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Review article

PULMONARY HYPERTENSION IN THE DOG

POSER Helen, GUGLIELMINI Carlo*

Department of Animal Medicine, Production and Health, University of Padua, Viale dell'Università, 16, Legnaro (Padua), Italy.

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Canine pulmonary hypertension is a clinical condition that needs to be adequately investigated and recognised because of the lack of specific clinical signs, the potential for rapid and irreversible deterioration of pulmonary vascular function and the development of right-sided heart failure. In recent years, many studies have been published on pulmonary hypertension, improving the understanding of its pathophysiology, the accuracy of diagnostic tests and the management of affected patients. This article provides updated information on pulmonary hypertension and serves as a resource for veterinarians regarding the interpretation of diagnostic tests and the clinical management of affected dogs.

Key words: Canine, echocardiography, heart, phosphodiesterase inhibitors, pulmonary arterial hypertension.

INTRODUCTION

Pulmonary hypertension (PH) is considered a physiological finding rather than a real primary disease. It can be the result of increased right ventricular cardiac output (CO), pulmonary artery flow, pulmonary vascular resistance (PVR) or pulmonary venous pressure [1]. In humans, PH is defined as an increase in mean pulmonary artery pressure (PAP) greater than 25 mmHg recorded by invasive catheterisation [2,3]. Another definition considers the haemodynamic mechanism underlying the increased PAP. In particular, if the increased PAP is due to increased PVR or pulmonary flow, PH is defined as pre-capillary, while if increased PAP is due to increased left ventricular end-diastolic pressure, pulmonary venous and capillary wedge pressure, PH is defined as post-capillary [2,3].

In recent years the scientific interest in PH has greatly increased and many studies focused on PH have permitted a better understanding of its pathophysiology and a refining of the diagnostic approach and management of affected humans [4] and dogs [5].

*Corresponding author: e-mail: carlo.guglielmini@unipd.it

The aim of this article is to review the recent literature on PH and to summarise useful information about its clinical aspects, diagnosis and treatment in the dog.

CLASSIFICATION OF PULMONARY HYPERTENSION

The first classification of PH was proposed by the World Health Organization (WHO) in the early seventies [6]. Since then, the classification system has been revised many times and modified according to the most recent scientific evidence. Thus, a clinical classification has been developed in order to characterise different types of human PH that share similarities in pathophysiologic mechanisms, clinical presentations, and therapeutic options [7,8]. Currently, diseases related to the development of PH have been classified into 5 groups: 1) pulmonary arterial hypertension; 2) pulmonary hypertension due to left heart disease; 3) PH associated with disorders of the respiratory system or hypoxemia, 4) PH caused by thrombotic or embolic diseases, and 5) PH with unclear multifactorial mechanisms [7,8] as reported in Table 1.

In veterinary medicine, a similar classification system has not been developed, and canine PH is often reported as a primary or secondary condition [9,10] or, according to the haemodynamic pathophysiologic mechanism, as pre-capillary or post-capillary [11].

Different pulmonary and cardiac diseases have been associated with canine PH and the underlying mechanism can often be attributed to some of the five groups of the WHO classification, although some diseases associated with PH in humans do not affect dogs (Table 1).

Group 1

Pulmonary arterial hypertension includes either primary or idiopathic PH. This condition has been associated with varying degrees of intra-parietal arteriolar lesions and is considered rare in dogs [12,13]. Some congenital heart malformations, such as patent ductus arteriosus [14] or large atrial or ventricular septal defects [15] with left-to-right shunting can cause PH due to pulmonary circulation volume overload [8]. This form is considered reversible, but in some cases arteriolar lesions similar to those described for the idiopathic type have been reported [16,17]. However, it is still not completely clear whether or not PH and the observed lesions are caused by a congenital predisposition of the animal to develop idiopathic PH, or by the shunt itself [16,18].

Group 2

Dogs with high pulmonary venous pressure, increased capillary wedge pressure and normal PVR are included in this group. This condition is the most frequently observed cause of PH in dogs and is secondary to increased left atrial pressure and left heart failure [19] occurring with myxomatous mitral valve disease (MMVD), dilated cardiomyopathy (DCM), myocarditis and atrial distension associated with atrial

fibrillation [9,14,20]. In dogs with MMVD, the severity of PH is correlated with the progression of the disease, increased left atrial pressure [21–23] and an increased risk of death [23].

Table 1. Classification of pulmonary hypertension (PH) according to the World Health Organization system and human and canine diseases associated with the pathophysiologic mechanism of each group

Group	Human disease	Canine disease
1 Pulmonary arterial hypertension	Idiopathic (Primary) Heritable Drug and toxin induced Connective tissue disease HIV infection Portal hypertension Congenital heart disease Schistosomiasis	Idiopathic Congenital heart disease associated with cardiovascular shunts
2 Pulmonary hypertension due to left heart disease	LV systolic dysfunction LV diastolic dysfunction Valvular disease Congenital/acquired left-heart inflow/outflow obstruction	MMVD DCM Congenital/acquired left-heart inflow/outflow obstruction
3 Pulmonary hypertension due to disorders of the respiratory system or hypoxia	Chronic-obstructive pulmonary disease Interstitial lung disease Pulmonary disease with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental lung diseases	Pulmonary fibrosis Chronic bronchitis Bronchiectasis Pneumonia Tracheobronchial disease Pulmonary neoplasia High altitude
4 Pulmonary hypertension due to thrombotic or embolic disease	Thrombo-embolic obstruction of proximal or distal pulmonary artery Pulmonary embolism	Systemic diseases associated with hypercoagulability (Hyperadrenocorticism, IMHA, Polycythaemia, Protein-losing nephropathy, Pancreatitis, Neoplasia, Sepsis) Heartworm disease Lungworm disease
5 Pulmonary hypertension with unclear multifactorial mechanism	Hematologic disorders Systemic disorders (Sarcoidosis, Pulmonary hystiocitosis, Limphangioleiomyomatosis) Metabolic disorders (Glycogen storage disease, Gaucher disease, Thyroid disorders) Others (Tumour obstruction, Fibrosing mediastinitis, Chronic renal failure, Segmental PH)	None recognized

LV = left ventricular; MMVD = myxomatous mitral valve disease;
DCM = dilated cardiomyopathy; IMHA = immune-mediated haemolytic anaemia

Group 3

Canine PH associated with acute or chronic hypoxia can be caused by exposure to high altitudes [24] as well as respiratory disease such as collapsing trachea [9], pulmonary fibrosis, pneumonia, tracheobronchial disease, chronic pulmonary disease, neoplasia [14] and canine monocytic ehrlichiosis [25].

Group 4

Canine diseases associated with pulmonary thromboembolism (PTE) and secondary PH include immune-mediated hemolytic anemia, neoplasia, protein-losing nephropathy, hyperadrenocorticism and sepsis [26]. Furthermore, parasitic infections of the pulmonary vessels such as heartworm disease (HWD) due to *Dirofilaria immitis* infection [26,27] and lungworm disease due to *Angiostrongylus vasorum* [28,29] can cause PH, more commonly as a complication after parasiticide administration and worm death [30–32].

Group 5

Currently there are no recognised canine diseases in this class.

PATHOPHYSIOLOGY

The pulmonary circulation is a high-flow, low-resistance system. In this way it can provide adequate oxygen supply to the pulmonary alveoli without damaging the thin alveolar walls [33]. In dogs, normal systolic PAP is 21.4 ± 1.5 mmHg and is positively correlated with age. [34]

There are three recognised mechanisms for the development of PH. The first is pulmonary circulatory overload, which occurs in cases of congenital heart disease with left-to-right shunts (group 1 of the WHO classification of PH). The second is an increase in PVR, which happens in groups 1, 3, 4 and 5, and the third is an increase in pulmonary venous pressure and capillary wedge pressure, which happens with left-sided heart failure (LHF) (group 2) [35].

Pulmonary circulatory overload

When the pulmonary arterial system is over-perfused a protective mechanism activates a reflex arteriolar vasoconstriction in order to limit the blood flow to the vulnerable alveolar circulation [10,36]. This mechanism, which can be reversible at the beginning, can become irreversible as a consequence of progressive arteriolar wall thickening, ranging from a reversible medial proliferation to an irreversible occlusion due to intimal fibrosis and necrotizing arteritis. The progressive increase in PVR in patients with a left-to-right shunt can be attributable mostly to these vascular lesions and only partially to the amount of the shunted blood [37]. Dogs with congenital heart disease often develop mild to moderate PH [9,14]. In a study of 24 adult dogs with patent ductus arteriosus (PDA) none developed PH [18], while in another study of five related

Pembroke Welsh Corgies with large PDAs, severe PH developed early in life most likely because of the circulatory overload associated with genetic and environmental factors [36]. In rare cases, the pulmonary pressure exceeds the systemic pressure causing shunt reversal. This phenomenon is known as Eisenmenger's physiology and has rarely been described in dogs [14].

Increased Pulmonary Vascular Resistance

Chronic pulmonary disease and chronic hypoxia are associated with increased PVR resulting from vasoconstriction and vascular remodelling [38]. When alveolar oxygen concentration falls, vasoconstriction of the local arterioles allows blood flow to be directed to the better oxygenated areas of the lungs, optimizing ventilation-perfusion matching [39]. In cases of generalized hypoxia, which happen at high altitude, this mechanism can cause an increase in PAP. In dogs, a species that has a reduced response to generalized hypoxia compared with other species [40], only mild to moderate PH has been observed after prolonged physical training at high altitudes [24]. The increase in PVR can be limited by some endogenous mediators like carbon monoxide, nitric oxide (NO) or prostacyclin [41]. Moreover, a compensatory polycythaemia secondary to chronic hypoxemia may further increase PVR because the increase in the erythrocyte number is the main determinant of blood viscosity, which is directly correlated with vascular resistance [42].

With chronic injury, the release of inflammatory mediators and the activation of platelets and endothelial cells contribute to arterial wall remodelling and worsening of PH [38], as a consequence of external compression against vascular walls (restriction) and internal reduction of the lumen (obstruction) [38]. The reduction in luminal diameter can be secondary to thromboembolism (commonly observed in dogs with heartworm [30] or lungworm disease [43], and other systemic disorders [26]) or to the thickening of the vascular wall [44]. In particular, an altered production of vasoactive mediators such as NO, endothelin-1, prostacyclin, serotonin and thromboxane, has been recognised [45]; increased release of platelet derived growth factors, and their receptors (tyrosine-kinases), may also contribute to disease progression and arterial obliteration as they stimulate the proliferation of muscle cells and fibroblasts in humans with idiopathic PH [46]. In chronic embolic pulmonary diseases, endothelin-1(ET-1) has a role in arterial remodelling and wall thickening, although a direct obstruction of the terminal vessel is considered the main mechanism responsible for the development of PH [47]. Moreover, the recruitment of arteriovenous pulmonary shunts can limit the development of severe PH [29].

Increased pulmonary venous pressure:

In LHF, the PVR is not initially increased, and PH results from the combination of increased left atrial pressure and reactive hypoxic vasoconstriction [19]. In chronic disease, the neuro-hormonal activation of the sympathetic nervous system, renin-angiotensin-aldosterone system, phosphodiesterase-5 and natriuretic peptides results in sodium and water retention, vasoconstriction and decreased sensitivity to

endogenous vasodilators [1]. Moreover, endothelial dysfunction occurs which activates endothelin-1 mediated vasoconstriction and smooth muscle cell proliferation, with a secondary increase in PVR [48]. Other mediators of vascular tone can play a role in the development of PH in LHF. The reduced production of NO (a potent vasodilator produced by endothelial cells) and reduced sensitivity of the arterial muscle cells to NO have been observed in humans with LHF [48].

Response of the right ventricle to increased PAP

The right ventricle (RV) is functionally coupled to the pulmonary circulation. The structural characteristics of the RV allow for the accommodation of a large increase in blood volume (i.e., preload) but not of a rapid increase in arterial resistance (i.e., afterload). Increased afterload induces increased RV contractility and hypertrophy while maintaining the internal diameter (concentric hypertrophy). If the magnitude or rate of the increase in PAP are too high, this mechanism fails and the RV internal diameter increases (eccentric hypertrophy) [42]. As demonstrated in a canine model of chronic PH, the RV is able to maintain the CO by increasing its elastance and stiffness as well as increasing atrial and ventricular contractility and distensibility [49].

The mechanisms underlying the compensatory adaptation of the RV to PH are not completely understood, but an important role can be attributed to the increased density of adrenergic receptors in the RV myocardium [50]. The development of RV hypertrophy is associated with an increased oxygen demand and sometimes with impaired coronary circulation. These conditions can cause an imbalance in oxygen supply and demand and the development of RV failure [46].

CLINICAL SIGNS

Pulmonary hypertension is often a subtle condition not associated with specific clinical signs. As it is often a secondary complaint in dogs, clinical history and signs are usually those of the primary disease [10]. Respiratory signs such as tachypnoea, dyspnoea, cough and laboured breathing are frequently reported in dogs with both primary and secondary PH [9,12,14,20,38,51]. In cases of PH secondary to pulmonary disease, abnormal lung sounds (crackles and wheezes) and cyanosis in cases of severe hypoxia have been reported [38]. In PTE, systemic signs like vomiting, melena, fever, lethargy, altered mental status and epistaxis have been described in addition to respiratory signs [26]. A right apical systolic murmur is present in cases of tricuspid regurgitation (TR) or, more rarely, a left basal diastolic murmur in cases of pulmonary insufficiency.

In dogs with PH secondary to MMVD, a left apical systolic murmur is usually present. Sometimes signs consistent with pulmonary oedema, such as dyspnoea, pulmonary crackles and fatigue are also present [19]. In these dogs, the tricuspid valve can also be affected by the degenerative process and a right apical systolic murmur can be audible [19]. A recent study found a positive correlation between PH and a loud right apical

systolic murmur (≥ 4/6 grade) or a louder murmur on the right side in dogs with MMVD [52].

In more advanced cases, signs consistent with right-sided CHF, namely ascites, jugular vein distension or peripheral oedema can be found [9,14,20,38] sometimes associated with signs of low output heart failure, such as weak femoral pulses, depressed mental status and syncope [9]. Clinical signs are usually progressive and the clinical picture in end-stage cases can be characterised by cyanosis, weakness, recumbency, reluctance to move and lethargy [9,12,13].

DIAGNOSIS

Right heart catheterisation

Right heart catheterisation (RHC) is the gold standard method to measure systolic, diastolic and mean PAP [3,19,53]. It also enables measurement of right atrial pressure, pulmonary wedge pressure, and left atrial pressure, calculation PVR and CO [42] and differentiation of pre-capillary from post-capillary PH. This technique also permits direct assessment of the haemodynamic effect of vasoactive substances or drugs (e.g., carbon monoxide, oxygen, sildenafil, iloprost, verapamil, bronchodilators) on PAP or PVR in order to predict the response to therapy [3,53]. Unfortunately, because of equipment cost and the need for general anaesthesia this technique is usually not accessible to veterinary practitioners and may carry a risk in severely compromised dogs [10,19].

Thoracic radiography

Thoracic radiography can provide useful information about respiratory and/or cardiac diseases associated with PH, although no pathognomonic radiographic changes can be found in dogs with PH. Severe PH is usually associated with cardiomegaly, right heart enlargement with a reverse-D shape on the ventro-dorsal or dorso-ventral projections and increased sternal contact on the lateral projection, as well as pulmonary infiltrates, enlargement of the main pulmonary artery, and enlarged, tortuous or blunted pulmonary arteries (Fig 1 A and B) [10,53]. Radiographic evaluation also helps to detect signs of right-sided CHF including dilation of the caudal vena cava, hepatomegaly, pleural effusion or ascites and to rule out cardiogenic causes of the respiratory signs [38]. In dogs with PH associated with MMVD, cardiomegaly and left atrial and ventricular dilation are often the main radiographic features (Fig 1 C and D). These aspects are evident as an increased long axis and short axis of the cardiac silhouette [54] and increased tracheal bifurcation angle [55]; moreover, dilated pulmonary vessels, and an interstitial and/or alveolar pattern can be present in cases of cardiogenic pulmonary oedema [56]. In a recent study evaluating the radiographic features of dogs with MMVD and PH, a short-axis diameter of the cardiac silhouette on lateral projection of > 5.2 thoracic vertebrae and a sternal contact of > 3.3 thoracic vertebrae were significantly correlated with PH with a predictive accuracy of 85.9%

[54], although these parameters may reflect both left and right ventricular enlargement [57].

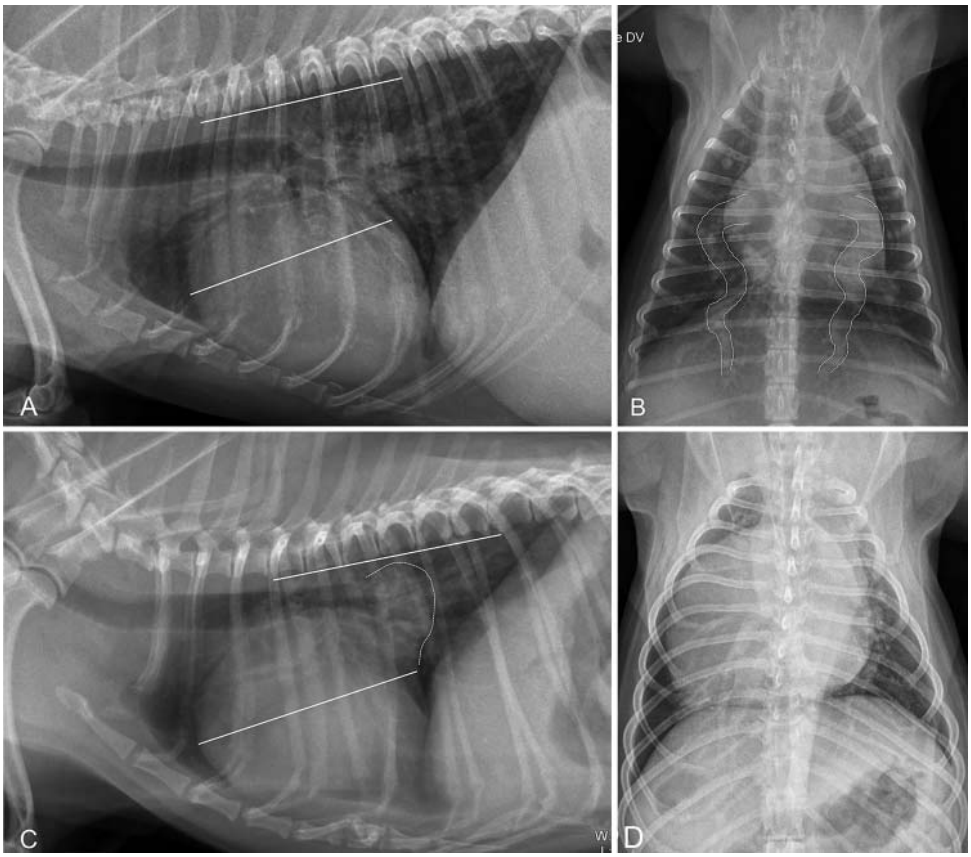

Figure 1. Right lateral (A) and dorso-ventral (B) views of the thorax of a 12-year-old mixed breed dog with pulmonary hypertension associated with pulmonary thromboembolism and right lateral (C) and dorso-ventral (D) views of the thorax of a 10-year-old Cavalier king Charles Spaniel with pulmonary hypertension associated with myxomatous mitral valve disease. (A) The cardiac silhouette is enlarged with an increased sternal contact and increased length of the short axis (white line) which is transposed onto the vertebral column for measurement beginning from the cranial edge of T4 (short axis length = 5.8 length thoracic vertebrae). (B) The large and tortuous caudal pulmonary arteries are outlined. (C) The cardiac silhouette is severely and globally enlarged with an increased sternal contact and increased length of the short axis (solid line) (short axis length = 6.2 length thoracic vertebrae); the contour of the severely enlarged left atrium is outlined (dotted line). (D) The severely enlarged cardiac silhouette has a reverse-D appearance and the right caudal pulmonary artery and vein are prominent.

Electrocardiography

Electrocardiography is neither a sensitive nor a specific test to diagnose PH [38]. However, right ventricular and atrial enlargement can be suspected if right axis deviation

of the QRS and high voltage P waves are found, respectively [10,58]. Arrhythmias can be associated with PH and are considered the effect of the increased RV afterload and impaired myocardial perfusion [59]. Atrial fibrillation, ventricular and supraventricular tachycardia, ventricular premature complexes, 1st degree atrioventricular block and bradycardia have been also reported in dogs with PH [9,14].

Echocardiography

Echocardiography is the most commonly employed method for the diagnosis of PH in dogs and can be useful for non-invasive calculation of certain haemodynamic parameters. Many echocardiographic modalities can be useful in the evaluation of dogs with PH such as two-dimensional real time (2D), M-mode, colour code, spectral and tissue Doppler [1,19].

2D and M-mode findings

2D and M-mode echocardiographic features of dogs with mild to moderate PH can often be normal. Only in cases of moderate to severe PH do some echocardiographic findings suggest an increased pressure in the RV or pulmonary artery including flattening of the interventricular septum [60], right atrioventricular dilation [9,14] or RV eccentric hypertrophy (Fig. 2) [13]. Right ventricular concentric hypertrophy has been described in cases of severe PH, but it seems to develop mainly in young dogs, before the first year of age [14,60]. Other echocardiographic findings suggestive of PH are a RV area larger than the LV area, a cardiac apex that includes the RV and coronary sinus dilation [60,61]. Some alterations can be also observed regarding the left ventricle which can appear small because of poor filling [13,53], with a triangular shape in the short axis (Fig 2D) and increased eccentricity index as shown in Fig 3A. The pulmonary artery is often dilated in dogs with PH [9,22]. Dilation can be suspected if the PA vs aortic root diameter ratio is above 1.15 [60] (Fig 3B). In some cases dilation results in lack of coaptation of the semilunar cusps and a diastolic ballooning of the leaflets can be observed [22,60]. The distensibility index of the right pulmonary artery (Fig 3C) was predictive of PH and highly correlated with invasively measured PAP in dogs with HWD [27]. In cases of post-capillary PH these findings are associated with left-sided valvular or myocardial dysfunction and severe left atrial enlargement [1]. The main 2D echocardiographic features of dogs with pre-capillary and post-capillary PH are shown in Fig 2.

Tricuspid annular plane systolic excursion (TAPSE) is a linear parameter widely used for the assessment of RV systolic function as it correlates with RV ejection fraction in humans [62]. Tricuspid annular plane systolic excursion has an inverse relationship with PAP and is predictive of survival in patients with heart failure [63]. In dogs, a study showed that TAPSE was inversely correlated with the severity of PH of different origins [64].

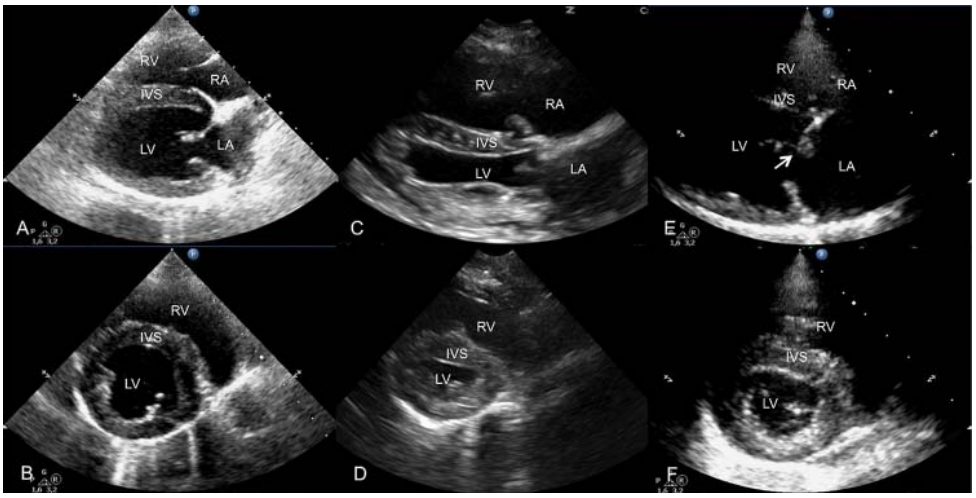

Figure 2. Right parasternal long-axis view (A, C and E) and short-axis view (B, D and F) obtained by a normal dog (A, B), a dog with pre-capillary pulmonary hypertension (PH) (C, D) and a dog with post-capillary PH associated with myxomatous mitral valve disease (E, F). Observe the severe RV dilation, small LV and septal flattening in images C and D and the severe left heart dilation associated with degenerative lesions of the mitral valve (arrow) in images E and F.
RV=Right ventricle; RA=right atrium; IVS=interventricular septum; LV=left ventricle; LA=left atrium.

Colour and spectral (pulsed and continuous wave) Doppler findings

Doppler echocardiography plays a main role in the evaluation of dogs with PH, permits detection of TR and pulmonary insufficiency and quantitatively estimates the trans-valvular gradients.

Tricuspid regurgitation is common in patients with PH especially when the PH exceeds 50 mmHg. The peak velocity (VMax) of the TR jet can be used to calculate the systolic RV to the right atrium peak gradient (PG) by applying the modified Bernoulli equation ($PG=4xVMax^2$) [65, 66]. Although there is no definitive consensus on the threshold of pulmonary pressure considered normal in the dog, normal resting values are usually considered for TR Vmax ≤ 2.8 m/s corresponding to a PG ≤30 mmHg) [20, 67]. Therefore, dogs with TR Vmax > 2.8 are considered affected by PH. Tricuspid regurgitation velocity can also be used to define the severity classes of PH as shown in Fig 3D [9]. Tricuspid regurgitation derived PG is correlated with invasively measured PAP [66] and the right atrial estimation can be added to estimate the true PAP [67] although with this method an overestimation of the PH severity is possible [19]. The accuracy of Doppler estimated PAP is also dependent on correctly interrogating the TR jet and on the RV function; therefore, if there is RV dysfunction, PAP can be underestimated or missed. Another limitation of this method is the inability to estimate PAP in patients with no recordable TR jet. However, despite these limits, the TR jet remains the non-invasive method of choice to estimate the RV and pulmonary artery systolic pressure in dogs with PH [19].

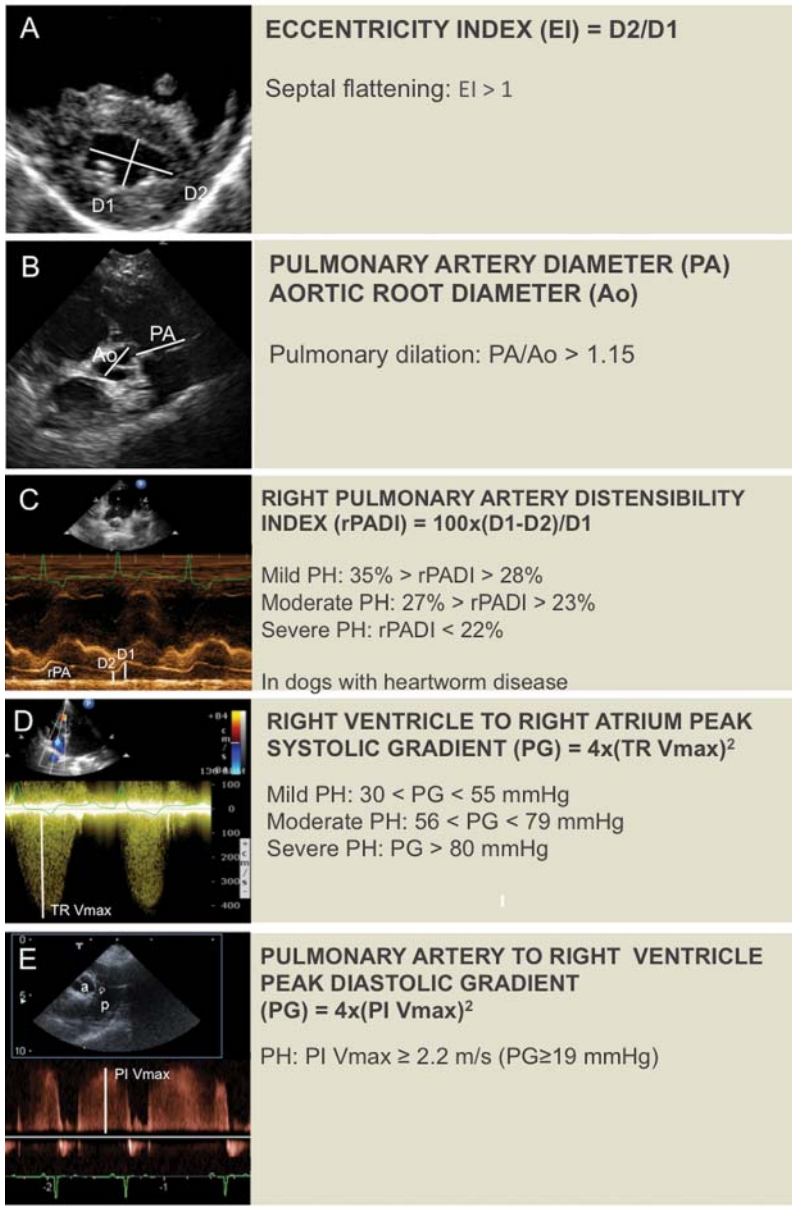

Figure 3. Echocardiographic two-dimensional (A, B), M-mode (C) and echo-Doppler (D, E) features suggestive of pulmonary hypertension (PH). The echocardiographic projection and the measured modalities are shown on the left side of the panel; equations and reference values are reported on the right side. See text for further details and references.
PA = Pulmonary artery; Ao = Aorta; rPADI = right pulmonary artery distensibility index TR = Tricuspid regurgitation; Vmax = peak velocity, PI = pulmonary insufficiency.

If pulmonic insufficiency is present, the modified Bernoulli equation can be applied to the pulmonic regurgitated jet (Fig 3E). In particular, the early diastolic velocity can be

used to calculate the mean PAP, and the late diastolic velocity to calculate the diastolic PAP [60,65]. Pulmonic insufficiency with a peak velocity ≥ 2.2 m/s is considered abnormal and suggestive of PH [14].

The pulmonary flow profile can change its shape in cases of PH as shown in Fig 4. Three pulmonary flow profiles have been described: Type 1 (normal) has a symmetrical profile with a dome shape; Type 2 (mild PH) has a rapid acceleration and an asymmetrical profile; Type 3 (severe PH) has a rapid acceleration and a notching during deceleration [14,60]. The rapid acceleration of the pulmonary ejection flow can be quantitatively assessed by the acceleration time (AT) which is inversely correlated with the PAP [68]. In a more recent study, AT, and its ratio with pulmonary artery ejection time (AT/ET), and heart rate (AT/heart rate) were useful for predicting PH in West Highland white terriers with chronic pulmonary disease (Fig 5A) [69]. In another study on dogs with MMVD and PH, pulmonary artery AT and AT/ET were also significantly correlated to PAP [22].

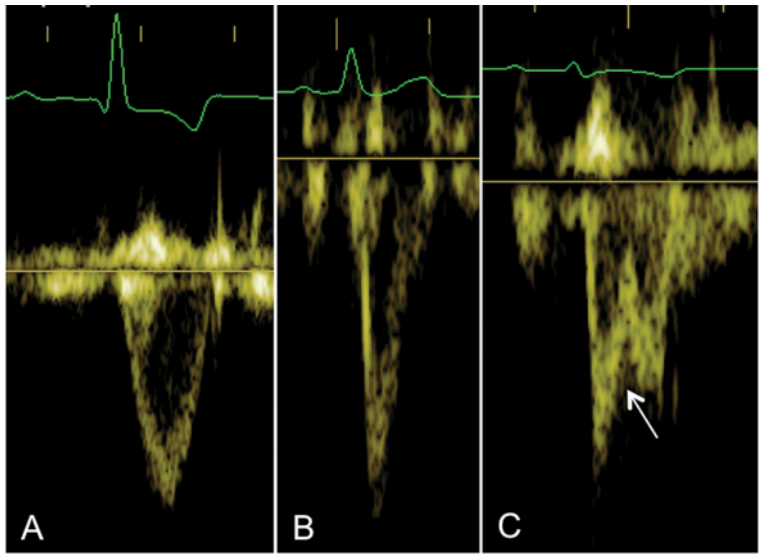

Figure 4. Pulmonary artery flow profile patterns. (A) Type 1, normal symmetric flow profile; (B) Type 2, steep flow profile with rapid acceleration phase, associated with mild PH; (C) Type 3, steep flow profile with a mid-systolic notch (arrow), associated with severe PH. See text for further details and references.

The myocardial performance index (MPI), could appropriately discriminate healthy subjects from patients with PH in humans [70]. This echocardiographic index was also investigated in dogs [71] and was a sensitive and specific predictor of PH [22].

Tissue Doppler imaging findings

Tissue Doppler imaging (TDI) of the lateral tricuspid annulus can provide indexes of RV systolic and diastolic function and can help in refining the diagnosis of PH,

especially when TR or pulmonary insufficiency are not present or not adequate for accurate interrogation [72].

Tissue Doppler imaging derived parameters could assess RV dysfunction more accurately than conventional Doppler echocardiography in a rat model of PH [73] and could accurately predict PH in human patients without TR independently of the presence of myocardial dysfunction [74]. In dogs, both diastolic and systolic TDI derived velocities showed a significant correlation with PAP and were highly sensitive and specific in predicting PH [72]. Moreover, the TDI of the tricuspid annulus can be used to calculate the right ventricle MPI as shown in Fig 5 B.

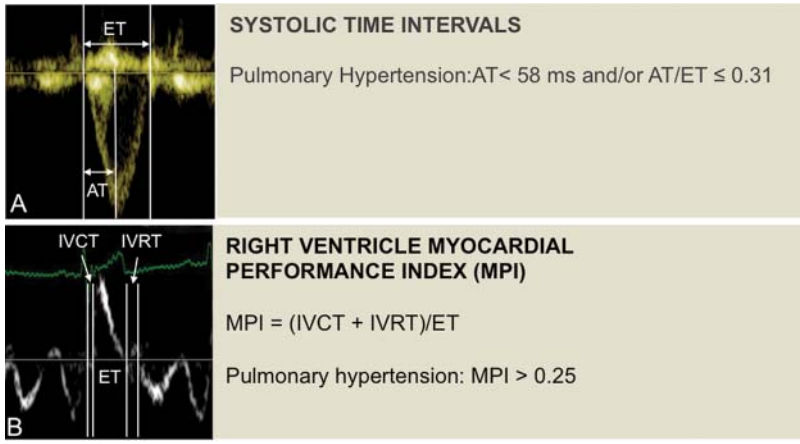

Figure 5. Systolic time intervals obtained by pulmonary artery systolic flow (A) and tissue Doppler imaging of the tricuspid annulus (B) showing the method of calculation of right ventricle myocardial performance index (MPI). The flow profiles and measured modality for each interval are shown on the left side of the panel, equations and reference intervals are reported on the right side. See text for further details and references.
AT = Acceleration time; ET = Ejection time; IVCT = isovolumetric contraction time; IVRT = Isovolumetric relaxation time.

Biomarkers

A biomarker is a protein or molecule that is easily obtained, quantitatively assessed and helpful in guiding diagnostics or treatment [75].

In recent years, different cardiovascular biomarkers able to discriminate between cardiac disorders and pulmonary disorders, including PH, have been investigated. Some of them, namely cardiac troponins and natriuretic peptides, are available as routine laboratory tests and have been studied in dogs with pre-capillary and post-capillary PH. Other biomarkers, like endothelins are currently employed in research settings but their use in clinical practice is not considered promising.

Cardiac troponins

Troponins are regulatory proteins that are part of the cardiac and skeletal contractile apparatus. They are also present to a minor extent in the cytosol of myocytes. Cardiac

troponin T (TnT) and troponin I (TnI) are considered specific markers of cardiac injury in humans and animals [75]. Cardiac TnI is elevated in dogs with both pre-capillary and post-capillary PH and is mildly positively correlated with PAP and with echocardiographic indices of atrioventricular dilation [11]; although, in another study on dogs with pre-capillary PH cardiac TnI did not correlate with PAP [76]. These conflicting results may be attributable to differences in patient population or underlying disease. Although elevations in cardiac TnI are significantly and positively correlated with mean PAP and are associated with increased risk of morbidity and mortality in human patients with PH [77], studies on the prognostic value of this biomarker in dogs with PH are still lacking. This biomarker is considered useful in detecting myocardial damage in cardiac and extra-cardiac conditions [78–81] and may serve as a global measure of adequacy of RV adaptation to increased afterload more than as an index of PH [77].

Natriuretic peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are pro-hormones involved in the control of plasma volume and are released by the atrial or ventricular myocardium following an increased parietal stretch. Their amino-terminal part (e.g., NT-pro-BNP), which is more stable than the biologically active C-terminal portion, is detectable in the plasma [75]. NT-pro-BNP is the most studied cardiac biomarker in veterinary medicine and is useful to help differentiate dyspnea of cardiac origin from non-cardiac origin in the dog [82,83]. Its plasma concentration is increased in dogs with pre-capillary PH and is significantly associated with TR VMax and the severity of PH [76]. Increases in ANP and NT-pro-BNP were also mildly correlated with PAP in a canine model of acute PTE, but their diagnostic value was significant only in the more severe cases with RV dilation or dysfunction [84]. NT-pro-BNP was also associated with PH in dogs with MMVD and its concentration decreased after pimobendan administration and associated improvement of clinical condition [85]. However, the predictive value of natriuretic peptides is considered low in dogs with PH and their increase can be considered a sign of RV overloading instead of PH itself [86].

Endothelin-1

Endothelin-1 plays an important role in the pathophysiology of PH as it is a mediator of both hypoxic vasoconstriction and vascular remodelling [87]. Its plasma concentration is highly correlated with PAP and other pulmonary haemodynamic variables in human patients with heart failure [88]. In dogs with HWD, both pulmonary and cardiac production of ET-1 was increased, and the plasma concentration of ET-1 was higher compared to dogs with other cardiac diseases and healthy controls [89]. In another study, big-ET-1, a more stable precursor of ET-1, was better correlated with TR VMax than NT-pro-BNP in dogs with cardiopulmonary diseases and was higher than in healthy dogs. Moreover, ET-1 was increased in dogs with varying malignancies [90].

For these reason, ET-1 may represent an effective clinical marker of cardiopulmonary and neoplastic disease in dogs, but must be combined with other tests for a correct interpretation [90]. Endothelin-1 is not routinely performed in the clinical setting and a point-of-care test has not been validated in small animals at present [75].

C-reactive protein

C-reactive protein is an acute phase protein widely used as an inflammatory marker. This biomarker was increased in dogs with mild to severe PH due to HWD or DCM and values higher than 6.8 mg/L have been recently proposed as a marker of PH in dogs with HWD [91].

TREATMENT

The first step in the management of dogs with PH is the correct assessment and control of the underlying causes of increased PAP [10] such as heart failure, heartworm or lungworm disease and conditions predisposing to PTE. In many cases however, PH is an irreversible or progressive disease that contributes to clinical deterioration and needs to be treated specifically.

Different drugs have been developed as pulmonary vasodilators and some of them have been investigated in dogs with primary or secondary PH while others are currently employed only in humans.

Inhibitors of phosphodiesterase-5 (PDE-5) are potent pulmonary vasodilators acting through the increase of intracellular cyclic guanosine monophosphate (cGMP) that consequently results in NO mediated vascular relaxation [92]. Sildenafil is approved as a first line treatment in humans with PH [3,4] and provides both haemodynamic and clinical improvement [93,94]. Use of sildenafil has been investigated in dogs with PH and amelioration of clinical signs like cough or ascites [51], quality of life [20,95] and exercise capacity [5,96] as well as improvement in haemodynamic parameters, were observed [20,51]. Sildenafil is well tolerated in dogs and no [96,97], or only mild, side effects have been reported [20,51]. Tadalafil, a long acting PDE-5 inhibitor approved for the treatment of PH in humans [4] has also been investigated in dogs, and has been effective in both lowering the PAP without reducing systemic blood pressure and in relieving clinical signs [98,99].

Pimobendan is a calcium sensitizer and mixed vasodilator with phosphodiesterase-3 (PDE-3) inhibiting activity. It is approved for the treatment of heart failure in dogs with MMVD and DCM [44]. In one study it was effective in reducing TR velocity and NT-BNP in dogs with post-capillary PH, and this effect was maintained long term [85]. A possible explanation for this positive effect could be the increased expression of PDE-3 and PDE-5 in PH which can influence vascular reactivity [100]. The efficacy of pimobendan in the treatment of dogs with pre-capillary PH has not been investigated.

Table 2. Clinical and hemodynamic effects of drugs used for the therapy of canine pulmonary hypertension (PH) in different studies

Drug (doses)	Study design	Animals (disease)	Diagnosis	Clinical effect	Hemodynamic effect	Side effects (n)	Reference
SILDENAFIL (Range 0.5 – 2.7 mg/Kg q 8-24 hrs, PO)	Retrospective	13 dogs (5 respiratory; 1 MMVD; 1 rPDA; 1 PTE; 5 unknown origin)	RHC or Echocardiography	Improved: Clinical signs	Reduced: PAP	Mild (3) Cutaneous flushing (2) Gastrointestinal (1)	(Bach et al. 2006)
SILDENAFIL (2.08-5.56 mg/ Kg q 24 hrs, PO)	Retrospective	22 dogs (10 respiratory, 9 CHF, 2 rPDA)	Echocardiography	Improved: Clinical signs	Reduced: Septal flattening; Increased: PA systolic time intervals	Mild (4) Lethargy Somnolence Nasal discharge Erect ears	(Kellum & Stepien 2007)
SILDENAFIL (1 mg/Kg q12 hrs; 1 mg/kg q 8 hrs, PO)	Case report	1 dog (unknown origin)	Echocardiography	Improved: Clinical signs PCV	Reduced: PA regurgitation velocity	None	(Toyoshima et al. 2007)
SILDENAFIL (1mg/Kg q 8 hrs, PO)	Prospective short-term, randomized, placebo-controlled, double-blind, crossover	13 dogs (13 MMVD)	Echocardiography	Improved: Quality of life Clinical signs	Reduced: TR peak gradient	None	(Brown et al. 2010)
SILDENAFIL (0.5 mg/Kg q 12 hrs, PO)	Prospective single arm, open label	5 dogs (5 Eisenmenger's syndrome)	Echocardiography	Improved: Clinical signs EPO	Not significant	None	(Nakamura et al. 2011)
TADALAFIL (1 mg/kg q 48 hrs, PO)	Case report	1 dog (PH of unknown origin)	Echocardiography	Improved: Clinical signs	Reduced: TR peak gradient	Systemic hypotension	(Serres et al. 2006)
TADALAFIL (50-200 mg/Kg/ hr i.v.); (4 mg/Kg PO)	Experimentally induced PH in a Beagle model	6 Beagle dogs	RHC	Not evaluated	Reduced: PAP, CVP, PCWP, SVR	Not evaluated	(Hori et al. 2014)

cont. Table 2.

Drug (doses)	Study design	Animals (disease)	Diagnosis	Clinical effect	Hemodynamic effect	Side effects (n)	Reference
PIMOBENDAN (0.18-0.3 mg/Kg q 12 hrs, PO)	Prospective short-term, double-blind, crossover with a long term open-label component	10 dogs (10 MMVD)	Echocardiography	Improved: Quality of life	Reduced: TR peak velocity Increased: PA systolic time intervals	None	(Atkinson et al. 2009)
IMANITINIB (3 mg/Kg q 24 hrs, PO)	Pilot study	6 dogs (4 MMVD, 2 HWD)	Echocardiography	Improved: Clinical signs ANP	Reduced: TR peak velocity Diastolic BP, HR Increased: LV dimension LA/Ao, LV systolic function	None	(Arita et al. 2013)

ABBREVIATIONS: hrs = hours; PO= orally; i.e. = intra venous; PH = pulmonary hypertension; MMVD = myxomatous mitral valve disease; rPDA = reverse patent ductus arteriosus; PTE = pulmonary thromboembolism; HWD = heartworm disease; RHC = right heart catheterization; PCV = packed cell volume; EPO = erythropoietin; ANP = atrial natriuretic peptide; PAP = pulmonary artery pressure; PA = pulmonary artery; TR = tricuspid regurgitation; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; BP = blood pressure; HR = heart rate; LV = left ventricle; LA/Ao = left atrium to aorta ratio.

In recent years some positive effects on the clinical condition of patients with PH have been obtained using tyrosine kinase inhibitors, and in particular imatinib, initially developed for anti-cancer therapy [101]. The mechanism of action of this drug is control of the expression of platelet-derived growth factor, a mediator associated with vascular remodelling and proliferation of smooth muscle arterial cells, inappropriately overexpressed in PH patients [102]. Imatinib had a positive effect on clinical, laboratory and haemodynamic parameters in a preliminary study in dogs [103]. These results are promising, however further studies are warranted to further demonstrate efficacy of this treatment.

High doses of calcium channel blockers are effective as acute vasodilators in humans who positively respond to dynamic tests during RHC, but they do not provide adequate long term control of PH [92].

Endothelin receptor antagonists bosentan, ambrisentan and sitaxentan reduce vasoconstriction and improve haemodynamic and clinical parameters in people with PH [101], even if their effectiveness in post-capillary PH seems to be limited [94]. Bosentan could improve stroke volume and limit deterioration of cardiac function in dogs with experimentally induced heart failure [104], but studies evaluating endothelin antagonists in veterinary medicine are still lacking. The high cost of these drugs also represents a limitation towards their use in canine clinical practice.

The prostacyclin analogue epoprosterenol, acts as a vasodilator and anti-proliferative drug in patients with PH [101]. Reports on the use of this class of vasodilators are not available in veterinary literature because of their high cost and the need for administration via constant rate intravenous infusion.

Other possible treatments for PH available in human medicine include lung or lung-heart transplantation or atrial septostomy (i.e. artificial creation of a right-to-left shunt to decompress the right heart) [92], but there are no reports about the use of these techniques in dogs. Published treatment options for canine PH are summarized in Table 2.

CONCLUSION

In recent years many advances have been made in the understanding of PH pathophysiology. In dogs, PH is often secondary to cardiopulmonary or systemic diseases, and it is associated with rapid worsening of the clinical condition and a decreased life expectancy. Echocardiography still represents the most commonly employed method for the definitive diagnosis of canine PH in the clinical setting but other diagnostic tests including thoracic radiography and laboratory tests are necessary for the complete evaluation of affected dogs. Currently, the treatment of the underlying disease, the management of heart failure, and the use of pimobendan and PDE-5 inhibitors seem to be a reasonable therapeutic approach to canine PH. Certain

newer drugs such as tyrosine kinase inhibitors may represent a valid therapeutic option for dogs in the future.

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PLUĆNA HIPERTENZIJA PASA

POSER Helen, GUGLIELMINI Carlo

Plućna hipertenzija pasa je kliničko stanje koje zahteva adekvatno ispitivanje i dijagnostiku s obzirom da ne postoje jasni i specifični klinički simptomi što može da uslovi brzi nastanak ireverzibilnih promena, oštećenje vaskularnog sistema pluća i razvoj slabosti desnog srca. U poslednjih nekoliko godina, objavljeno je više radova koji se odnose na plućnu hipertenziju, čime je u velikoj meri unapređeno razumevanje patofizioloških karakteristika ovog poremećaja, tačnost dijagnostičkih testova i tretman pacijenata. U radu se navode najnovija saznanja o hipertenziji pluća pri čemu je cilj teksta da se veterinari bolje upoznaju sa interpretacijom rezultata dijagnostičkih testova kao i sa kliničkim tretmanom obolelih pasa.