Diagnosis and Management of Pulmonary Hypertension
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Introduction

Pulmonary hypertension (PH), defined by abnormally great pressures in the pulmonary vasculature, is a hemodynamic state that can develop in association with a variety of cardiovascular, respiratory and systemic diseases. Clinical signs of PH include cough, tachypnea and exertional syncope. These signs are not diagnostically specific and because of this, the identification of patients for which PH is an appropriate therapeutic target can be difficult. During this presentation, the pathophysiology and therapy of PH will be addressed; clinical findings which help to distinguish patients with primary left heart disease from those with pulmonary arterial hypertension will be outlined.

Pathogenesis

In healthy individuals, pulmonary vascular resistance (PVR) – the hydraulic forces that must be overcome for a pressure difference to result in flow – is lower than is systemic vascular resistance. As a result, pulmonary arterial pressures are lower than systemic arterial pressures. Pulmonary hypertension (PH) refers to the abnormally great pressures in the pulmonary vascular system. In people, PH is defined by a mean pulmonary artery pressure that exceeds 25 mmHg. Mean pulmonary artery pressure can be only be obtained invasively, by right heart catheterization (RHC). Diagnostic RHC is rarely performed in veterinary patients, and the diagnosis is generally based on echocardiographic findings.

Pulmonary artery pressure (PAP) is related to pulmonary blood flow (Q) and PVR according to Ohm's Law: PAP_{mean} - LAP_{mean} = Q x PVR, where: LAP = left atrial pressure, Q = cardiac output [flow] and PVR = pulmonary vascular resistance.

None of these quantities is routinely measured, but the concept of PVR is important because it relates to therapeutic approach. PH can result from a rise in PVR, an increase in pulmonary blood flow, an increase in LAP or combinations of these factors.

Pathophysiology

When PH results from high PVR, it is described as "pre-capillary PH"; vasoconstriction and/or vascular remodeling are the principal causes of high PVR, although pulmonary thrombosis can contribute. Left atrial hypertension resulting from left heart disease is the primary cause of "post-capillary PH'. The right ventricle must generate a pressure that is adequate to propel the stroke volume not just to the lungs, but to the left atrium; as a result, a pathologic increase in left atrial pressure necessitates an increase in right ventricular and pulmonary arterial systolic pressure. In some patients with left heart disease, the increase in right ventricular – and therefore pulmonary arterial – pressure, initiates a cascade of vasoconstriction and vascular remodeling, increasing PVR and

resulting in PAP that is disproportionately high relative to left atrial pressure. PH imposes a pressure load on the right ventricle and potentially results in right ventricular hypertrophy, functional pulmonary and tricuspid valve regurgitation, myocardial dysfunction and right-sided congestive heart failure.

Clinical presentation

Clinical signs associated with PH include cough, tachypnea, exercise intolerance, syncope, and abdominal distention due to ascites. It is relevant that these clinical signs are associated with PH, but the association is not necessarily causal. For example, cough is unlikely to result directly from PH, but is more apt to reflect an underlying disease that has caused PH.

Physical findings may include adventitious lung sounds and a right apical systolic murmur resulting from tricuspid valve regurgitation. Pulmonary valve regurgitation is commonly detected echocardiographically but is rarely audible. When the clinical presentation includes respiratory distress and a right apical murmur, PH [and pulmonary thromboembolism] should be diagnostic considerations because the therapeutic approach to these disorders is different from that which is appropriate for left-sided congestive failure.

Diagnostic Evaluation

The definitive diagnosis of PH is through direct measurement of pulmonary artery pressures, but in veterinary patients, the diagnosis is more based on echocardiographic findings.

<u>Echocardiography</u>

Echocardiographic evidence of tricuspid valve regurgitation (TR) is commonly observed in patients with PH. The velocity of the TR jet, obtained by continuous-wave Doppler, is related to the systolic pressure difference between the right atrium and the right ventricle by the simplified Bernoulli equation ($\Delta P = 4v^2$ where ΔP is the pressure difference and v is the velocity of the regurgitant jet measured by Doppler echocardiography).

In the absence of pulmonary stenosis (PS), right ventricular and pulmonary artery pressures are *equal* during systole. Thus, measurement of the velocity of the TR jet provide a noninvasive *estimate* of systolic pulmonary artery pressure. The diagnostic accuracy of other echocardiographic variables including various systolic time intervals, tricuspid annuluar plane systolic excursion (TAPSE) as well the fractional change in dimensions of the right pulmonary artery have been evaluated. In general, these surrogate measures can provide supportive evidence and are considered in addition to the velocity of TR or when TR is absent. It is axiomatic that they are less accurate than the criterion ["gold"] standard to which they have been compared. Partly because of the inaccuracy of Doppler echocardiographic estimation of PAP, the ACVIM consensus panel recommended a *<u>probabilistic approach</u>* to the diagnosis of PH. That is, the velocity of TR is considered in the context of other echocardiographic variables, and a low, intermediate or high diagnostic probability of PH is assigned based on these findings. Echocardiographic evaluation of left atrial size is generally used

to determine if pulmonary hypertension is the result of high pulmonary vascular resistance [“pre-capillary”] or is the consequence of increases in left atrial pressure resulting from left heart disease [“post-capillary”]. In patients for which there is an intermediate or high probability of PH, normal or diminished left atrial dimensions provide indirect evidence that PH is pre-capillary; left atrial enlargement provides evidence that the PH is at least partly post-capillary.

An etiologic classification of types of PH, based on pathophysiologic mechanisms, recently was proposed:

Classification

- Group 1 - PAH
    - idiopathic pulmonary arterial hypertension
- Group 2 - LHD
    - canine mitral valve disease
- Group 3 - hypoxia
    - canine respiratory tract disease
    - high mountain disease
- Group 4 - thrombotic
- Group 5 - parasitic
    - heart worm disease
- Group 6 - multifactorial/unclear mechanisms

Reinero C, et al. ACVIM consensus statement guidelines for the diagnosis , classification , treatment , and monitoring of pulmonary hypertension in dogs. 2020; (January):1–25.

Therapy of Pulmonary Hypertension

Treatment of causative or underlying disorders such as heartworm disease or specific pulmonary diseases is essential. Various vasodilators have been used in attempts to decrease pulmonary vascular resistance, but sildenafil is the agent that use most often in canine patients. Sildenafil is an inhibitor of phosphodiesterase type 5 and is a relatively selective dilator of pulmonary arterioles; it generally is indicated when clinical signs result from pre-capillary pulmonary hypertension

There are numerous causes of PH, but after Dirofilariasis is excluded, the distinction between pre- and post-capillary PH is the most important therapeutically relevant goal. In general, the initial therapeutic approach to patients with post-capillary PH is directed toward optimization of treatment for left-heart disease. Agents such as sildenafil that result in relatively selective dilation of pulmonary arterioles are intended to reduce PVR. The resultant increase in pulmonary blood flow can potentially raise left ventricular filling pressures and precipitate the development of cardiogenic pulmonary edema. As a result, agents such as sildenafil should not be used, or used only with caution, in patients with left heart

disease, and generally only after resolution of pulmonary edema.
In contrast, when clinical signs are the result of high pulmonary vascular resistance and decreased systemic output, as is often the case in pre-capillary PH, the use of specific therapies such as sildenafil often is appropriate.

Idiopathic Pulmonary Arterial Hypertension

For mostly valid reasons, aggressive diagnostic evaluation including advanced diagnostic imaging and lung biopsy are seldom performed in patients with respiratory distress and PH. Arguably then, pre-capillary PH, or pulmonary arterial hypertension (PAH), often is idiopathic only because diagnostic evaluation is incomplete. Regardless, there is an important syndrome of PAH in patients that do not have Dirofilariasis or a history of chronic respiratory disease, which is typically observed in older, small- breed dogs. Brachycephalic dogs might be over-represented. Clinical signs include cough, tachypnea/respiratory distress, and syncope, the latter typically observed on exertion. The precise cause is unknown but the pathogenesis relates to vasoconstriction / vascular remodeling that causes an increase in PVR, and the development of PAH. As implied, the diagnosis is presumptive and based on exclusion of known causes of PH, such as heartworm disease. The syndrome is echocardiographically characterized by a normal or small left atrium / left ventricle - caused by diminished pulmonary venous return - and evidence of PH.

The prognosis is generally poor, although some patients respond favorably to administration of sildenafil and supplementary oxygen. The distinction between PAH and acutely decompensated left-sided heart failure can be challenging, but important because diuretic treatment is potentially harmful in the setting of idiopathic PAH. In these patients, the clinical signs are not the result of high pulmonary venous pressures. Conversely, as stated, agents such as sildenafil can harm in the setting of severe left sided heart disease. If echocardiography is not available, it is important to consider the possibility that idiopathic PAH is responsible for clinical signs such as tachypnea/ respiratory distress/exertional syncope, particularly when:

- distinct radiographic left atrial enlargement is absent
- there is a lack of response to diuretic therapy
- a cardiac murmur that is loudest over the *right* apex is identified.

Additional Readings / Complete References Available On Request

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