	2 (9%)	0
Heartworm disease	5 (9%)	3 (6%)	0	0	0
Pulmonary thromboembolism	5 (9%)	2 (4%)	1 (8%)	0	1 (2%)
Miscellaneous	6 (11%)	2 (4%)	5 (38%)	0	1 (2%)

hypoxic tissue, the pulmonary vasculature responds to hypoxia by pulmonary artery vasoconstriction. Presumably, pulmonary arteries constrict to divert blood from diseased lung and preserve arterial oxygen content. In studies of dogs with mitral valve disease, prevalence of PH has been reported to be as low as 14% and as high as 31%.^{14,37}

SIGNALMENT AND CLINICAL SIGNS

With the exception of dogs with PH related to congenital heart diseases, the populations of dogs that have been reported with PH are of smaller breeds and typically middle-aged to older; this distribution may reflect the predisposition of older small-breed dogs for mitral valve disease and chronic pulmonary conditions.^{1,3,4,6,13} The clinical history of dogs with symptomatic PH typically includes combinations of cough, dyspnea, lethargy, syncope or collapse episodes, exercise intolerance, or reported heart murmurs or abdominal distension (ascites).^{1,3-6,12-16,21-23,25,31-33,35,36,38,39} These clinical signs may be caused by the elevated pulmonary pressures or reflect the underlying disease that led to PH (eg, chronic obstructive pulmonary disease [COPD]).

PHYSICAL EXAMINATION

Physical examination findings associated with PH in dogs are variable and again may reflect elevated pulmonary arterial pressure, the underlying disease condition, or a combination of the two. Typical physical examination abnormalities include heart murmurs of mitral and/or tricuspid insufficiency, split or abnormally loud second heart sounds, pulmonary crackles, increased bronchovesicular pulmonary sounds, cyanosis, and ascites.^{1,3,5,6,14,16,23,25,30,36} In most cases, detection of these physical examination findings in patients with typical historical presentations leads the clinician to suspect PH as a clinical diagnosis, but confirmation of PH requires further diagnostic testing.

DIAGNOSIS

The goals of diagnostic testing in the syndrome of PH are to identify the underlying etiology or etiologies resulting in PH (ie, classification), to quantify the degree of PH, to assess evidence of hemodynamic impairment, and to assist in patient prognostication. Right heart catheterization is the most accurate method of diagnosing PH but is often unavailable for routine clinical use. Ancillary testing, including thoracic radiography, electrocardiography, and measurement of biomarkers may provide supportive

evidence for PH and information about concurrent or causative diseases in an individual patient. Two-dimensional and echocardiographic examinations provide the diagnosis in most clinical veterinary patients.

Right Heart Catheterization

Right heart catheterization is the gold standard for diagnosing PH. In clinical veterinary medicine the right heart catheterization procedure may be considered unacceptably invasive in a compromised patient, but when available, provides multiple hemodynamic parameters that assist in the diagnosis and etiologic classification of PH. Introduction of a hemodynamic catheter into the right atrium, right ventricle, and main pulmonary artery provides hemodynamic information regarding the presence and degree of PH as well as information regarding the function of the right heart (eg, elevated end diastolic right ventricular pressures may indicate right ventricular systolic or diastolic impairment). The systolic, diastolic, and mean PAPs can be measured directly, and the pulmonary arterial wedge pressure (PAWP) can be measured to detect elevated pulmonary venous pressures.

In veterinary patients, the systolic PAP is often used to quantify the degree of PH because this value can also be estimated by noninvasive methods (Doppler echocardiography, see Echocardiography, later). Invasively measured mean PAP and PAWP can be used to calculate the PVR index (PVRI, per m^2), a measure of the vascular resistance to pulmonary blood flow that can assist in distinguishing precapillary (attributable to pulmonary vascular disease) from postcapillary (attributable to pulmonary venous hypertension) PH (**Table 3**).⁴⁰ PVRI is calculated according to the following equation and expressed as $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}/m^2$:

$$\text{PVRI} = [\text{PAPm} - \text{PAWP}] \times 80/\text{CI},$$

where PAPm indicates mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; and CI, cardiac index.

The definition of pulmonary arterial hypertension (precapillary, elevated PAP with normal left atrial pressure, usually seen in pulmonary vascular diseases) is increased PAPm, increased PVRI, and normal PAWP. The definition of pulmonary venous hypertension (postcapillary, elevated PAP with elevated left atrial pressure, usually seen with left heart disease) is increased PAPm, increased PAWP, and normal PVRI. When reactive precapillary PAH (eg, attributable to hypoxia from pulmonary edema) there is increased PAPm, increased PAWP, and increased PVRI (see **Table 3**).⁴¹

Table 3 Invasive hemodynamic definitions of pulmonary hypertension		
Definition	Characteristics	Clinical Group(s)
Pulmonary hypertension	↑ PAP	All
Precapillary PH (pulmonary arterial hypertension)	↑ PAP ↑ PVRI Normal PAWP	Pulmonary arterial hypertension (class 1) PH secondary to pulmonary disease or hypoxia (class 3) PH secondary to thromboembolic disease (class 4)
Postcapillary PH (pulmonary venous hypertension)	↑ PAP Normal PVRI ↑ PAWP	PH secondary to left-sided heart disease (class 2)

When noted, classes are as indicated in **Table 1**.

Abbreviations: PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVRI, pulmonary vascular resistance index.

Thoracic Radiography

Pulmonary hypertension cannot be diagnosed based on thoracic radiographic findings alone, but radiographic findings suggestive or supportive of PH include pulmonary artery enlargement, pulmonary infiltrates, right-heart enlargement, pulmonary arterial tortuosity, and the pulmonary arterial “pruning” associated with heartworm (HW) disease. Conversely, in some severe cases of PH, the radiographic abnormalities may be minimal (**Fig. 1**). Often, the thoracic radiographic findings are complicated by underlying cardiopulmonary disease; these findings may help in determining the underlying etiology of the PH (ie, left-heart disease, patent ductus arteriosus [PDA], pulmonary neoplasia).

Electrocardiogram

Electrocardiographic findings are often normal in patients with pulmonary hypertension, but findings supportive of a diagnosis of PH include right axis deviation or other evidence of right-heart enlargement (**Fig. 2**). The electrocardiographic findings may also represent changes that have occurred secondary to the underlying disease process (ie, supraventricular or ventricular arrhythmias associated with left-sided cardiac disease, bradyarrhythmias and atrioventricular blocks associated with increased parasympathic tone seen in pulmonary disease).

Biomarkers

NT-proBNP (N-terminal-pro-B-type natriuretic peptide), a peptide released by ventricular myocardium under circumstances of stress or strain, appears to have some potential in aiding in the diagnosis of PH. Typically, NT-proBNP has been used to discriminate between cardiac and respiratory disease in dogs.⁴² In people, NT-proBNP is elevated in the presence of precapillary PH, and it has been used to stratify disease severity, monitor response to treatment, and serve as a prognostic parameter.^{43–45} NT-proBNP measurements were found to be higher in canine clinical patients with precapillary PH than in normal dogs, and moderate to severe and severe PH resulted in higher NT-proBNP concentrations versus dogs with no or mild PH (Heidi B. Kellihan, DVM, unpublished data, Madison, WI, June 2009). There was

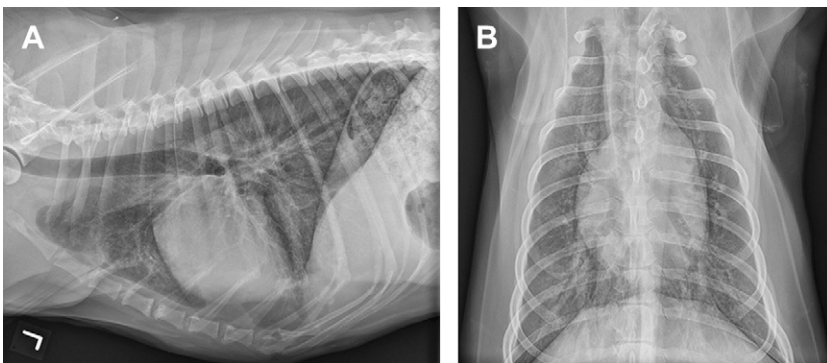


Fig. 1. Thoracic radiographs. Lateral (A) and ventral dorsal (B) thoracic radiographs from a dog with severe PH secondary to presumed pulmonary fibrosis. The cardiac silhouette and pulmonary vessels are normal in size and shape despite the presence of significant PH (systolic PAP estimated at 86 mm Hg). Interstitial to alveolar infiltrates cranial and caudal to the cardiac silhouette reflect the presence of chronic pulmonary disease.

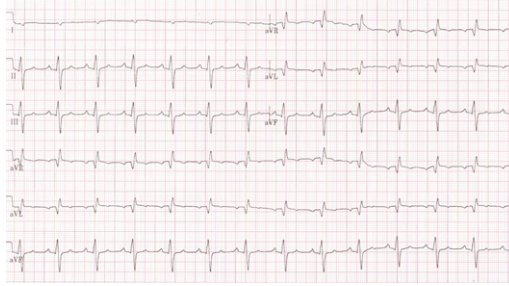


Fig. 2. Electrocardiogram. Electrocardiogram from a dog with severe PH secondary to a large thrombus in the main pulmonary artery. Right axis deviation consistent with right heart enlargement is present: 50 mm/s, 0.5 cm: 1 mV.

a strong positive correlation between the measured tricuspid regurgitation (TR) peak systolic gradient (estimated systolic pulmonary artery pressure) and NT-proBNP concentrations ($r = 0.89$, $P = .0005$) (Heidi B. Kellihan, DVM, unpublished data, Madison, WI, June 2009).

Echocardiography

Echocardiography is the standard, noninvasive method of diagnosing PH in clinical veterinary patients. Multiple echocardiographic modalities, including 2-dimensional imaging, Doppler flow examinations, and tissue Doppler examinations offer complementary information in the diagnosis of PH. Doppler flow interrogations of tricuspid insufficiency and pulmonary insufficiency jets provide estimates of systolic and diastolic PAP pressure respectively, allowing diagnosis and quantification of PH. Tissue Doppler imaging has been used to detect elevated PAP based on right ventricular myocardial movement.¹³ Echocardiographic examination can be used to detect PH-related right-sided cardiac abnormalities, such as main pulmonary artery enlargement, functional changes, through the use of systolic time intervals, and concurrent left-sided heart disease. Two-dimensional echocardiography also allows identification of related disease findings such as thrombi or, occasionally, heartworms. Clinical signs such as respiratory distress may interfere with examination and limit the quality of individual echocardiographic recordings; the use of multiple echocardiographic imaging modalities for diagnosis is recommended to identify the maximum number of “supportive” findings in patients in whom direct estimation of PAP via Doppler flow interrogation is not possible.

Tricuspid regurgitation

In the absence of right ventricular outflow tract obstruction, right ventricular and pulmonary artery pressures are equivalent during systole and quantitative assessment of a TR jet provides an estimate of systolic PAP. The tricuspid transvalvular pressure gradient is estimated using the peak TR velocity (m/sec) in the modified Bernoulli equation (pressure gradient = $4 * [\text{peak flow velocity}]^2$). This estimated pressure difference approximates the systolic PAP (**Fig. 3**). The TR systolic peak velocity and resulting estimated right ventricular systolic pressure is used to classify PH severity (**Table 4**).^{1,3,5} In people, there is conflicting evidence as to the correlation of noninvasive TR gradient-derived estimations of PAP to invasively measured systolic PAP obtained by right heart catheterization.^{46,47} The addition of estimated right atrial pressures to the measured TR peak gradient is performed by some investigators, and is

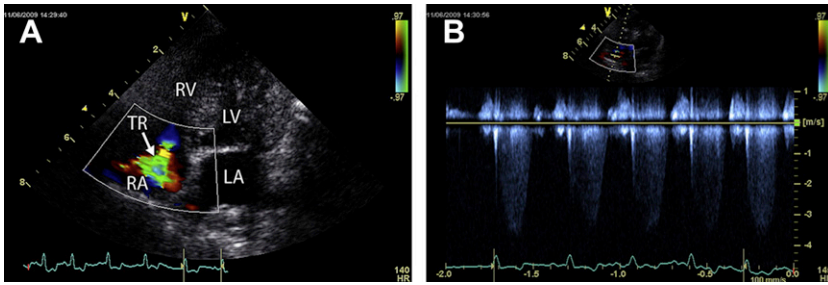


Fig. 3. Tricuspid regurgitation. Doppler echocardiographic images from a dog with moderate pulmonary hypertension secondary to presumed pulmonary fibrosis. (A) Color Doppler map of tricuspid regurgitation (TR). The TR flow is from the higher pressure right ventricle (RV) to the lower pressure right atrium (RA). The left ventricle (LV) and left atrium (LA) are also labeled. Image obtained from the left apical 4-chamber view. (B) Spectral Doppler trace of TR. Tricuspid systolic velocity of approximately 3.7 m/s, indicating a peak tricuspid gradient of approximately 54 mm Hg (moderate pulmonary hypertension). Velocities were recorded from the left apical 4-chamber view.

believed by some investigators to provide a more accurate assessment of PH.^{5,46} More recent human data suggest that the addition of estimated right arterial (RA) pressure may lead to overestimation of PH severity, and confirmed that inaccurate TR jet velocity measurement (related to poor signal strength or poor jet alignment) leads to underestimation of PAP.⁴⁷ Difficulty obtaining an optimal peak systolic TR measurement is common in clinical patients and may be attributable to poor patient compliance with the echocardiographic procedure, poor image quality secondary to pulmonary disease/dyspnea, or poor jet alignment with the Doppler interrogation beam. Tricuspid insufficiency jet peak velocity is also affected by right ventricular function; in cases where right ventricular myocardial failure is present, PAPs assessed by echocardiography may inadequately reflect the severity of pulmonary vascular disease because of the inability of the right ventricular (RV) myocardium to generate high pressures.⁸ Some patients with PH do not have identifiable TR and other findings (eg, pulmonary insufficiency peak velocity) must be used to identify elevated PAP. Peak TR systolic velocity gradients are the most frequently used echocardiographic surrogate for PAP in clinical patients, but the situational limitations of such estimates must be kept in mind during examination, and additional supportive information sought when a diagnosis of PH is contemplated.

Pulmonic insufficiency

The presence of pulmonic insufficiency (PI) allows for the quantitative assessment of estimated diastolic PAP. Pulmonic insufficiency occurs in diastole and allows estimation of the PA-to-RV pressure difference. Similar to TR measurements, the velocity of

Table 4
Pulmonary hypertension severity grading system based on peak tricuspid regurgitation velocity and associated TR gradient

	Mild	Moderate	Severe
TR peak systolic velocity (m/s)	≥ 2.8 to < 3.5	3.5–4.3	>4.3
TR systolic gradient (mm Hg)	≥ 31.4 to < 50	50–75	>75

Abbreviation: TR, tricuspid regurgitation.

the PI jet (m/s) is used to calculate the gradient (mm Hg) using the modified Bernoulli equation. This echocardiographic measurement is especially helpful in diagnosing PH if TR is not present. A PI velocity 2.2 m/s or more or a gradient of 19 mm Hg or higher is elevated and suggestive of PH (Fig. 4).¹

Pulmonary artery systolic flow profiles

Scrutiny of PA systolic flow profiles has been used in people and dogs to estimate the severity of PH.^{1,3,5,13,22,26,35,41,48,49} Pulmonary artery systolic flow profiles are obtained by measuring the PA blood flow with pulse wave Doppler immediately after the pulmonic valve in the PA. Type I PA flow (considered to be normal) is relatively symmetric in appearance, with the peak velocity occurring close to the middle of the envelope with relatively equal acceleration and deceleration times. Type II PA flow profile is typically associated with mild and moderate PH and is characterized by a peak velocity occurring earlier in systole with a longer deceleration phase. A Type III PA flow profile is associated with more severe PH. The pattern is similar to Type II but there is a “notch” in the deceleration phase, thought to be caused by flow reversal (Fig. 5). Although identifiable PA flow patterns may aid in the diagnosis of PH, it is often difficult to obtain “clean” signals in dyspneic clinical patients.

Tei index of myocardial performance of the right ventricle

The Tei index of myocardial performance is a computed value that combines Doppler-derived RV systolic and diastolic functional estimates to provide a quantitative assessment of RV function.^{50,51} The Tei index has been used to aid in the diagnosis of PH in people and dogs.^{13,51,52} The Tei index formula is as follows: (isovolumetric contraction + isovolumetric relaxation)/ejection time, and Tei index values are increased when PH is present.⁵⁰ Right ventricular Tei index can be calculated using the pulsed-wave Doppler of the tricuspid valve (TV) inflows measurements and the pulmonic valve ejection measurements. The index can be calculated from the formula $(a - b)/b$ where “a” represents the interval from cessation to onset of the TV inflow (time from the end of the TV A wave to the beginning of the TV E wave, and “b” represents ejection time across the pulmonic valve (time from the beginning to the end of the PA flow profile). The inflow and outflow signals cannot be recorded

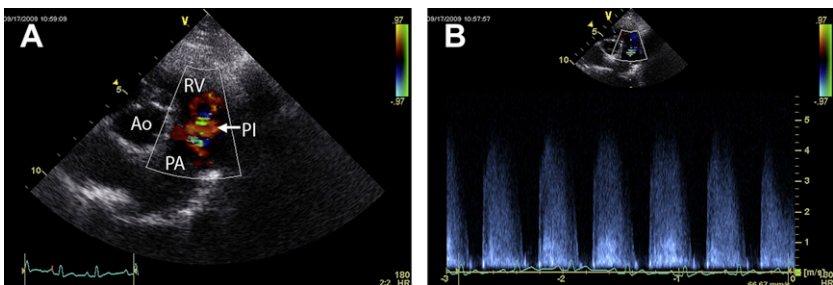


Fig. 4. Pulmonic insufficiency. Doppler echocardiographic images from a dog with severe pulmonary hypertension and a reversed patent ductus arteriosus. (A) Color Doppler map of a pulmonic insufficiency (PI) jet. The PI flow is from the higher pressure pulmonary artery (PA) to the lower pressure right ventricle (RV). The aorta (Ao) is also labeled. Image obtained from the right parasternal basilar short axis view. (B) Spectral Doppler trace of PI. Pulmonic insufficiency velocity of approximately 4.7 m/s, indicating a pulmonic gradient of approximately 86 mm Hg in early diastole. Velocities were recorded from the right parasternal basilar short-axis view.

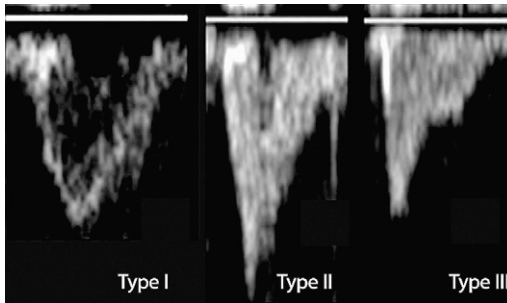


Fig. 5. Pulmonary artery systolic flow profiles. Pulmonary artery systolic velocity flow profiles: type I (normal, a domelike profile with the peak velocity flow occurring in the middle of systole with symmetric acceleration and deceleration phases), type II (the peak velocity flow occurring early in systole with a steep and rapid acceleration phase and slower deceleration phase), or type III (the same as type II but a notch occurs in the deceleration phase caused by PA flow reversal).

simultaneously, so both recordings are from unrelated cardiac cycles. Serres and colleagues¹³ described a cutoff value of 0.25 as being predictive of PH in dogs with a sensitivity of 78% and a specificity of 80%. Drawbacks to the use of the Tei index to identify increased PAP in dogs include high inpatient variability and the difficulty of obtaining good signals in a clinically dyspneic patient.⁵¹

Right ventricular tissue Doppler imaging

Tissue Doppler imaging (TDI) indices of RV function, such as *S_{tdi}* (longitudinal peak velocity of the right myocardial wall measured during systole by the use of color TDI), *E/A_{tdi}* (ratio of longitudinal peak velocities of the right myocardial wall measured in early [E] and late [A] diastole by using color TDI), and *G-TDI* (global TDI index defined as *S_{tdi}*E/A_{tdi}*) have been described in dogs with PH by Serres and colleagues.¹³ A *G-TDI* value of less than 11.8 cm/s was predictive of PH with a sensitivity of 89% and a specificity of 93%.¹³ An *E/A_{tdi}* value of less than 1.12 was predictive of PH with a sensitivity of 89% and a specificity of 90%.¹³ Detailed tissue Doppler interrogation of the RV can be difficult in patients with significant respiratory effort and TDI assessment of the RV can be considered supportive of PH rather than diagnostic.

2-Dimensional echocardiography

Right ventricular hypertrophy (concentric or eccentric) may occur in patients with PH owing to chronic increases in RV afterload. The presence of RV hypertrophy in a patient suspected of having PH is supportive evidence of the syndrome (**Fig. 6**).^{1,3,12,16,21,25,31}

Septal flattening can be noted in patients with moderate to severe PH if the RV pressure exceeds the left ventricular pressure. The presence of septal flattening in conjunction with RV eccentric or concentric hypertrophy is supportive of significantly increased RV pressure and is an indication for further investigations to identify PH (see **Fig. 6**).^{1,39}

Main pulmonary artery enlargement may be noted in dogs with moderate to severe PH.^{1,13,16,21} The diameter of the main pulmonary artery in relation to the diameter of the aorta in the right parasternal basilar short axis view (PA:Ao ratio) can be used to identify abnormal PA size. PA:Ao ratios exceeding 0.98 indicate PA enlargement (when the aorta is of normal diameter) and support a tentative diagnosis of PH (**Fig. 7**).¹³

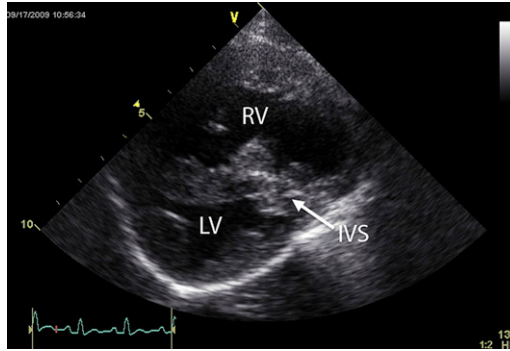


Fig. 6. Right ventricular hypertrophy and septal flattening. Two-dimensional imaging from a dog with severe pulmonary hypertension and a reversed patent ductus arteriosus. The right ventricle (RV) and the left ventricle (LV) are shown in short axis from the right parasternal view at the level of the papillary muscles in diastole. There is subjectively severe concentric (thickened RV walls and papillary muscles) and eccentric (dilated RV lumen) hypertrophy present. The RV walls appear “fluffy” and thickened owing to the extensive trabeculation of the RV walls associated with concentric hypertrophy. There is severe septal flattening of the interventricular septum (IVS) toward the LV lumen in diastole, which indicates high right ventricular pressure.

Right ventricular systolic time intervals

RV systolic time intervals (acceleration time [AT], ejection time [ET], AT:ET, and pre-ejection period [PEP]) have been used to support the diagnosis of PH in dogs and people.^{1,5,13,26,35,48,49,53} These values, obtained from echocardiographic and electrocardiographic findings associated with the pulmonic outflow velocities (RV ejection), reflect changes in RV loading. Schober and Baade⁵ demonstrated that AT:ET of 0.31 or less and AT value of 0.058 or less were predictive of PH. Abnormal RV systolic time intervals would be particularly supportive of the diagnosis of PH when other clinical findings suggest PH and a measurable TR Doppler gradient is absent.

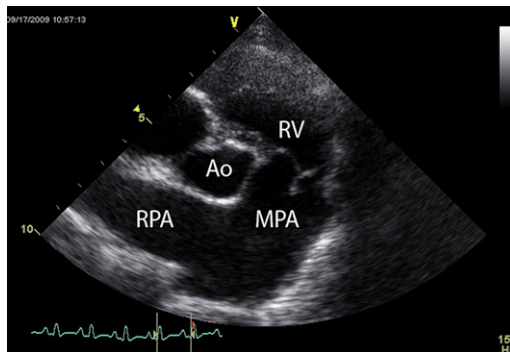


Fig. 7. Main pulmonary artery enlargement. Two-dimensional imaging from a dog with severe pulmonary hypertension and a reversed patent ductus arteriosus. The main pulmonary artery (MPA), right pulmonary artery (RPA), aorta (Ao), and right ventricle (RV) are shown in short axis from the right parasternal basilar view. The Ao:PA is 0.76 (indicating enlargement of the PA) and the RPA is subjectively enlarged suggestive of PH. The PA should be equal in size or smaller than the adjacent Ao in normal dogs.

TREATMENT

Pulmonary hypertension reflects abnormalities or imbalances in multiple signaling pathways, resulting in a final common pathway of medial hypertrophy, intimal proliferation, and a decrease in vascular compliance. The targets of PH therapy focus on these derangements.

The goals of treatment for PH patients are to ameliorate clinical signs, improve exercise tolerance, decrease the PAP, decrease the RV workload, prolong progression of disease (decrease hospitalization), improve survival, and improve quality of life. Because most cases of PH are secondary to an underlying disease process, treatment aimed at eliminating or improving the underlying disease status is the basis for therapy. If the PH is not controlled by primary disease therapy or if the etiology of the PH appears to be idiopathic, then direct PAP modulation through the use of pulmonary vasodilators should be implemented. Pulmonary vasodilating drugs currently in use target the pathophysiologic abnormalities associated with the pulmonary arterial endothelin pathway (endothelin receptor antagonists), prostanoid pathway (prostacyclin analogs), and nitric oxide pathway (specific or nonspecific phosphodiesterase-3 inhibitors). More recently, calcium-sensitizing agents with phosphodiesterase-3 inhibiting actions have also been used for clinical PH, especially when left heart disease is a contributing cause.

Endothelin Pathway

Endothelin-1 (ET-1), released by the vascular endothelium, is a potent vasoconstrictor, stimulates PA smooth muscle cell proliferation, and can ultimately lead to vascular remodeling.⁵⁴ In patients with PH, clearance of ET-1 appears to be impaired in the pulmonary vasculature.⁵⁵ Plasma concentration of ET-1 is elevated in people with PH and ET-1 concentration correlates with the severity of PH and prognosis.⁵⁶

Endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan) are oral medications and have had promising results in people with idiopathic PH,⁵⁷⁻⁶¹ but at present, are usually cost prohibitive for veterinary patients.

Prostanoid Pathway

Prostacyclin and thromboxane A2 are arachidonic acid metabolites. Prostacyclin is a potent vasodilator, inhibitors platelet activation, and has antiproliferative effects in the pulmonary artery. Thromboxane A2 is a potent vasoconstrictor and promotes platelet activation. In patients with idiopathic PH, there is an imbalance of these metabolites, favoring the production of thromboxane A2, leading to vasoconstriction, proliferation, and thrombosis.⁴⁵

The administration of prostacyclin analogs (epoprostenol, treprostinil, iloprost) has been the mainstay of treatment for PAH in people.⁶²⁻⁶⁴ Epoprostenol is administered to human patients as a continuous rate infusion with an ambulatory pump through a central venous indwelling catheter. Treprostinil is also administered intravenously or in frequent subcutaneous injections. Iloprost is in an inhaled formulation requiring dosing 6 to 12 times daily.⁴⁵ At present, these required methods of delivery prohibit the use of these medications in veterinary patients.

Nitric Oxide Pathway

Nitric oxide (NO) is a potent vasodilator, inhibitor of platelet activation, and inhibitor of vascular smooth muscle cell proliferation. NO is synthesized endogenously from L-arginine and oxygen by nitric oxide synthase (NOS) isoenzymes in the vascular endothelium. NO activates guanylate cyclase, which increases cyclic guanosine

monophosphate (cGMP). cGMP enhances vascular relaxation and is rapidly inactivated by phosphodiesterase (PDE), particularly PDE-5 isoenzymes.^{54,55} PDE-5 inhibitors are used to block the inactivation of cGMP and use of PDE-5 inhibitors results in enhanced pulmonary artery vasodilation.

Selective phosphodiesterase inhibitors

PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) were originally investigated in coronary artery research with positive results, yet the short half-life and interaction with nitrates precluded sildenafil use in this clinical situation. PDE-5 is abundantly expressed in the lungs, hence the rationale for its use with PH.⁶⁵

Sildenafil (Viagra, Revatio) is an orally active, highly selective PDE-5 inhibitor. Multiple studies have demonstrated the benefits of sildenafil in people with PH.^{66–72} Sildenafil appears to produce beneficial effects in PH by multiple mechanisms,⁷³ but the primary mechanism operative in patients with PH appears to be direct pulmonary artery vasodilation. In mice, sildenafil blocks the intrinsic catabolism of cGMP within the myocardium by suppressing chamber and myocyte hypertrophy and improving in vivo cardiac function when exposed to chronic pressure overload.⁷⁴ Sildenafil also reversed preexisting hypertrophy in pressure-loaded mice hearts.⁷⁴ Sildenafil has been shown to decrease PVR, therefore preventing the increase in PAP by partially preventing an increase in medial thickness of pulmonary arteries in piglets with PAH.⁷⁵ Borlaug and colleagues⁷⁶ have demonstrated that sildenafil can modify or blunt the response to beta-adrenergic stimulation by suppressing cardiac contractility in people. In addition to improved PAP, Ghofrani and colleagues⁷⁷ showed that sildenafil also ameliorated ventilation-perfusion mismatch, which improved oxygen saturation in people. In people, chronic sildenafil usage has been shown to significantly improve the functional ability of exercise as represented by an improved 6-minute walk test, which is considered a surrogate measure of mortality.⁶⁶

In dogs, sildenafil has been administered for PH with encouraging results.^{1,4,39} Bach and colleagues⁴ demonstrated that in the 8 of 13 dogs with PH for which follow-up data were available, sildenafil (1.9 mg/kg orally every 8–24 hours) significantly decreased the PAP (measured invasively or estimated by Doppler echocardiography). The median survival time for dogs that survived 1 day after initiation of therapy was 175 days (range: 28–693). Kellum and Stepien¹ did not find a significant reduction in PAP (based on TR estimations) after sildenafil (1 mg/kg orally every 8–12 hours), but there was a significant improvement in patients' (n = 22) clinical scores (clinical signs and quality of life). Dogs with PH in the latter study had a 95% probability of survival at 3 months, an 84% probability of survival at 6 months, and a 73% probability of survival at 1 year.¹ There were no limiting adverse side effects noted in either the Bach or Kellum studies. The only study evaluating survival times in dogs before sildenafil use was by Johnson and colleagues³ in 1999, and the median survival times for dogs that died and were euthanized was 3.5 days and 3 days, respectively.

Tadalafil (Cialis) is a longer-acting (once-daily oral dosing), selective PDE-5 inhibitor. In a human study, tadalafil decreased PAP but did not improve arterial oxygenation as sildenafil did.⁷⁷ In a study by Tay and colleagues,⁷⁸ use of tadalafil and sildenafil resulted in similar clinical improvement in people with idiopathic PH, suggesting that tadalafil could be used in place of sildenafil for improved compliance with once-daily dosing and potentially reducing the cost of treatment. Recently, Pepke-Zaba and colleagues⁷⁹ and Galie and colleagues⁸⁰ reported that there was improved health-related quality of life, improved exercise capacity, and reduced clinical worsening in people receiving once-a-day oral tadalafil for idiopathic PH. A single veterinary case study evaluating tadalafil in a dog with PAH showed a reduction in the estimated

PAP and clinical improvement.⁸¹ The appeal of tadalafil as a treatment for PH in veterinary medicine is the once-a-day dosing as compared with the recommended every 8 hours dosing for sildenafil, and possible cost reductions.

Vardenafil (Levitra) is a longer-acting, once daily, selective PDE-5 inhibitor. When vardenafil was compared with sildenafil and tadalafil by Ghofrani and colleagues⁷⁷ in people with idiopathic PH, vardenafil produced a decrease in the PAP but did not improve arterial oxygenation and decreased the systemic vascular resistance to the same degree as the PVR. In a single long-term study in people receiving vardenafil for PAH, PAP was decreased, exercise capacity improved, and patients tolerated the medication well.⁸² In rabbits, Toque and colleagues⁸³ demonstrated that vardenafil, and not sildenafil or tadalafil, had additional calcium channel blocking action in the pulmonary arteries. To date, there have been no published clinical veterinary investigations into the effects of vardenafil in dogs with PH.

Nitric oxide substrates

L-arginine is a substrate (available orally) for NO synthesis and a few studies have shown pulmonary vasodilatory effects in PH.^{84–86} The potential mechanisms by which L-arginine works in PH is by augmenting endogenous NO production, reducing oxidative stress in the PA, and by promoting angiogenesis and increasing pulmonary vessel length, hence decreasing PVR.^{86,87} A study by Souza-Silva and colleagues⁸⁸ demonstrated that L-arginine did increase NO levels, yet there was no additional attenuation in PAP when given in conjunction with sildenafil. There are no reported studies in veterinary medicine regarding the use of L-arginine in the syndrome of PH.

Calcium-sensitizing agents

Pimobendan and levosimendan are calcium-sensitizing agents and PDE-3 inhibitors. PDE-3 has activity at the level of large and small (resistance) PAs, whereas PDE-5 exerts its activity in primarily large pulmonary arteries. PDE-3 inhibitors promote PA vasodilation via enhancement of adrenergic relaxation. The dual action of PDE-3 inhibition and the positive inotropic effects of calcium sensitization may provide some attenuation of PH, especially in PH secondary to left-sided heart disease.^{8,89–92} Recently, pimobendan has been used in dogs with PH associated with mitral valve disease, and there was a significant decrease in estimated PAPs and an improved quality of life in the short term.³⁵

Nonselective Phosphodiesterase Inhibitors

The use of nonselective PDE inhibitors (3, 4, and 5), such as theophylline, have occasionally been recommended for the treatment of PH in dogs and people with little evidence of sustained improvement of PH.^{93–95} Theophylline is a bronchodilator and a weak, nonselective PDE inhibitor. In people, the degree of PDE inhibition is very small at concentrations that are considered to be of therapeutic relevance for COPD.⁹³ Signs of clinical improvement in dogs with pulmonary hypertension may occur if the underlying etiology of the PH is COPD, and in this setting theophylline may prove beneficial.

The use of nonselective vasodilators/peripheral vasodilators such as calcium channel blockers (eg, diltiazem and amlodipine), hydralazine, angiotensin-converting enzyme (ACE) inhibitors, and nitroprusside may result in adverse side effects (eg, systemic hypotension) if used for the treatment of PH. Often these medications are given for afterload reduction with left-sided heart disease, yet blood pressure should be closely monitored. In people, there have been limited positive benefits seen with

the use of calcium channel blockers (eg, diltiazem and nifedipine) for the treatment of PH.⁹⁶

SUMMARY

Pulmonary hypertension has been recognized as a clinical syndrome for many years in veterinary medicine, but routine accurate clinical diagnosis in dogs was greatly enhanced by widespread use of echocardiography and Doppler echocardiography. In addition, effective medical therapy is now available to treat this often-devastating clinical complication of common chronic diseases, making accurate diagnosis even more important to patient longevity and quality of life.

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