Focus on pulmonary hypertension – Part one (diagnosis)



***James McMurrough*, *Charlotte Duncan* and *Bethany Thomas* from Vets Now Manchester have written a two-part series on pulmonary hypertension. In this the first article in the series they focus on the work-up to making an accurate diagnosis.**

VIDEO CONTENT
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Pulmonary hypertension (PH) is defined by abnormally increased pressure within the pulmonary vasculature.[1] It can be associated with a variety of cardiorespiratory and systemic diseases. PH can be present without overt clinical signs (pre-clinical) in many cases, but in others can lead to significant haemodynamic effects. The clinical signs can be varied and non-specific. The diagnosis can be challenging in the primary-care setting, but there are many cases which may benefit from screening. The treatment is based on identifying and treating any underlying causes, although some patients will also benefit from phosphodiesterase 5 inhibitor (PDE5i) therapy. The outcome can be varied depending on the severity and the underlying cause. This two-part series presents a summary of the pathophysiology, categorization, diagnosis, and treatment of patients with PH in the primary-care setting.

Pathophysiology

Pulmonary circulatory physiology

The lungs have a double circulatory system; oxygenated blood is supplied by the bronchial arteries, originating from the aorta, whilst deoxygenated blood is supplied via the pulmonary artery. The pulmonary arteries decrease in size very rapidly to become a network of capillaries where gas exchange takes place. These capillaries empty into the pulmonary venules and eventually the left side of the heart to provide oxygen to the body. Pulmonary circulatory pressures are maintained at much lower levels than the systemic circulatory system. Normal mean pulmonary arterial pressure ranges from 10 to 15 mmHg[2] (Figure 1). It is a low pressure, low vascular resistance and high-capacity system.[1]

Deoxygenated blood leaves the right ventricle (RV) via the pulmonary artery into the lungs where gas exchange takes place. In the lungs, carbon dioxide is removed to be exhaled, and oxygen diffuses into the blood. As all of the blood pumped through the RV enters the lungs, cardiac output and the perfusion of the lungs are governed by the same factors.[3] The pulmonary circulatory system is constructed to allow for fluctuations in blood flow without increasing vascular resistance. The anatomical make-up of the vessels plays a large part in this; the proximal pulmonary arteriolar walls are made of mostly elastic tissue whereas the distal pulmonary arterioles are made of smooth muscle.[4] This allows for increased capacity (increased blood flow) without increasing vascular resistance.

A combination of passive capillary vasodilation in response to pressure increases and capillary recruitment allows for further adaptations when increases in cardiac output (e.g., exercise) occur.[1] Hypoxic pulmonary vasoconstriction (HPV) controls the local dilation of the vessels within the lungs based on the partial pressure of oxygen present. HPV is primarily mediated by calcium which acts to increase vasoconstriction and block potassium channels.[4] Contrary to the systemic circulatory system; when hypoxia is encountered in the lungs vasoconstriction occurs.[4] The purpose is to push deoxygenated blood towards well-ventilated parts of the lungs and to protect adequate gas exchange and

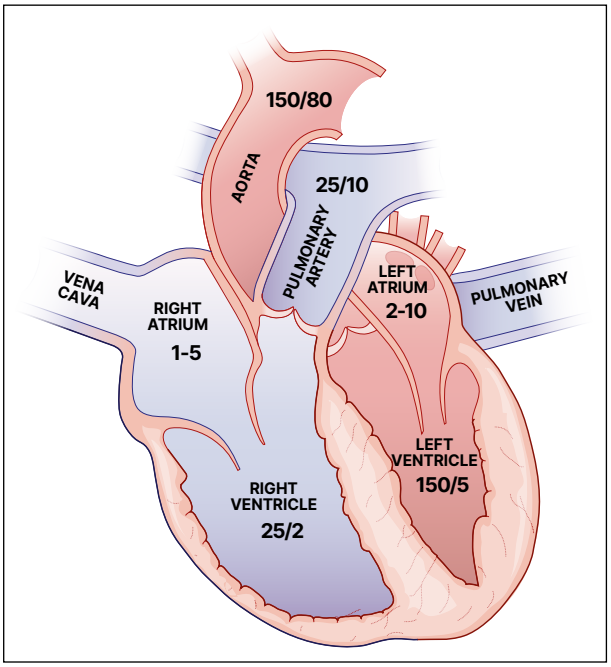

FIGURE 1: Normal cardiac pressures. (Adapted from *BSAVA Manual of Canine and Feline Cardiorespiratory* Figure 11.4 p. 81. Original drawing by S.J. Elmhurst BA Hons (www.livingart.org.uk) and reproduced with her permission)

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therefore systemic oxygenation. This compensatory mechanism is beneficial in the acutely hypoxic patient; however, chronic hypoxia can lead to prolonged pulmonary vascular resistance and vascular remodelling.[4]

The size mediation of larger vessels is controlled by endothelium derived vasoconstrictors (such as, endothelin-1) and vasodilators (such as, nitric oxide (NO) and prostacyclin).[5] Increases in endothelin in combination with reductions in NO synthase facilitates pulmonary vasodilation by reducing the production of cyclic guanosine 3-5 monophosphate (cGMP) which allows calcium to act on the smooth muscle cells of the arterioles.[4] PDE5 isoenzyme limits this process by inactivating cGMP production.[6]

Pulmonary hypertension (PH) pathophysiology

The occurrence of PH is dependent on failure of mechanisms that maintain the low pressure pulmonary circulatory system. Development of PH results from increased pulmonary blood flow, increased pulmonary vascular resistance and/or increased pulmonary venous pressure.[1] These disturbances to normal pulmonary circulation can occur alone; however, often one will lead to another – increased pulmonary blood flow can lead to increased pulmonary vascular resistance due to pulmonary artery vasoconstriction and pulmonary vascular remodelling.[1] Vascular remodelling occurs due to several different factors. Hypoxia leads to increases in vasoconstrictive mediators and decreases vasodilators, subsequent slower blood flow can lead to platelet aggregation and thrombosis and increased pulmonary vascular resistance (PVR).[4] Elevated levels of platelet-derived growth factor and vascular endothelial growth factor (VEGF) seen during hypoxic periods can lead to pulmonary vascular damage and subsequent vascular remodelling.[4]

It is important prognostically to establish the extent of vascular remodelling as the severity corresponds with reversibility and so response to therapy.[4] This can be achieved via invasive pulmonary parenchymal biopsy or vasodilation tests using inhaled NO.[7] Both interventions are technically challenging, costly and can pose risk to the patient making them widely unavailable within veterinary medicine; therefore, serial pulmonary arterial pressures are used as a pseudo-marker.

Normal movement of the RV in systole is governed by longitudinal fibres in cardiac muscle which are the most physiologically active.[4] These fibres begin at the tricuspid valve anulus and extend into the right ventricular outflow tract allowing for peristaltic-like movement of blood when in systole, enhancing the heart's ability to eject a large pulmonary stroke volume at low pressures.[4] When PH occurs, there is an increase in right ventricular afterload leading to compensatory hypertrophy of the RV and subsequent right atrial (RA) dilation. The adequacy of this compensatory mechanism is termed ventricular-arterial coupling (VA-coupling) and is what determines the clinical signs shown by the patient.[4] VA-coupling can be influenced by many factors; age of the patient, underlying disease process and the acute versus chronic nature of the disease.

Clinical presentation

PH can be considered a primary vascular disorder in some dogs or more commonly as a sequel to other cardiorespiratory or systemic diseases.[1] The need to screen for PH can be determined based on the clinical presentation of the case and the relative probability of the presence of PH. The clinical signs most strongly associated with PH include syncope (most commonly observed during periods of exertion or excitement), dyspnoea at rest, reduced exercise tolerance, and signs of right-sided congestive heart failure (R-CHF). Other clinical signs which are suggestive of PH include tachypnoea or increased respiratory effort at rest, and cyanotic or pale mucous membranes. It is important to note that these signs are not specific to PH and can be caused by several other cardiopulmonary diseases.

Cardiac auscultation over the tricuspid valve on the right side of the thorax is particularly important to check for the presence of a systolic heart murmur suggestive of tricuspid regurgitation. A diastolic left basal murmur is less frequently detected, due to pulmonic insufficiency, in some patients with advanced PH.[8] A split-second heart sound may also be noted in patients with PH, due to delayed closure of the pulmonic semi-lunar valve.[7] Clinical signs of R-CHF secondary to pulmonary hypertension (cor pulmonale) may include ascites, pleural effusion, jugular vein distension and jugular vein pulsation (Video 1). A constellation of other clinical examination findings may be present in patients with PH due to the underlying cardiopulmonary disease including abnormal respiratory pattern or effort, cyanosis, tachypnoea, crackles, wheezes, or increased bronchovesicular sounds.[1]

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VIDEO 1: Jugular vein pulsation.

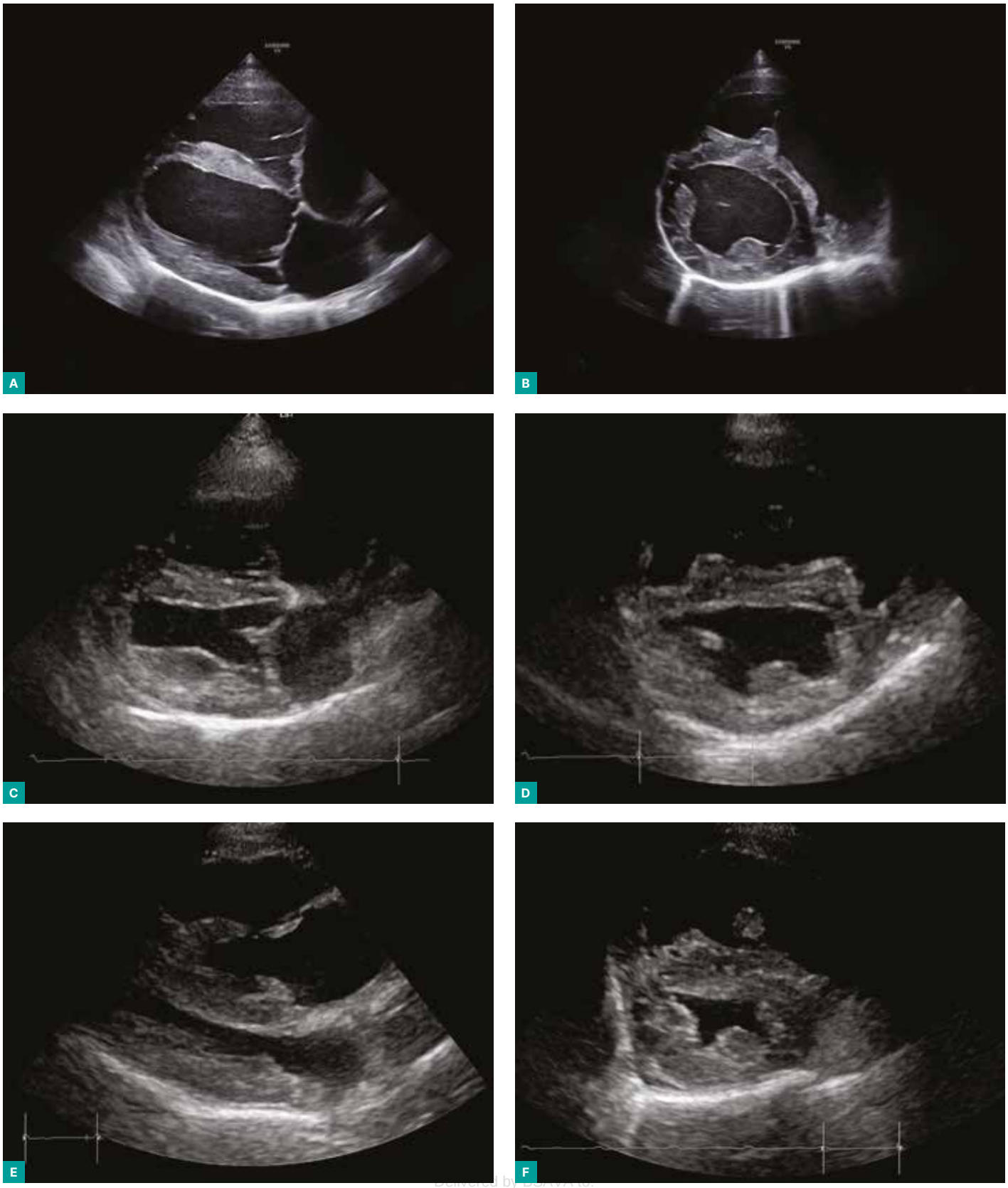
Diagnosis

The optimal means of PH diagnosis in humans is direct measurement of the pulmonary arterial pressure (PAP) by right-sided cardiac catheterization.[2] Given the need for sedation or anaesthesia in veterinary patients for cardiac catheterization, indirect assessment of PAP utilizing Doppler echocardiography is preferred. Given the indirect method of the Doppler echocardiography we should consider the technique a method of assessing probability of PH rather than a

definitive diagnosis. The results of echocardiographic assessment should be interpreted in light of the clinical signs which can help support the probability of a diagnosis of PH.

Echocardiography is used to assess the right heart for various structural heart changes associated with PH. These include:

- Tricuspid regurgitation (TR)
- Right ventricular cardiomegaly
- Right ventricular systolic dysfunction
- Right atrial cardiomegaly
- Flattening of the interventricular septum
- An underloaded left ventricle
- Dilation of the main pulmonary artery
- Increased peak early diastolic pulmonic regurgitation (PR) velocity
- Decreased right ventricular (RV) outflow acceleration time or acceleration time to ejection ratio
- Systolic notching of the RV outflow profile
- Enlargement of the caudal vena cava (Figure 2).



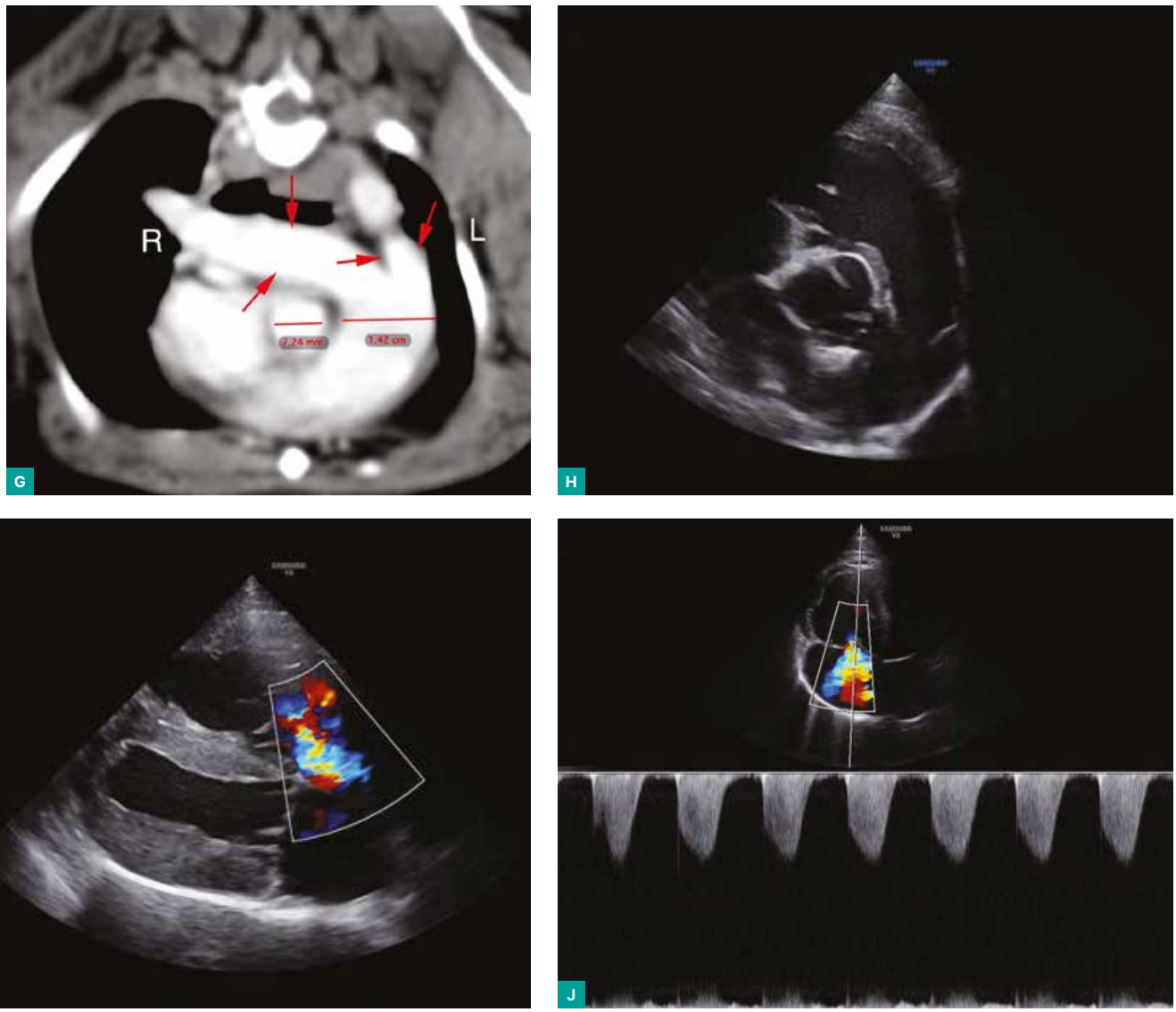


FIGURE 2: Echocardiographic and advanced imaging of pulmonary hypertension: (A) Right parasternal (RPS) long-axis four chamber view of the heart. Note the subjective mild-moderate right ventricular and right atrial cardiomegaly in a patient with PH due to diffuse pulmonary arterial thrombosis; (B) RPS short-axis view at the level of the papillary muscles in the patient from Figure 2A. Note the mild-moderate right ventricular cardiomegaly and mild flattening of the interventricular septum due to PH; (C) Right parasternal (RPS) long-axis four chamber view in a patient with PH due to pulmonary fibrosis. Note the subjective moderate-marked right ventricular and right atrial cardiomegaly; (D) RPS short-axis view at the level of the papillary muscles in the patient from Figure 2C. Note the moderate-marked right ventricular cardiomegaly and moderate flattening of the interventricular septum; (E) Right parasternal (RPS) long-axis view. Note the subjective marked right ventricular, with septal deviation towards the left ventricle and marked right atrial cardiomegaly in a patient with PH due to Angiostrongylosis; (F) RPS short-axis view at the level of the papillary muscles in the patient from Figure 2E. Note marked right ventricular cardiomegaly and marked flattening of the interventricular septum. (G) Computed tomography image of an enlarged main pulmonary artery (1.42 cm diameter) and enlarged right and left pulmonary arteries (red arrows) in a patient with PH. (H) RPS short-axis view at the level of the aortic semilunar valve in a patient with PH. Note the enlarged pulmonary artery (blue arrow) in relation to the aorta (red arrow). A PA:Ao >1.1 is considered enlarged. (I) RPS long-axis four chamber view in a patient with PH. Note the colour flow Doppler of tricuspid regurgitation. (J) Spectral Doppler of the tricuspid regurgitation in Figure 2I. Peak flow velocity of 4.8 m/s was consistent with PH (estimated systolic pulmonary pressure of 92 mmHg). (K) Dorsoventral radiograph of a patient with pulmonary hypertension and a pulmonary arterial bulge at 1 o'clock (red arrow).

The systolic PAP can be estimated using the peak TR velocity in the absence of pulmonic stenosis. This velocity can be used to derive the pressure gradient between the right atrium and ventricle using the modified Bernoulli equation (pressure gradient [ΔP] = $4v^2$). The estimated right atrial pressure is added to the pressure gradient giving the systolic PAP. The mean PAP can be estimated using the peak pulmonic regurgitation velocity. Given the inherent inaccuracy in estimating the right atrial pressure it is currently recommended to use continuous wave Doppler measurement of the tricuspid regurgitation velocity alone to determine the probability of PH1. The normal cardiac pressures are demonstrated in Figure 1.

Doppler interrogation of the TR should be performed from several standard (and non-standard) views to achieve parallel alignment with flow. The peak TR should be measured from the dense outer edge of the velocity profile not the 'feathered edge' (see Figure 2).[1] A TR peak velocity of >3.4 m/s has been proposed as a robust cut off for the diagnosis of PH in patients with an intermediate or high probability of PH.[1] This correlates to a systolic PAP of >46 mmHg. The previous classification system of mild, moderate, or severe pulmonary hypertension (based on respective increases in estimated systolic PAP) is considered outdated and not recommended given a lack of correlation between clinical severity of PH and estimated PAP.1

Thoracic radiography may demonstrate a pulmonary arterial bulge, right-sided cardiomegaly, evidence of tortuous, blunted or dilated pulmonary arteries suggestive of PH. Radiography can be used in the investigation of causes of PH but cannot be used to diagnose PH itself (Figure 3).

Classification

Pulmonary hypertension has been classified into six groups.

1. Pulmonary arterial hypertension (PAH)
2. Left-sided heart disease
3. Respiratory disease/ hypoxia
4. Thromboembolic disease
5. Parasitic disease
6. Multifactorial disorders or those with an unclear mechanism (Table 1).

This classification was based on that used in human medicine, and groups those with similar causes of PH, pathophysiology, and presentation of disease as well as its treatment.[1, 7, 9, 10]

These diseases all ultimately lead to increased pressure within the pulmonary vasculature through one of three mechanisms; increased pulmonary blood flow, increased pulmonary vascular resistance, or increased pulmonary venous pressure.[4, 11, 12]

The overall prevalence of PH is still uncertain, but the most common cause is thought to be left-sided heart disease; however, among severely affected dogs, respiratory diseases tend to predominate.[13]

Pulmonary hypertension can also be divided into pre-capillary PH; pulmonary vascular system abnormalities on the arterial side, and post-capillary PH where left-sided heart disease leads to pulmonary venous and therefore capillary hypertension. Postcapillary PH will have an enlarged left atrium along with other echocardiographic findings suggestive of PH, whereas in precapillary PH the left atrium is of normal size. Precapillary PH includes those diseases classed as group 1, 3, 4, 5 and 6 whilst postcapillary PH consists of group 2 and 6.[1,12]

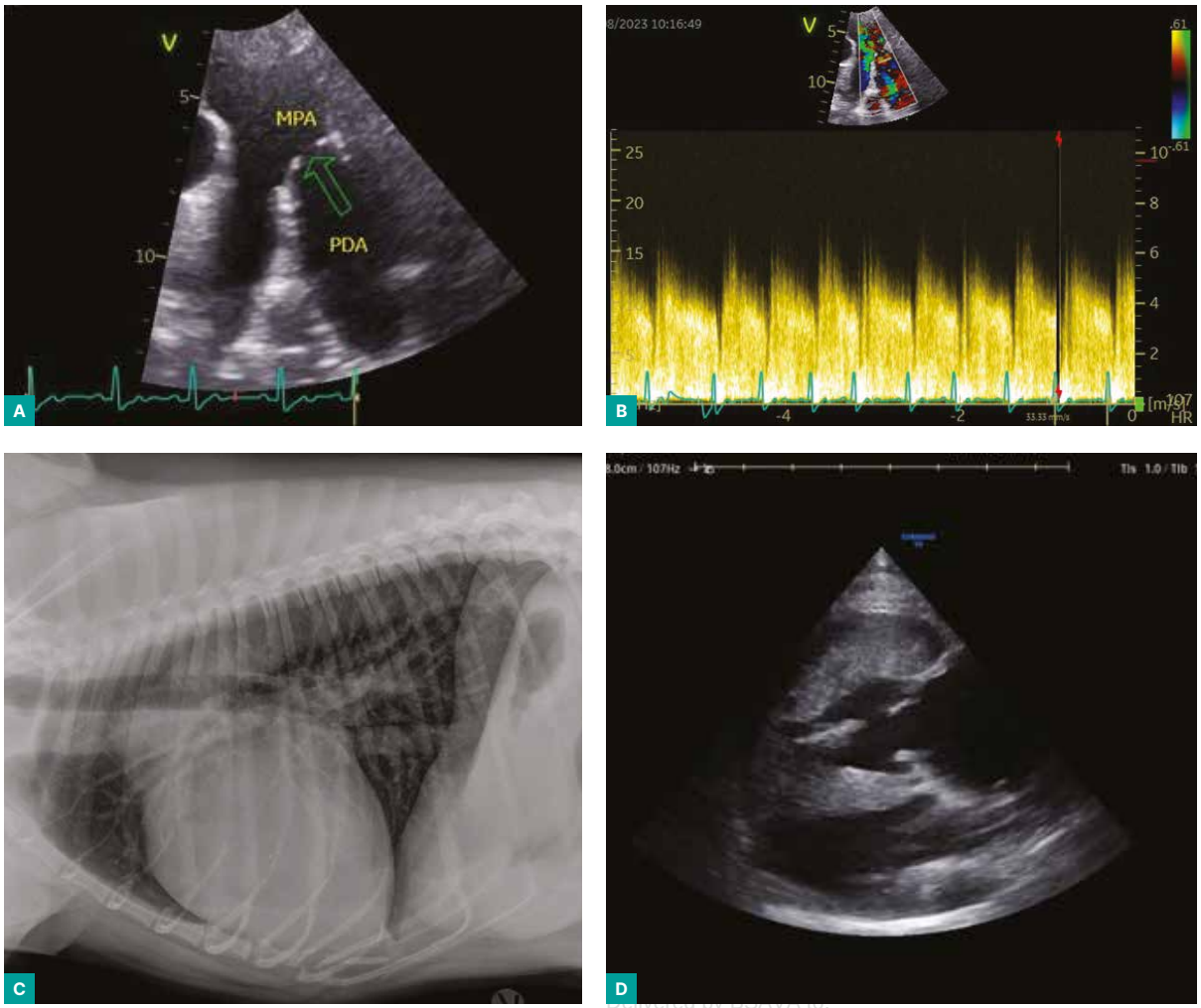


FIGURE 3: Congenital heart diseases: (A) RPS short-axis view optimized for the pulmonary trunk. Note the patent ductus arteriosus (PDA) and opening of the ampulla (green arrow), communicating with the main pulmonary artery (MPA). (Image courtesy of Chris Linney, Paragon Referrals); (B) Spectral Doppler interrogation of the PDA from Figure 3A. Note continuous flow (in both systole and diastole) giving the characteristic 'saw tooth' appearance. The high peak velocity in this patient (>4.5 m/s) does not suggest the presence of PH. (Image courtesy of Chris Linney, Paragon Referrals); (C) Right lateral radiograph of patient in Figure 3A. Note both the pulmonary lobar arterial (red arrow) and venous (blue arrow) dilation due to the overperfusion of the lungs associated with a left to right shunt; (D) RPS long-axis four chamber view of a patient with severe pulmonic stenosis. Note the similarities in the right-sided (right ventricular concentric hypertrophy, marked right atrial and ventricular cardiomegaly, and deviation of the interventricular septum to the left side of the heart) changes compared to a patient with PS.

TYPE 1 – Pulmonary arterial hypertension

- Idiopathic (IPHA)
- Heritable
- Drugs and toxin induced
- Associated with (APAH) – congenital cardiac shunts, pulmonary vasculitis, or vascular amyloid deposition
- Pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH)

TYPE 2 – Left heart disease

- Left ventricular dysfunction: DCM, myocarditis
- Valvular disease: MMVD, valvular endocarditis
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

TYPE 3 – Respiratory disease, hypoxia or both

- Chronic obstructive airway disorders
  - Tracheal or mainstem bronchial collapse
  - Bronchomalacia
- Primary pulmonary parenchymal disease
  - Interstitial lung disease
  - Infectious pneumonia
- Pulmonary neoplasia
- Obstructive sleep apnoea/sleep disordered breathing
- Chronic exposure to high altitude
- Miscellaneous

TYPE 4 – Pulmonary emboli/thrombi/thromboemboli

Acute or chronic PE/PT/PTE
(Massive PE/PT/PTE with RV dysfunction or submassive PE/PT/PTE without RV dysfunction)

- DIC
- Hyperadrenocorticism
- Recent surgery/trauma
- IMHA
- PLE/PLN
- Sepsis

TYPE 5 – Parasitic disease

- *Dirofilaria immitis*
- *Angiostrongylus vasorum*

TYPE 6 – Multifactorial/unclear mechanism

- Disorders having clear evidence of two or more underlying types 1–5 pathologies contributing to PH
- Masses compressing the pulmonary arteries (e.g. neoplasia, fungal granuloma, etc.)
- Other disorders with unclear mechanisms

TABLE 1: Causes of pulmonary hypertension.

Reflect on your reading

1. What is the normal range for mean pulmonary arterial pressure (mmHg) in a dog?

   a) 5–15 mmHg
   b) 10–15 mmHg
   c) 15–25 mmHg

2. Which of the following changes in physiology do not lead to the development of PH?

   a) Increased pulmonary blood flow
   b) Increased pulmonary vascular resistance
   c) Increased central venous pressure

3. Which of the following clinical signs is least commonly associated with PH?

   a) Dyspnoea
   b) Syncope
   c) Cough

4. Which of the following echocardiographic changes is least consistent with PH in a dog?

   a) Left ventricular concentric hypertrophy
   b) Right atrial enlargement
   c) Pulmonary arterial dilation

Answers available online in the BSAVA Library.

About the authors

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James graduated from the University of Bristol in 2008 and began work in a busy first-opinion emergency and referral practice in Manchester. He is an advanced practitioner in internal medicine, gaining his CertAVP(SAM) in 2012. He is also an advanced practitioner in veterinary cardiology, having gained his CertAVP(VC) in 2018.

James currently works as a referral clinician in both internal medicine and cardiology at Vets Now Referrals Manchester. He enjoys lecturing on a variety of subjects to members of the veterinary profession, examining on the certificate of advanced veterinary practice, and has a particular clinical interest in cardiorespiratory diseases and flexible endoscopy.

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Charlotte graduated from the Royal Veterinary College in 2021 following which she worked in general practice in Surrey for 2 years. She then relocated and completed a rotating internship at Vets Now Hospital in Manchester, where she now works on the Out of Hours team.

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Beth has been an internal medicine nurse at a referral hospital in Manchester since 2019. She qualified as a veterinary nurse in 2014 and gained her veterinary technician specialist (VTS-SAIM) status in small animal internal medicine in 2021. Her interests include emergency medicine, endocrinology and haematological disease.

References and further reading are available at **www.bsavalibrary.com**.

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