Pulmonary hypertension in canine degenerative mitral valve disease

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Abstract   Pulmonary hypertension secondary to degenerative mitral valve disease has been recognized clinically for many years in veterinary medicine, and clinical diagnosis of this syndrome in dogs has been enhanced greatly by widespread use of echocardiography and Doppler echocardiography. Medical therapy is now available to treat this clinical complication of mitral valve disease, making timely diagnosis even more important to patient longevity and quality of life.
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Introduction

In veterinary medicine, pulmonary hypertension (PH) has been described as echocardiographically-estimated pulmonary arterial systolic pressure (based on a peak systolic tricuspid regurgitation gradient) greater than ∼30 mmHg.[1–5] In people, the accepted definition of pulmonary hypertension is a mean pulmonary artery pressure (mPAP) of greater than 25 mmHg at rest. Pulmonary hypertension can be further classified as pulmonary arterial hypertension (PAH) (i.e. pre-capillary, resulting from abnormalities on the arterial side of the pulmonary vascular system, also described as

"active") or pulmonary venous hypertension (PVH) (i.e. post-capillary, resulting from pulmonary venous hypertension associated with left-sided heart disease and leading to pulmonary capillary hypertension, also described as "passive"). Pulmonary arterial pressure (PAP) is influenced by pulmonary blood flow, pulmonary vascular resistance (PVR) and pulmonary venous pressure. By definition, PAH or pre-capillary PH occurs when there is an elevation in PAP (i.e. increased mPAP) as a result of an increased PVR with a normal left atrial pressure (i.e. normal pulmonary artery wedge pressure [PAWP]). Diseases that result in PAH or pre-capillary PH include idiopathic PAH, heartworm disease, congenital systemic-to-pulmonary shunts (i.e. atrial septal defect, ventricular septal defect and patent ductus arteriosus) and necrotizing

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Abbreviations		NOS	nitric oxide synthase
		NP	natriuretic peptide
ACE	angiotensin-converting enzyme	PA	pulmonary artery
Ao	aorta	PAP	pulmonary artery pressure
AT	acceleration time	PAWP	pulmonary artery wedge pressure
A_{TDI}	peak velocity of late diastole tissue Doppler imaging	PDE	phosphodiesterase
		PEP	pre-ejection period
cGMP	cyclic Guanosine mono phosphate	PH	pulmonary hypertension
CT	computed tomography	PVH	pulmonary venous hypertension
dPAP	diastolic pulmonary artery pressure	PVR	pulmonary vascular resistance
ET	ejection time	RAP	right atrial pressure
ET-1	endothelin-1	RHC	right heart catheterization
ETA	endothelin-A receptor	RIMP	right ventricular index of myocardial performance
E_{TDI}	peak velocity of early diastolic tricuspid annular motion		
		RV	right ventricle
G-TDI	global tissue Doppler imaging	sPAP	systolic pulmonary artery pressure
LV	left ventricle	S_{TDI}	peak velocity of systolic tricuspid annular motion
mPAP	mean pulmonary artery pressure		
MPI	myocardial performance index	STI	systolic time interval
MRI	magnetic resonance imaging	TDI	tissue Doppler imaging
MV	mitral valve	TR	tricuspid regurgitation
NO	nitric oxide		

vasculitis/arteritis. Other etiologies causing elevated PAP but not considered as causes of PAH include chronic lung disease/hypoxia and thrombotic disease. In contrast, the definition of PVH or post-capillary PH is an elevated PAP as a result of increased PAWP with a normal PVR. The phenomenon of PVH or post-capillary PH occurs most commonly in dogs with mitral valve (MV) disease and myocardial disease (i.e. dilated cardiomyopathy). Pulmonary arterial hypertension and PVH may occur concurrently in patients with left-sided heart disease. Hypoxia-induced PAH may occur in the setting of left-heart failure when pulmonary artery (PA) vascular narrowing secondary to acute hypoxia (e.g. due to pulmonary edema), or potentially irreversible PA vascular narrowing (e.g. secondary to vascular remodeling due to chronic PVH secondary to chronic hypoxia) augment the post-capillary PH. The syndrome of PVH associated with mitral insufficiency in dogs will be the focus of this review.

Pathophysiology and pathology

Pathophysiology of pulmonary venous hypertension

Pulmonary venous hypertension with left-sided heart disease is due to a combination of hypertension from increased left atrial pressures, and reactive pulmonary arterial vasoconstriction associated with acute or chronic hypoxia.[6] The pathophysiologic changes associated with PVH are not fully understood but in addition to increased left atrial pressure, an increase in PVR due to loss of endothelium-dependent vasodilation and the effects of chronic neurohormonal activation likely contribute to reactive PH.[7–9] In addition, RV performance influences the degree of PH that is associated with left-heart disease through a variety of mechanisms.

Mediators of pulmonary vascular tone

The normal pulmonary circulation is comprised of a vast network of thin-walled arteries, veins and capillaries characterized by very low vascular resistance, low pressure and high capacitance. Endogenous pulmonary arterial vasoconstrictors and vasodilators influence vascular tone in the acute setting. Chronically, they may cause pulmonary arterial intimal proliferation, medial hypertrophy, and thrombosis, thereby influencing PAP.

Endothelin pathway
Endothelin-1, as described in people, is released by pulmonary vascular endothelium and causes potent PA and vein vasoconstriction, smooth muscle cell proliferation and increased collagen synthesis.[7,10] ET-1 release is increased in canine heart failure[11,12] and leads to sodium and water

retention, potentiation of other neurohormonal systems and promotion of myocardial hypertrophy, fibrosis and remodeling.[13–20] In people with heart failure, increased local production and decreased pulmonary clearance of ET-1 as well as upregulation of endothelin-A receptors (ETA) on vascular smooth muscle cells contribute to PA reactive vasoconstriction.[12,21,22]

Prostanoid pathway

Prostacyclin and thromboxane A2 are endogenous and counterbalancing arachidonic acid metabolites produced from membranes of PA endothelial cells and platelets and are involved in maintenance of vascular tone in normal physiologic and pathophysiologic states.[23] Prostacyclin is a vasodilator, inhibitor of platelet activation and has antiproliferative effects on the PA.[24] In contrast, thromboxane A2 is a potent vasoconstrictor and promotor of platelet activation. In cases of PH, the balance of prostacyclin and thromboxane A2 formation favors thromboxane A2 leading to vasoconstriction, cellular proliferation and thrombosis.[25]

Nitric oxide pathway

Nitric oxide (NO) is synthesized endogenously from L-arginine and oxygen by nitric oxide synthase isoenzymes in the PA vascular endothelium. Nitric oxide activates guanylate cyclase and the formation of cyclic guanosine monophosphate (cGMP) which results in a reduction of intracellular calcium concentration in vascular smooth muscle cells. The NO pathway enhances smooth muscle cell relaxation, inhibits smooth muscle cell proliferation and hypertrophy, and inhibits platelet aggregation and adhesion. cGMP is rapidly inactivated by phosphodiesterase (PDE), particularly PDE-5 isoenzymes. In experimental models and clinical studies of heart failure in people, a deficiency in basal NO synthesis as well as a decrease in endothelial release and response to NO has been found, suggesting that the loss of NO-dependent vasodilation may contribute to the production of PH through vascular remodeling.[8,9]

Natriuretic peptides

Pulmonary artery vasodilation is thought to be NO-cGMP mediated in normal people. In contrast, in people with heart disease, it has been found that PA vasodilation is linked to a natriuretic peptide (NP)-cGMP pathway, independent of the NO-cGMP pathway.[26] In the presence of advanced heart failure, this NP-cGMP-mediated PA vasodilation is attenuated and may contribute to the production of PH. Mechanisms for this phenomenon likely include NP downregulation and PDE-5 upregulation in heart failure.

The influence of the right ventricle on pulmonary hypertension in heart failure

The degree of PH associated with left-sided heart disease is partially dependent on the performance of the right ventricle (RV). In people, the normal RV can typically create a peak systolic pressure of around 45–50 mmHg.[27] If the RV is chronically exposed to a high afterload, RV hypertrophy will occur and allows the generation of the elevated peak systolic pressures required to maintain forward flow. However, if RV systolic function is impaired, ability to generate adequate peak systolic pressures is limited, and overt signs of right-sided congestive heart failure or clinical signs of low output (exertional syncope, lethargy, or weakness) may be observed. In this situation, although the PVR is unchanged, echocardiographic diagnosis of PH may underestimate true PAP because the peak systolic RV pressure used to estimate PAP using the tricuspid insufficiency jet is decreased. If the RV becomes severely dilated in response to increased afterload, pericardial restriction of diastolic filling can result. Although this restriction from the pericardium limits further RV dilation, displacement of the interventricular septum toward the left ventricular (LV) lumen affects LV filling and reduces LV ejection fraction.[7] Both of these changes result in a net decrease in cardiac output and can exacerbate progressive ventricular failure, eventually leading to development of systemic hypotension, decreased RV perfusion and RV ischemia. This downward spiral may ultimately result in hemodynamic collapse.

Histopathologic changes of pulmonary venous hypertension

The term "congestive vasculopathy" is used in people to describe the changes found in the pulmonary arteries, veins and lymphatics in patients with PH and left-sided heart disease (particularly with MV disease).[6,28] Compared to normal histopathology (Fig. 1), the most prominent change seen with PVH and MV disease is medial hypertrophy of the muscular pulmonary arteries (arterial muscularization) (Fig. 2A and B) and is often more extensive than the medial hypertrophy seen in people with idiopathic PAH.[7] Plexiform lesions (Fig. 2B), characterized by clusters of thin-walled and dilated vessels around a muscular artery lumen occluded by hyperplastic intimal/endothelial cells, occur in severe cases of PH.[29]
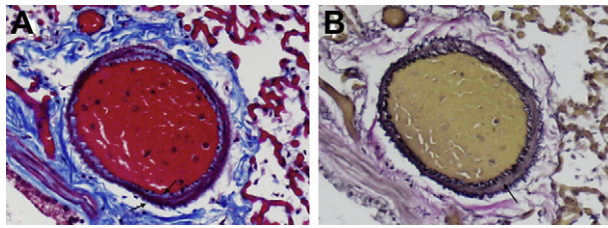
Figure 1 Histopathologic findings in a normal dog in the absence of pulmonary hypertension. Normal dog lung showing a small-sized pulmonary artery filled with blood. (A) Internal and external elastic lamina highlighted by stain (indicated by arrows). (*Verhoeff Van Giseon Elastin; 20×*). (B) Thin smooth muscle highlighted by stain (indicated by arrow). (*Masson trichrome; 20×*).

Intimal fibrosis, which is typically eccentric and non-obstructive, is also seen with PVH associated with left-heart disease (Fig. 2A, B, C and D).[7] Pulmonary venous abnormalities, such as medial hypertrophy, arterialization, intimal fibrosis and dilation also occur (Fig. 2E).[7] Pulmonary capillary distension, thickening, and basement membrane rupture with translocation of erythrocytes into the alveolar spaces are frequently noted (Fig. 2F), and pulmonary hemosiderosis may be present and can lead to fibrosis.[7] Changes in the lymphatic vessels include marked dilation with possible lymphangiectasia.[7] Ultimately, the degree of change seen in the pulmonary arteries, veins and lymphatics will determine the severity of PH. In cases of reactive PAH, some dynamic changes such as acute arterial vasoconstriction may be reversible, and although the reversibility of histopathologic lesions of reactive PAH in the setting of naturally-occurring MV disease have not been studied in dogs, it seems likely that the more severe histopathologic changes will not be completely reversible.

Clinical characteristics of pulmonary venous hypertension

Prevalence

Pulmonary venous hypertension is a common finding associated with left-sided heart disease, particularly MV disease in people and dogs. In people, approximately 60—80% of patients with left-sided heart disease have PVH, including those with primary LV systolic dysfunction, primary LV diastolic dysfunction, and LV dysfunction secondary to MV disease.[25,30—33] The degree of functional mitral insufficiency and the degree of diastolic LV dysfunction are independent predictors of PVH in patients with primary LV systolic dysfunction.[34] In people, an increase in morbidity and mortality is associated with PVH secondary to left-sided heart disease, particularly if there is evidence of RV failure.[22,30,35—41]

The true prevalence of PVH in dogs with MV disease is unknown. There have been a limited number of published studies that have evaluated naturally-occurring PH in dogs and in those studies, prevalence of MV disease as a cause of PH ranged from 30 to 74% and the prevalence of PH in MV disease dogs ranged from 14 to 53% (Table 1 and Table 2).[1—3,5,42—47] In two studies, the severity and prevalence of echocardiographically-estimated peak systolic pulmonary artery pressures in dogs with MV disease increased with the degree of heart failure present.[45,47] In general, MV disease-related PVH appears to be the most common cause of PH in dogs and the severity is typically mild to moderate.

Clinical presentation

The signalment and clinical presentation of dogs with PVH secondary to MV disease are often nonspecific and frequently similar to dogs with varying degrees of MV disease and left-sided heart failure. Dogs may be asymptomatic, or clinical signs may include exercise intolerance, cough, dyspnea, syncope, cyanosis and evidence of right-sided heart failure (jugular vein distension, positive hepato-jugular reflux, ascites). Typically, dogs presented with MV disease and more severe PH have multiple clinical abnormalities.[48] The sequence of development of certain clinical signs may be suggestive of development of PVH; a patient with known severe MV insufficiency may begin to have exertional syncope, or evidence of right-sided heart failure may develop.

Physical examination findings are also similar and may be indistinguishable between dogs with MV disease with and without PVH.[1] A left apical systolic murmur is present with MV insufficiency, but a new right-sided murmur or a switch of the point of maximal intensity to the right side may occur with the development of PVH. A fixed splitting of the second heart sound or an accentuated second heart sound may be present in dogs with severe PVH but difficult to hear in dogs with advanced mitral insufficiency. Pulmonary crackles may be detected, and when present, may be due to pulmonary edema in acute left-sided heart failure or may reflect chronic pulmonary parenchymal disease in a MV patient without pulmonary edema.
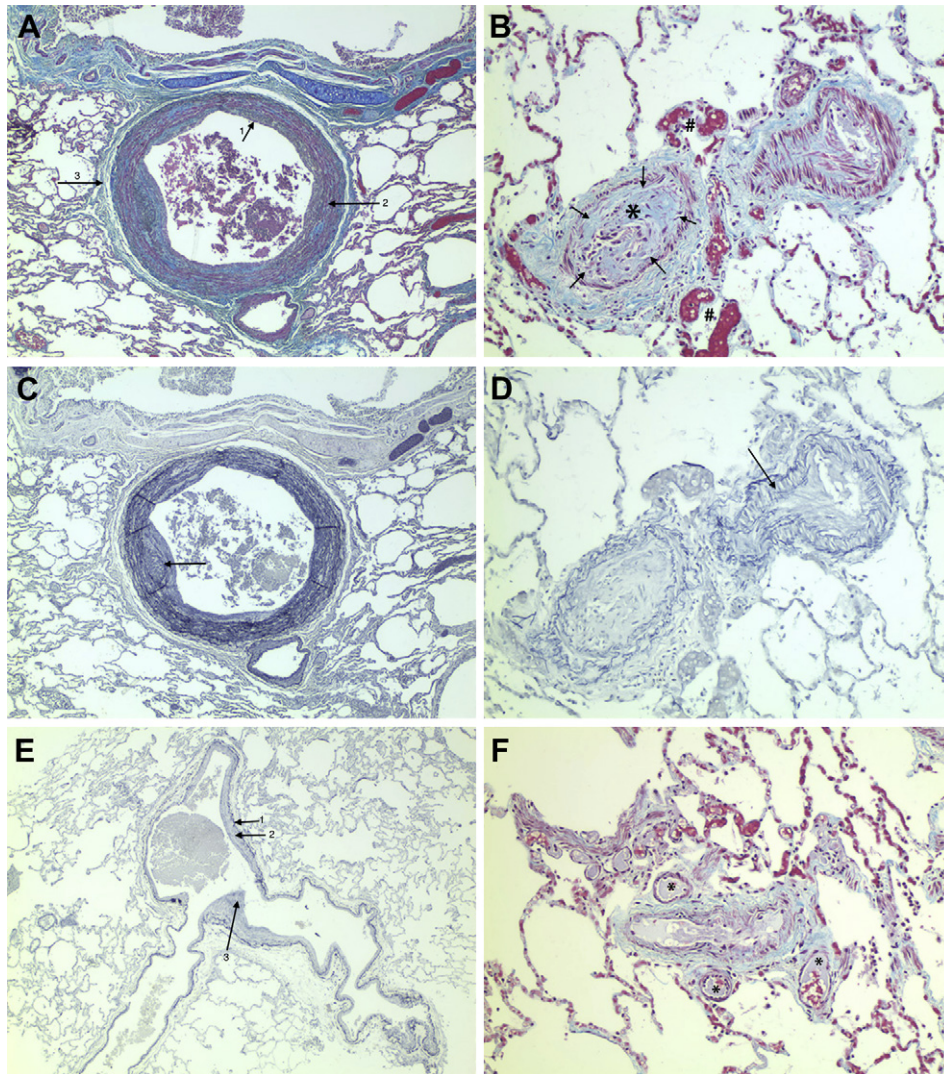
Figure 2 Histopathologic findings in a dog with severe, chronic pulmonary venous hypertension secondary to mitral valve disease and treated left-sided congestive heart failure. The estimated systolic pulmonary artery pressure based on the peak systolic tricuspid regurgitation gradient was 130 mmHg. (A) Medium-sized pulmonary artery in cross-section. Muscular arterial walls are thickened with moderate intimal thickening (indicated by arrow 1), medial smooth muscle hypertrophy (indicated by arrow 2) and adventitial edema (indicated by arrow 3). (*Masson trichrome ; 4×*) (B) Small-sized pulmonary arteries in cross-section. Muscular small arterial walls are thickened with moderate intimal proliferation with hyperplasia, medial smooth muscle hypertrophy and adventitial edema. Plexiform (angio-matoid) lesion characterized by clusters of thin-walled and dilated vessels around an occluded muscular artery showing mesh of hyperplastic intimal/endothelial cells fills the arteriolar lumen (arrow heads outline the mesh filling the lumen). #indicates the region of clusters of thin-walled and dilated vessels; * indicates the center of mesh of hyperplastic intimal/endothelial cells filling the arteriolar lumen. (Masson trichrome; 20×). (C) Same image of medium-sized pulmonary artery as seen in Figure 2A. Pulmonary artery is dilated with irregular thickening of the intima with fibroelastosis. Thickening and splitting of the internal and external elastic lamina with an "onion skin" appearance (indicated by arrow). (*Verhoeff Van Giseon Elastin; 4×*). (D) Same image of small-sized pulmonary artery as seen in Figure 2B. Discontinuity of the internal and external elastic lamina due to smooth muscle cells (indicated by arrow) traversing elastic laminae. (*Verhoeff Van Giseon Elastin; 20×*). (E) Pulmonary vein. Tortuous vein with aneurismal dilation, external elastic lamina thickening (indicated by arrow 1), mild smooth muscle hypertrophy (indicated by arrow 2) and irregular intimal thickening due to fibroelastosis (indicated by arrow 3). (*Verhoeff Van Giseon Elastin; 4×*). (F) Small- to medium-sized pulmonary artery and prominent and dilated pulmonary capillaries. *indicates prominent and dilated pulmonary capillaries. (Masson trichrome stain; 20×).*

Table 1 Studies reporting on the incidence of mitral valve disease (MVD) in dogs with pulmonary hypertension.

	Year					
	1999[2]	2004[5]	2006[3]	2007[1]	2007[42]	2010[43]
Total PH diagnosis (all etiologies) (n)	53	54	13	22	60	65
Dogs with MVD (n; %)	16; 30	22; 41	1; 8	9; 41	45; 75	48; 74
Dogs with MVD and respiratory disease (n; %)	NA	NA	NA	3; 14	6; 10	NA
Dogs with isolated MVD (n; %)	16; 30	22; 41	1; 8	6; 27	38; 63	48; 74
Characteristics of PH	NA	Mild (30—55 mmHg): 12(55%) Moderate (56—79 mmHg): 8 (36%) Severe (>79 mmHg): 2 (9%)	NA	Median: 62 mmHg Range: 39—131 mmHg	NA	Mean: 53 mmHg ± SD 13

Abbreviations: PH, pulmonary hypertension; TR, tricuspid regurgitation.

Diagnostic strategy

Invasive hemodynamic assessment

Right heart catheterization (RHC) is the gold standard for diagnosis of PH in people.[25] In clinical veterinary medicine, RHC may be an unacceptable semi-invasive procedure in a potentially compromised patient due to the need for sedation or anesthesia, but when available, can provide multiple hemodynamic parameters that aide in the diagnosis and etiologic classification of PH. Right heart catheterization provides hemodynamic information regarding the right atrial (RA), RV and PA pressures as well as PAWP. The PAP in systole and diastole can be measured directly, and the mean PAP calculated.[49] Pulmonary artery wedge pressure, a reflection of pulmonary venous and left

Table 2 Studies reporting on the incidence of pulmonary hypertension in dogs with mitral valve disease (MVD).

	Year			
	2004[44]	2006[45]	2010[43]	2010[46]
MVD Diagnosis (n)	107	617	90	Total: 45 No CHF: 21 CHF: 24
Dogs with PH (n; %)	33; 31	86; 14	48; 53	Total: 20; 44 No CHF: 3; 15 CHF: 17; 71
Characteristics of PH	Mean (mmHg): GSD: 47.6 ± SD 12.6 Small dogs: 52.6 ± 14.6	Mean (mmHg): Total: 56 ± SD 21.4 Range: 30—123 Mild: 56% Moderate: 23% Severe: 21%	Mean (mmHg): 53 ± SD 13	No CHF median (5 and 95 percentiles) (m/s): 2.81 (2.19—3.15) CHF median (5 and 95 percentiles) (m/s): 3.43 (2.08—4.61)

Abbreviations: PH, pulmonary hypertension; TR, tricuspid regurgitation; CHF, congestive heart failure; GSD, German shepherd dog.

atrial pressure, can be measured to document elevated pulmonary venous pressures. Pulmonary vascular resistance, the resistance that the heart must overcome to pump blood into the pulmonary blood vessels, is a measure of PH and is often indexed to body surface area. The mPAP and the PAWP can be used to calculate the PVR.

$$PVR \ is \ calculated \ as \ PVR = ([mPAP - PAWP] \times 80)/CO$$

$PVR(dynes * sec * cm^{-5})$, $mPAP(mmHg)$, $PAWP(mmHg)$, $CO(L/min)$.

PVR is an important calculation that can be used to distinguish PVH from PAH. When PVR is normal and PAWP is elevated, the elevated PAP is considered to be due to PVH. If PVR and PAWP are simultaneously elevated in a PH patient with the mPAP disproportionately increased more than the PAWP, the patient may be diagnosed with "reactive PH", an additive situation in which PA vasoconstriction secondary to acute hypoxia augments PVH.[7]

Echocardiographic estimates of pulmonary arterial pressure

Echocardiography is the most common, non-invasive method for diagnosing MV disease and PH in veterinary patients. There are multiple echocardiographic imaging modalities that may contribute to a PH diagnosis, including two-dim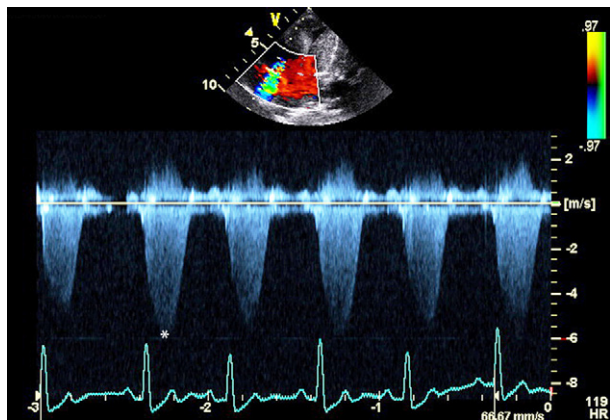ensional, M-mode, spectral Doppler, color Doppler and tissue Doppler imaging. Although echocardiographic examination may be considered a familiar test in clinical veterinary medicine, full echocardiographic evaluation in terms of PH quantification and right ventricular functional analysis in canine PH patients is still not routine.

Systolic pulmonary artery pressure (sPAP)
Estimation of sPAP by echocardiographic examination relies on the presence of tricuspid regurgitation (TR) (Fig. 3). The interrogation of a TR jet, in the absence of a RV outflow tract obstruction, allows for a non-invasive estimation of peak systolic PAP. The systolic trans-tricuspid pressure gradient (mmHg) is estimated using the peak systolic TR velocity (m/sec) in the modified Bernoulli equation (p1-p2 = $4v^2$, where p1-p2 represents the systolic velocity gradient between the RV and RV and v = peak systolic velocity of the TR jet). The TR jet peak systolic velocity is recorded using the view that gives the most optimized alignment of the interrogation beam with the TR jet; this is often the left parasternal 4-chamber view optimized for the RV inflow tract. The peak systolic TR velocity and gradient reflect, although not equal to, the estimated peak systolic RV pressure and is used to arbitrarily classify systolic PH as mild ($\geq$2.8 to <3.5 m/s, $\geq$ 31.4 to <50 mmHg), moderate (3.5–4.3 m/s, 50–75 mmHg) or severe (>4.3 m/s, >75 mmHg) (Table 3).[1,2,4]

Evaluation of TR gradients for the diagnosis and quantification of PAP is common in clinical practice, but some caveats must be kept in mind. In human patients, there is conflicting evidence as to the correlation of echocardiographically-estimated TR gradients and invasively obtained direct PAP measurements from a RHC.[50–53] To the authors' knowledge, similar data do not exist in available veterinary literature. Studies describing PH in people and dogs may add the estimated right atrial pressures (RAP) to the estimated peak systolic RA-RV pressure gradients to more accurately describe the estimated sPAP (sPAP = RA-RV pressure gradient + RAP). Some investigators, including the authors, believe that the addition of estimated RAP may result in overestimation of PH severity in human patients[51] and dogs. To date, there have been no studies validating echocardiographically-derived estimates of RAP in dogs. Similarly, although measurement of the diameter of the inferior vena cava and its variation with respiration provides a semi-objective estimation of RAP in people, this type of estimation has not been evaluated in dogs.[54] Other important limitations of use of TR jet systolic velocity to estimate PAP include: availability of views allowing optimal TR

Figure 3 Doppler echocardiographic image from a dog with severe pulmonary venous hypertension and mitral valve disease. Spectral Doppler trace of tricuspid regurgitation. Peak systolic tricuspid regurgitation velocity of approximately 5.7 m/s, indicating a peak systolic tricuspid regurgitation gradient of approximately 130 mmHg. Velocities were recorded from the left apical 4-chamber view.

Table 3 Selected echocardiographic findings suggestive of pulmonary hypertension (PH) in dogs.

Variable	Suggested values considered consistent with PH
Two-dimensional	
Interventricular septal motion	Flattening of septum in systole and/or diastole and/or paradoxical septal motion
Right ventricular size/appearance	Subjective: eccentric and/or concentric hypertrophy
Main pulmonary artery size	MPA:Ao >0.98 (Se 0.73, Sp 0.76)[48]
Spectral Doppler	
TR peak systolic velocity and gradient	≥2.8 m/s, ≥31.4[1]
PR peak diastolic velocity and gradient	≥2.2 m/s, ≥19 mmHg[1]
Systolic time intervals	AT:ET ratio ≤ 0.31 (Se 0.73, Sp 0.87)[4] AT ≤ 58 ms (Se 0.88, Sp 0.80)[4]
Tei index of myocardial performance	>0.25 (Se 0.78, Sp 0.80)[43]
Pulmonary artery systolic flow profiles	Type II or Type III profiles[1]
Tissue Doppler	
RV wall E/A ratio (tdi)	<1.12 (Se 0.89, Sp 0.90)[48]
Global tissue Doppler index	<11.8 cm/s (Se 0.89, Sp 0.93)[48]

Adapted from Stepien RL.[93]
Abbreviations: MPA, main pulmonary artery; Ao, aorta; TR, tricuspid regurgitation; PR, pulmonic regurgitation; AT, acceleration time; ET. ejection time; RV, right ventricle; S, systole; E, early diastole; A, late diastole; tdi, tissue Doppler imaging.

jet alignment (i.e. angle of interrogation beam to TR jet must be <20°), inadequate signal strength of the TR jet, inadequate patient compliance during the echocardiogram and limitations in image quality that may be present secondary to pulmonary pathology, body condition and body conformation. If one or more of these limitations affect the quality of the TR jet interrogation, underestimation of PH may occur, and if TR is not present or cannot be interrogated, the PH diagnosis may be missed. Because estimated peak systolic PAP is based on peak systolic TR velocity, the accuracy of these estimates is also dependent on RV function. If RV systolic dysfunction is present, the peak systolic RA-RV pressure gradient may indicate relatively "normal" PAPs despite elevated PVRI and the diagnosis of PH may be missed. Each of these limitations can be clinically important, but estimation of peak systolic RA-RV pressure gradient via interrogation of a TR jet in dogs with PH remains the non-invasive gold standard for estimation of sPAP when efforts are made to adjust for these possible problems.

Diastolic pulmonary artery pressure (dPAP)
Diastolic PAP can be estimated echocardiographically by assessment of end-diastolic pulmonary regurgitant jet velocity using the modified Bernoulli equation (Fig. 4). In people, this measurement has been added to the estimated RA pressure to more precisely describe the diastolic PA pressure (dPAP = 4 × [end-diastolic pulmonary regurgitant velocity]^2 + RA pressure).[54]

Mean pulmonary artery pressure (mPAP)
In people there are several echocardiographic methods described to calculate the estimated mPAP by echocardiography (Fig. 2).[54,55] With no clinical data available in dogs regarding the relative accuracy of these methods, mPAP can be estimated by multiple methods if required in a clinical patient. A peak diastolic pulmonic regurgitation jet velocity can be used in the modified Bernoulli equation to render an estimate of mPAP. Without the addition of RAP, ≥ 2.2 m/s or a gradient ≥ 19 mmHg has been described as suggestive of PH in dogs (Table 3).[1]
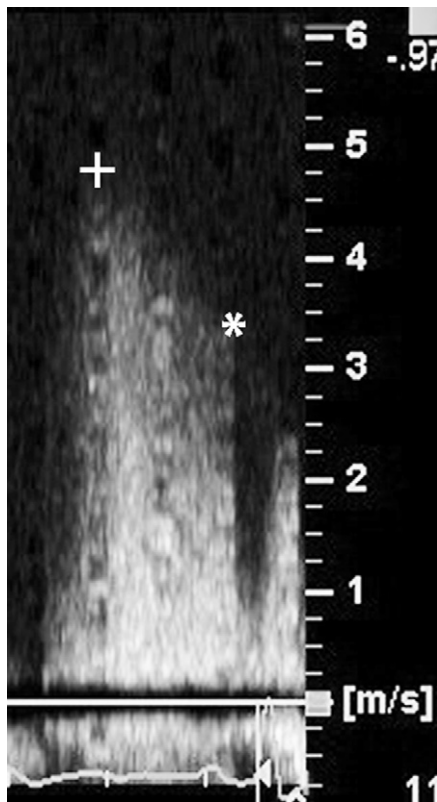
Figure 4 Continuous wave Doppler echocardiographic flow profile of pulmonary insufficiency from a dog with severe pulmonary hypertension. +denotes the maximal pulmonic regurgitation velocity (4.7 m/s) at the beginning of diastole, which when converted to the pressure gradient (88.4 mmHg), represents the estimated mean pulmonary artery pressure. *denotes the maximal pulmonic regurgitation velocity (3.4 m/s) at end-diastole, which when converted to the pressure gradient (45 mmHg) represents the estimated diastolic pulmonary artery pressure.

Supportive echocardiographic findings in pulmonary hypertension

Pulmonary artery systolic flow profiles
Evaluation of the systolic PA flow profile may aide in the diagnosis and estimation of PH severity in people and dogs (Fig. 5) (Table 3).[1,2,4,42,56—61] Normally, the systolic PA flow profile has a "domed" appearance indicating an equal acceleration and deceleration time (Type I). Mild and moderate PH may result in an altered systolic PA flow profile (Type II) where the acceleration time is decreased and deceleration time is prolonged. Severe PH often results in a systolic PA flow profile similar to Type II with a "mid-systolic notch" in the deceleration phase (Type III), indicating a high PAP resulting in flow reversal. Assessment of PA flow profiles does not provide a precise estimate of
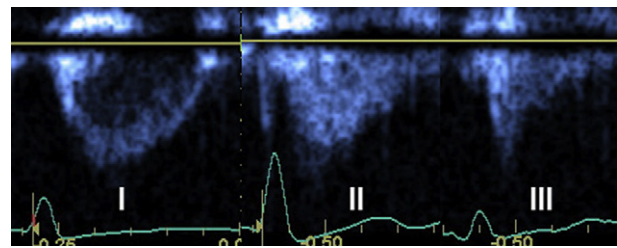

Figure 5 Pulmonary artery systolic velocity flow profiles: type I (dome-like profile), type II (rapid acceleration), and type III (mid to late systolic notch in the flow profile).

PAP, and is fraught with many technical inaccuracies, rendering it useful only as additive information in cases in which a TR jet is not available or when TR jet velocity cannot be accurately measured.

Tei index of myocardial performance of the right ventricle
Tei index (myocardial performance index [MPI] or right ventricular index of myocardial performance [RIMP]) is a global index of systolic and diastolic RV performance and has been described in both dogs and people.[42,54,62—64] The pulsed-wave Doppler of the tricuspid inflow measurements and the pulmonic valve ejection measurements are used to calculate this index (Fig. 6). An increase in Tei index is potentially supportive of a diagnosis of PH. In dogs, a Tei index value of >0.25 (sensitivity 78%,
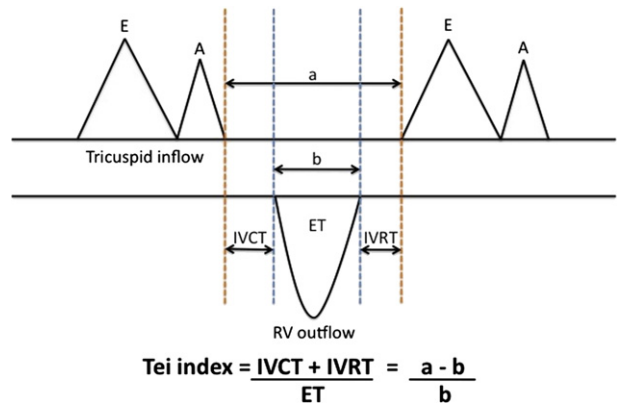

$$\text{Tei index} = \frac{\text{IVCT} + \text{IVRT}}{\text{ET}} = \frac{a - b}{b}$$

Figure 6 Schematic drawing of pulsed-wave Doppler recordings from tricuspid inflow and right ventricular outflow tract projections demonstrating the calculation of Tei index. The Tei index can be calculated as (a−b)/b, where "a" represents the interval between the cessation and onset of tricuspid inflow and "b" represents ejection time of the right ventricular outflow. E, peak velocity during early diastole; A, peak velocity during atrial contraction; ET, ejection time; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time.
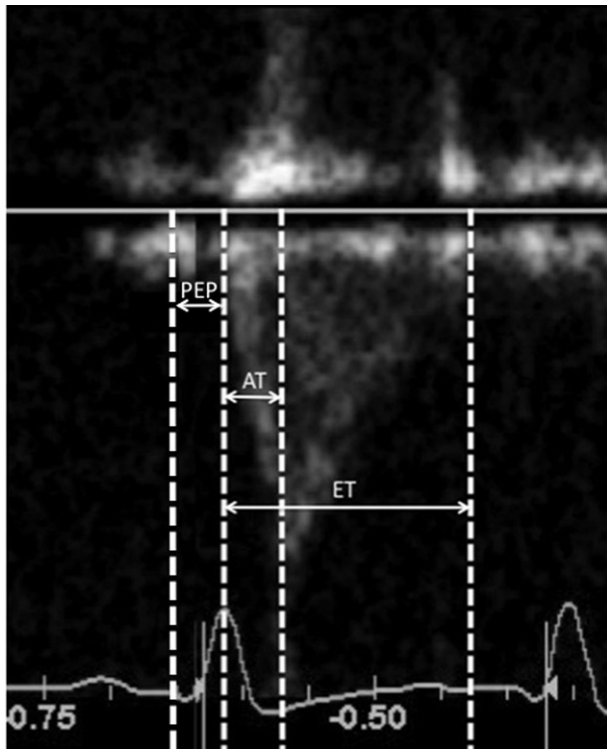
Figure 7 Right ventricular systolic time interval obtained from a right ventricular outflow velocity in a dog with pulmonary venous hypertension. PEP, pre-ejection period; AT, acceleration time; ET, ejection time.

specificity 80%) is supportive of a diagnosis of PH when compared to normal dogs (Table 3).[42] In dogs, application of the Tei index is limited by inaccuracies owning to rapidly changing R—R intervals during data acquisition and high intra-patient measurement variability.[63]

Right ventricular systolic time intervals

Right ventricular systolic time intervals (STIs) include acceleration time (AT), ejection time (ET), AT:ET, and pre-ejection period (PEP) calculated from the Doppler pulmonic outflow velocity profiles (Fig. 7). These measurements are influenced by RV loading (among other factors) and have been used in dogs and people to support the diagnosis of PH.[1,4,42,54,57,58,60,61,65] In a group of West Highland White Terriers, an AT:ET of 0.31 or less (sensitivity 73%, specificity 87%) and an AT value of 58 ms or less (sensitivity 88%, specificity 80%) were consistent with PH (Table 3).[4]

Right ventricular tissue Doppler imaging

Tissue Doppler imaging (TDI) of the lateral TV annulus can provide indices of RV systolic and diastolic function. Longitudinal peak velocities of the right myocardial wall in early (E_{tdi}) and late

(A_{tdi}) diastole and systole (S_{tdi}) may be used to calculate measurements used in the assessment of PH in dogs and people (Fig. 8).[42,54] TDI velocities may be reduced for multiple reasons, including PH but also any cause of RV systolic dysfunction. In dogs, including those with MV disease, a global tissue Doppler imaging index (G-TDI = S_{TDI} * [E_{TDI}/A_{TDI}]) of <11.8 cm/s was predictive of PH with a sensitivity of 89% and a specificity of 93% (Table 3).[42] E_{TDI}/A_{TDI} < 1.12 are likewise considered suggestive of PH with a sensitivity of 89% and a specificity of 90%.[48]

Two-dimensional echocardiographic findings

Several 2-D echocardiographic findings can be used to support a diagnosis of PH, including RV hypertrophy, septal flattening and pulmonary arterial dilation (Table 3). Right ventricular hypertrophy (eccentric and/or concentric) may occur with acute and chronic RV pressure overload and has been described in dogs with PH.[1,2,66—70] Septal flattening in dogs, a situation in which the interventricular septum moves toward the LV lumen in systole and/or diastole, can be observed when RV pressure approach or exceed LV pressure in cases of moderate to severe PH.[1,71] Main PA enlargement occurs with moderate and severe PH and can be assessed by calculation of the pulmonic/aortic (PA/Ao) ratio, which can be obtained using the right basilar short axis view. The aortic annular diameter in the short axis is compared to the PA diameter at the level of the pulmonic valve in long axis at end-diastole. In dogs, a PA/Ao ratio exceeding 0.98 (sensitivity 73%, specificity 76%) was supportive of a diagnosis of PH (Table 3).[42]
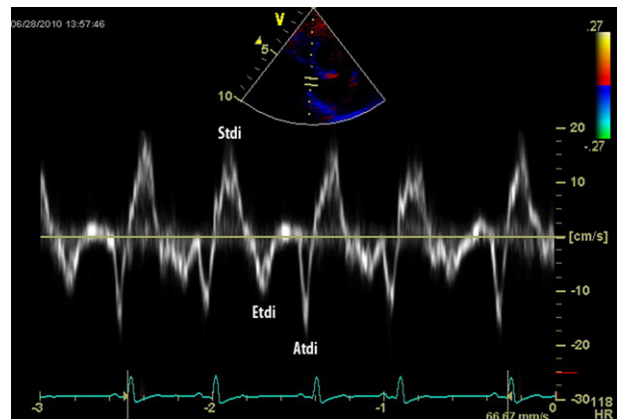

Figure 8 Tissue Doppler imaging velocities obtained from the lateral tricuspid valve annulus in a 7 year old dog with severe, chronic, pulmonary venous hypertension. E_{TDI}, peak velocity of early diastole; A_{TDI}, peak velocity of late diastole; S_{TDI}, Peak systolic velocity.

Miscellaneous echocardiographic findings

In people, guidelines for the echocardiographic examination of the right heart include measurements and indices that have not yet been fully described and validated in dogs. These include RA size and volume measurements, linear RV chamber measurements, 2-D and 3-D volumes, fractional area change, ejection fraction, PVR estimations, tricuspid annular motion amplitude and regional RV strain and strain rate measurements.[54] These measurements and indices have potential in the non-invasive evaluation of canine PH, and future studies will likely result in standardization of right heart evaluation and evaluation of such variables in canine patients.

Cardiac biomarkers

NT-proBNP (N-terminal-pro-B-type natriuretic peptide), a peptide released by the left and right ventricular myocardium in response to volume and pressure load, has been shown in to be elevated in dogs in the presence of PAH and PVH.[58,72] In dogs with MV disease, an increase in NT-proBNP concentration is not diagnostic for PH, but successful treatment of congestive heart failure in dogs with MV disease with pimobendan decreased NT-proBNP concentration in the short term and was associated with a decrease in PVH severity.[58]

Computed tomography and magnetic resonance imaging

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are imaging modalities used to evaluate human PH patients,[73–76] and hold promise for evaluation of veterinary patients when such modalities are more readily available. CT is useful to assess pulmonary vascular and pulmonary status, and MRI provides more information regarding cardiac structure and function including but not limited to PVR and PA stiffness. With regard to PH and MV disease, MRI can provide quantitative measures of both left- and right-sided morphology and function.

Treatment

Successful therapy of PH related to MV disease is aimed at decreasing PAP by decreasing LA pressure, improving LV systolic and diastolic function, and direct pulmonary artery vasodilation. The goal of treating elevated left atrial pressures and LV dysfunction associated with MV disease typically involves the use of diuretics (e.g. furosemide or torsemide), balanced vasodilators (e.g. angiotensin-coverting enzyme [ACE] inhibitors, pimobendan), neurohormonal blockers (e.g. ACE inhibitors, aldosterone antagonists) and positive inotropes (e.g. pimobendan). In addition to the standard therapies used to treat MV disease in dogs, medications that directly affect abnormalities in the PA endothelin pathway, prostanoid pathway and NO pathway have been described as possible PH therapies.[1,3,77] No clinical data have been published to date regarding the use of ET-1 antagonists (e.g. bosentan) or prostacyclin analogs (e.g. epoprostenol) in canine PH patients. Some of these therapies may be prohibitively expensive for veterinary patients and others must be administered intravenously, via continuous subcutaneous administration or be inhaled, limiting clinical veterinary use. At present,

Table 4 Recommended treatment of pulmonary hypertension (PH) secondary to mitral valve disease.

Scenario	Left-sided CHF present	Mild to moderate PH present	Severe PH present	Syncope present	Right-sided CHF present	Treatment
#1		X				None
#2	X	X				CHF medications
#3	X		X			CHF medications
#4	X		X	X		CHF medications + sildenafil
#5	X		X		X	CHF medications + sildenafil
#6	X		X	X	X	CHF medications + sildenafil

Abbreviations: CHF, congestive heart failure.

calcium-sensitizing PDE-3 inhibitors (e.g. pimo-bendan) and PDE-5 inhibitors (e.g. sildenafil) represent the most often used pulmonary vasodilators in dogs.[1,3,58] To date, there is no published consensus on when and how to treat PVH associated with MV disease. Since many clinical signs of PH are identical to signs seen in dogs with left-sided congestive heart failure (e.g. exercise intolerance, dyspnea, cough, syncope), screening for evidence of PH should be included in all echocardiographic evaluations of dogs with MV disease, particularly those with severe MV insufficiency and/or evidence of congestive heart failure. When evidence of PH is documented, the patient can be reassessed clinically. If clinical signs suggestive of PH (e.g. right heart failure, syncope with exertion) are present after pulmonary edema is controlled, addition of a pulmonary vasodilator may be considered. It has been the authors' experience dogs that specific treatment for PVH with sildenafil (in concert with standard therapy for left-sided heart disease/failure) is clinically effective and well tolerated in such patients. Specific combinations of clinical findings that may guide therapy appear in Table 4.

Calcium sensitizers and phosphodiesterase-III inhibitors

Calcium-sensitizing and phosphodiesterase-III (PDE-3) inhibiting agents, such as pimobendan and levosimendan, improve PAP through their direct actions on the heart and pulmonary vasculature, treating both heart failure due to MV disease and PVH in dogs.[58] PDE-3 inhibition causes PA vasodilation at the level of the large and small pulmonary arteries via potassium channel activation and enhancement of cAMP-dependent/adrenergic vasorelaxation.[78,79] The calcium-sensitizing properties enhance left and right ventricular inotropic function, which may result in decreased left and right atrial pressures, ultimately improving left- and right-sided CHF. Levosimendan, a drug similar to pimobendan that has been studied in human PVH patients, attenuates PH by direct antiproliferative and anti-inflammatory effects on the pulmonary arteries, direct inhibitory effects on RV hypertrophy and enhancement of RV contractility.[79–81] In canine patients with simultaneous PVH and concurrently treated left-sided heart failure due to MV disease, the addition of pimobendan reduced estimated PH severity as compared to placebo and improved quality of life in the short term.[58] It remains unclear whether improvement in heart failure status, direct pulmonary vasodilatation or the combination of these effects is responsible for the clinical improvement noted.

Phosphodiesterase V inhibitors

Phosphodiesterase V (PDE-5) inhibitors are pulmonary arterial vasodilators and include sildenafil, tadalafil, vardenafil, udenafil and avanafil. The usefulness of PDE-5 inhibitors in PH therapy is based on the interaction of PDE-5 and NO. Since PDE-5 isoenzymes are responsible for the rapid inactivation of cGMP and are abundantly expressed in the pulmonary vasculature, PDE-5 inhibition has become a major target for therapy of PH in dogs and people.

Sildenafil
Sildenafil (Viagra™, Revatio™) is a highly selective, orally administered PDE-5 inhibitor typically given three times a day. Sildenafil has been used to treat PH in people in the clinical setting, and improves PH via multiple mechanisms.[82,83] In addition to directly improving PH via PA vasodilation and improving RV function, sildenafil has also been shown to improve left-heart function in people. Sildenafil has been shown to decrease left LV wall thickness and mass, improve LV systolic function and improve LV diastolic function via presumed mechanisms related to LV antihypertrophic and anti-fibrotic effects.[83] It has also been proposed that the improved right heart hemodynamics seen with sildenafil positively influence ventricular interdependence resulting in improved LV relaxation and compliance in people. As a result of these effects, central venous pressure decreases and improvement of pulmonary lymphatic drainage and a decrease in total lung fluid content may be seen.[83] Overall, sildenafil has been shown to decrease PH severity,[26,82,84,85] improve quality of life,[27] improve exercise capacity,[27,82] and improve peak oxygen uptake[82] in human patients with PVH due to left-heart disease. In dogs with PVH associated with left-sided heart disease (primarily MV disease), sildenafil has been empirically administered (approximately 1 mg/kg [range 0.5–2 mg/kg] PO every 8 h) with encouraging clinical results.[1,86] In studies of dogs with PH of many causes including left-heart disease, sildenafil administration has been found to decrease PH severity,[3,86] increase exercise capacity,[86] and improve quality of life.[1] All studies regarding survival of dogs with PH are limited by small patient groups, the absence of control groups and in some cases, mixed or uncertain etiologies for development of PH. In a single dog study,[1] even though the estimated PAP did not improve with

sildenafil, the quality of life and survival times improved from dogs reported to have PH prior to sildenafil therapy.[2] In the authors' experience, current survival times of clinical patients with MV disease and PH treated with sildenafil appear to be longer than those reported prior to use of sildenafil in such patients; whether this apparent survival benefit is due to the direct effects of the medication or to improvement in quality of life or other undetermined factors remains unclear. The short and long term effects of sildenafil in dogs with MV disease and PVH are not yet well-defined, and a randomized, prospective, controlled large clinical trial addressing survival benefit has not been performed.

In people, there are theoretical concerns about pulmonary artery vasodilators causing pulmonary edema or the worsening of pulmonary edema in patients with elevated LV filling pressures and increased left atrial pressures. In these patients, excessive fluid may accumulate in the pulmonary capillaries as pulmonary arterioles dilate in response to pulmonary vasodilators. To the best of the authors' knowledge, while there has been speculation as to the mechanism for this phenomenon, there is no literature in people or dogs that directly supports this theory.[87–91] Due to the lack of controlled studies evaluating the dose and administration of sildenafil in dogs with MV disease and PVH, such treatment should be approached cautiously, and simultaneous therapy of congestive heart failure and PH should be closely monitored. Specific attention should be paid to patients already receiving multiple vasodilators for therapy of heart failure (e.g. hydralazine, amlodipine, angiotensin-converting enzyme inhibitors) when sildenafil therapy is considered; concurrent use of systemic and pulmonary vasodilators may increase the risk of systemic hypotension.

Tadalafil and vardenafil

Tadalafil (Cialis™) and vardenafil (Levitra™) are long-acting, once daily, orally administered PDE-5 inhibitors. A single study by Serres et al. reported short-term improvement of clinical signs in a dog with MV disease and severe PH when given tadalafil (1 mg/kg every 48 h).[92] Currently, there is no published information regarding the use of vardenafil for the treatment of PVH in human or canine patients with left-sided heart disease. The appeal of using these specific PDE-5 inhibitors is ease of once-daily dosing and a potential reduction in cost of treatment. Further studies are required to delineate the clinical effects and potential clinical value of these medications.

Conclusion

Pulmonary hypertension secondary to MV disease has been recognized as a clinical syndrome in dogs with degenerative MV disease and an accurate clinical diagnosis is commonly achieved with echocardiography. Medical therapy, specifically targeting both left-heart disease and PVH is available and may improve longevity and quality of life.

Acknowledgments

Conflict of interest

None.

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