Pulmonary arterial hypertension secondary to chronic left-sided cardiac dysfunction in dogs

Pulmonary arterial hypertension is a description of a physiological finding rather than a diagnosis. Pulmonary arterial pressure is the result of interactions among pulmonary blood flow (right ventricular cardiac output), pulmonary vascular impedance and post-capillary pressure (typically reflecting left atrial pressure). When elevations in pulmonary arterial pressure (systolic/diastolic pulmonary arterial pressure > ~30/19 mmHg at rest) are accompanied by increased left atrial pressure, pulmonary arterial hypertension may be considered secondary to left-heart failure. Introduction of Doppler methods to diagnose pulmonary arterial hypertension has increased the awareness of the prevalence and importance of pulmonary arterial hypertension dogs with left-heart failure. Increasing understanding of the mechanism of development of pulmonary venous hypertension and reactive pulmonary arterial hypertension in dogs with left-heart disease has led to the development of successful additive therapies for progressive clinical signs in the setting of chronic therapy for congestive heart failure due to left-sided valvular and myocardial dysfunction. Because effective therapies for pulmonary arterial hypertension secondary to chronic left-sided cardiac dysfunction are now available, screening for pulmonary arterial hypertension should be a regular part of the Doppler echocardiographic examination in a clinical setting of chronic therapy for left-sided congestive heart failure due to valvular or myocardial disease.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a description of a physiological finding rather than a diagnosis. Pulmonary arterial pressure (PAP) is the result of interactions among pulmonary blood flow (right ventricular (RV) cardiac output), pulmonary vascular impedance and post-capillary pressure (typically reflecting left atrial pressure). PAH may be primary (idiopathic) or occur secondary to multiple abnormalities of the pulmonary or cardiovascular systems, as well as systemic inflammatory or infectious diseases (Simonneau and others 2004). When elevations in pulmonary arterial pressure (systolic/diastolic pulmonary arterial pressure > ~30/19 mmHg at rest) are accompanied by increased left atrial pressure (elevated pulmonary capillary wedge pressure (PCWP) ≥15 mmHg), the term pulmonary venous hypertension (PVH) is sometimes used (O’Callaghan and McNeil 2008).

PREVALENCE

Pulmonary arterial hypertension is common in human beings with chronic severe left ventricular dysfunction, occurring in approximately three-quarters of patients with left-heart failure (Costard-Jackle and Fowler 1992, Butler and others 1999, Ghio and others 2001) and has a detrimental effect on quality of life, exercise tolerance and survival (Abramson and others 1992, Silver and others 1993, DiSalvo and others 1995, Butler and others 1999). When PAH is accompanied by RV dysfunction or failure, the prognosis worsens (Ghio and others 2001). Clinical syndromes described as “right heart failure secondary to left-heart failure” have been discussed anecdotally for many years in veterinary cardiology, but increasing understanding of the prevalence of PAH as a consequence of left-heart dysfunction awaited development of commonly available non-invasive methods of detection (i.e. Doppler echocardiography). While the true incidence of PAH in dogs with chronic left-sided heart failure is unknown, one study of adult-onset valvular disease found the prevalence of detected PAH to be 14 per cent and the prevalence of PAH increased with increasing MV regurgitant jet size (Serrers and others 2006). In another study of dogs with adult-onset myxomatous mitral valve disease (MVD), 31 per cent of dogs had PAH (Borgarelli and others 2004). Left-sided cardiac dysfunction appears to be a common cause of PAH diagnosed clinically in dogs; combined data from three recent
PAH secondary to chronic left-sided cardiac dysfunction

retrospective studies of PAH in dogs suggest that approximately 40 per cent of patients with diagnosed PAH are thought to have increased LA pressure as the aetiology (Johnson and others 1999, Pyle and others 2004, Kellum and Stepien 2007) while another study of dogs with tricuspid insufficiency found 75 per cent of dogs with equivocal or elevated PAP had left-sided heart disease noted as the probable cause (Serres and others 2007).

**PATHOPHYSIOLOGY**

PAH may occur through three mechanisms: left-to-right cardiac shunting, increased vascular resistance or elevated pulmonary venous pressure (Klodell Jr. 2005). Some have argued that so many (human) patients have both PVH and reactive pulmonary vascular disease that discussing a “post-capsillary” aetiology for PAH may be misleading (Forfia 2007). Reactive PAH is diagnosed when the difference between mean pulmonary arterial pressure (PAPm) and pulmonary capillary wedge pressure (PCWP) exceeds 10 mmHg (Silver and others 1993). Butler and others (1999) found right atrial (RA) pressure increased with exercise whereas PCWP fell, implying that the problem was in pulmonary vasculature during exercise. In this study, up to 36 per cent of patients with heart failure had evidence of reactive PAH based on cardiac catheterisation. Silver and others (1993) found that 29 per cent of 48 patients with aortic stenosis and no other valvular or pulmonary disease had PAH, and 46 per cent of these PAH patients had evidence of reactive PAH as well as elevated left atrial pressure. Little comparable data exists for naturally occurring heart disease in dogs. To date, PAH due to adult-onset left-sided heart disease in dogs is most commonly associated with left-sided valvar or myocardial diseases, including adult-onset valvar disease (degenerative valve disease), and pulmonary hypertension related vasoconstriction that may occur if cardiac pulmonary oedema is present. Elevated PAP may be augmented by fixed changes in the pulmonary vasculature (medial hypertrophy, intimal thickening) that occur as a consequence of chronic vasoconstriction (Mancini 1995). These changes lead to decreased vascular compliance and the resistance to flow (pulmonary vascular resistance, (PVR)) is increased. The development of fixed changes may be related to the chronicity of heart failure; dogs with an experimental heart failure of 7 weeks’ duration developed increased PAP without increased PVR (Ray and others 2008), but rats with experimental heart failure of 4 months’ duration developed increased PVR and medial hypertrophy (Ben Driss and others 2000). Multiple intermediary endogenous substances are involved in regulating pulmonary arterial pressure, including prostacyclin, nitric oxide, endothelin and PD 5 (Fig. 1). Right ventricular function is also integral to cardiac output in PAH. Review of selected physiologic changes associated with PAH due to left-heart failure provides a rationale for therapeautic approaches.

**Role of prostacyclin**

Prostacyclin is produced by the vascular endothelium and has vasodilating effects mediated by stimulation of cAMP and inhibition of smooth muscle cell growth. The role of prostacyclin in patients with PAH due to left-heart failure is unclear;

<table>
<thead>
<tr>
<th>Table 1. Mechanisms of development of pulmonary arterial hypertension</th>
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<tbody>
<tr>
<td><strong>Mechanism</strong></td>
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<tr>
<td>Increased volume of pulmonary blood flow</td>
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<tr>
<td>Enhanced pulmonary vascular resistance</td>
</tr>
<tr>
<td>Elevations in pulmonary venous pressure (LA hypertension)</td>
</tr>
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</table>

LA left atrial, LV left ventricular.
when epoprostenol (intravenous prosta-
cyclin) was administered to patients with
Class III or IV heart failure, exercise ca-
pacity and heart failure symptoms did not
improve despite decreases in PCWP and car-
diac index (CI), leading to speculation
that the systemic vasodilating effects of
the drug may have lead to increased NHA
that offset any gain from the medication
and increased mortality (Califf and oth-
ers 1997). Increased prostacyclin release has
been documented in dogs with experi-
mental heart failure (Newman and oth-
ers 1983), but no information on the role
of prostacyclin in dogs with naturally occur-
ring heart failure could be found.

Role of nitric oxide
Nitric oxide (NO) is released from pul-
monary vascular endothelial cells and dif-
fuses into adjacent smooth muscle cells,
activating guanylyl cyclase and thereby
increasing the intracellular concentration
of cGMP. cGMP inhibits calcium release
from the sarcoplasmic reticulum, resulting
in smooth muscle relaxation. NO is re-
sponsible for maintaining basal pulmo-
nary vascular tone (Moraes and others
2000). Decreases in synthesis of NO due
to endothelial dysfunction (Katz and oth-
ers 1999) and decreased smooth muscle
responsiveness to NO caused by increased
PDE 5 (see the section Role of PDE 5) con-
tribute to the development of increased
pulmonary vascular tone in heart failure
(Forfia 2007).

Role of endothelin
Endothelin-1 (ET-1) is a potent arterial
and venous vasoconstrictor that is released
primarily from vascular endothelial cells
and causes both acute vasoconstriction and
under some circumstances, smooth muscle
cell proliferation that may result in long-
term vascular remodelling (Moraes and
others 2000). Although there are two ET-1
receptor subtypes with opposing effects –
$\text{ET}_{\alpha}$ receptors (found on vascular smooth
muscle cells) mediate vasoconstriction and
cell growth and $\text{ET}_{\beta}$ receptors (on vascu-
lar endothelial cells) mediate release of the
endogenous vasodilators nitric oxide and
prostacyclin – the overall effect of ET-1 in
the pulmonary vasculature is vasoconstric-
tion. ET-1 is released as part of the NHA
that occurs in heart failure and is increased
in human patients (Cody and others
1992) and dogs with heart failure (Prosek
and others 2004, Tessier-Vetzel and others
2006, Ray and others 2008). In the initial
stages of increased PAP in heart failure, in-
creased PAP associated with ET-1 is likely
dynamic rather than fixed and develops in
proportion to increases in LA pressure. In
a study of experimentally induced heart
failure in dogs, Ray and others (2008)
found that a development of increased
pulmonary arterial pressures accompanied
decreases in cardiac output and increased
ET-1. PVR was unchanged in these ani-
mals, suggesting that increased PAP was
appropriate for the amount of LA pressure
increase and this reversible vasoreactivity
(rather than remodelling) may be the initial
response of the pulmonary vascular system.
to heart failure. Increased ET-1 concentrations are correlated to increased PAP in heart failure patients, although it is unclear if ET-1 is a mediator or a marker of PAH in this situation (Cody and others 1992, Moraes and others 2000). The vasoproliferative effects of ET-1 are likely responsible for the “remodelling” of arterial walls, abnormalities of elastic fibres, intimal fibrosis and medial hypertrophy and increased vascular stiffness (“fixed changes”) may accompany reversible “reactive” pulmonary vasoconstriction. These fixed changes may or may not be responsive to vasodilators (Moraes and others 2000).

Increased ET-1 concentrations have been reported in dogs with naturally occurring cardiac disease and concentrations increase with increasing severity of heart failure. ET-1 concentrations were significantly increased in dogs with heart failure compared to normal dogs and dogs with compensated heart disease, but there was no difference between dogs with DCM or MR and PAP pressures were not reported (Prosek and others 2004). A similar relationship between ET-1 concentrations and worsening class of heart failure was identified by Tessier-Vetzel and others (2006) and a small subgroup of dogs with PAH was documented to have ET-1 concentrations correlated to severity of PAH, although not all PAH dogs had heart failure as the aetiology.

**Role of phosphodiesterase 5**

Phosphodiesterase 5 is the rate limiting enzyme of cGMP catabolism and is upregulated in various experimental models of PAH (Black and others 2001, Zhao and others 2001). The increased catabolism of cGMP related to increased presence of PDE 5 may contribute to attenuation of vasodilating response to endogenous NO and NP and is especially marked in the lung (Forfia and others 2007). Circulating NP concentrations are increased in dogs with naturally occurring heart failure (Prosek and others 2004, Häggström and others 2000, Oyama and others 2008, Fine and others 2008). These studies support human patient findings that suggest that heart failure is a state of NP resistance, rather than deficiency (Burnett and others 1986, Mukoyama and others 1991). This resistance may be mediated in part by increased catabolism of cGMP, the mediator of the vasodilating effects of NP. A study of experimental heart failure in dogs noted that heart failure was associated with elevated NP concentrations and decreased plasma cGMP activity, which was restored when sildenafil, a PDE 5 inhibitor, was administered (Yamamoto and others 2004). Forfia and others (2007) found similar responses to experimental heart failure in dogs and documented that the increased NP concentrations were associated with increased PDE 5 concentration. Again, sildenafil restored vascular responsiveness to NP to a level equal to that of infused BNP (B-type natriuretic peptide) (Forfia and others 2007).

**Role of right ventricular function**

Normal right ventricular (RV) function may be present despite the presence of PAH in left-sided dysfunction, the development of RV dysfunction may be time dependent or occur in patients in whom RV remodelling in response to increased load is inadequate (Ghio and others 2001). RV function is a critical factor in congestive heart failure (CHF), affecting both exercise capacity and survival (DiSalvo and others 1995), and it is likely that the outcome of patients with PAH due to left-sided dysfunction is affected by both the severity of PAH (Butler and others 1999) and the functional state of the RV (Ghio and others 2001, Forfia 2007). In a study of 379 human patients with moderate to severe heart failure, patients with a high PAPm and low RV function (as measured by RV ejection fraction) had a hazards ratio for non-survival that was four times higher than those with a high PAPm/preserved RV function. The survival of patients with a normal PAPm/preserved RV function did not differ from those with high PAPm/preserved RV function, indicating that the presence of PAH alone in this group of patients did not affect survival unless RV function was impaired (Ghio and others 2001).

Because left-sided cardiac filling is directly dependent on right-sided output, the presence of reduced RV cardiac output typically reduces LA pressure. As LA pressure decreases, delivered volume to the LA decreases and clinical signs of PHV may resolve. Patients with RV dysfunction may show a lack of CO responsiveness to low systemic blood pressure, decreased cardiac response to exercise (DiSalvo and others 1995) and often, intolerance of systemic vasodilating medications.

In veterinary patients, PAH may be suspected based on physical examination findings in the absence of right heart failure signs (Johnson and others 1999, Pyle and others 2004, Kellum and Stepien 2007), but PAH is often first suspected in left-sided CHF patients when ascites or pleural effusion is diagnosed (right heart failure secondary to left-heart failure) or syncope is reported. In these patients, the RV function is already significantly impaired. Although RV systolic function is rarely measured in clinical cases, a recent study of dogs with PAH of many aetiologies found that diastolic right ventricular function was abnormal in more than 85 per cent of dogs, based on tissue Doppler measures (Serres and others 2007). Minimal clinical data have been published regarding the impact of RV dysfunction on survival in canine PAH patients. It is likely, however, that as in people (DiSalvo and others 1995, Ghio and others 2001), the presence of right-sided heart failure signs in a patient with significant left-sided dysfunction worsens the prognosis because RV dysfunction is more likely in the presence of longstanding disease and may limit tolerance of systemic vasodilators.

**Clinical presentation**

Clinical signs of PAH may be subtle and similar to signs of left-sided CHF and the presence of PAH may not even be suspected if overt signs of right-sided CHF are not present. In a study of dogs with naturally occurring valvular disease, 24 per cent of dogs diagnosed with PAH secondary to valvular disease had no clinical signs, but the remaining dogs had various combinations of cough, exercise intolerance, dyspnoea, ascites or syncope reported (Serres and others 2006). Beyond identification of probable left-sided CHF, physical examination and radiographic findings are not helpful to distinguish dogs with PAH due to left-sided heart failure from dogs with left-sided CHF without PAH. In three clinical studies of PAH dogs with mixed aetiologies, cardiac
murmurs were common (63 to 83 per cent of patients with PAH) on physical examination and often more than one murmur was detected. Some PAH patients in all studies had no detected murmurs. Abnormal pulmonary sounds were detected in dogs with heart failure and in dogs with primary pulmonary disease. Splitting of the second heart sound (split S-2) was detected in some patients with PAH. Radiographic findings typically included cardiomegaly and pulmonary infiltrates of various descriptions, and do not predict PAH reliably (Johnson and others 1999, Pyle and others 2004, Kellum and Stepien 2007).

In a clinical setting of chronic therapy for left-sided CHF due to valvular or myocardial disease, screening for PAH should be a regular part of the Doppler echocardiographic examination. PAH may be suspected if complaints or findings of cough, shortness of breath, lethargy or exercise intolerance or syncope persist despite optimisation of “routine” therapy (loop diuretics, angiotensin-converting enzyme inhibitors, aldosterone antagonists, pimobendan, control of any dysrythmias). If PAH is more advanced and chronic, the first clinical sign noted may be development of ascites or pleural effusion in a canine patient previously managed for left-sided CHF (Fig. 2). Rarely, peripheral oedema may be noted when severe right-sided failure occurs.

When right-sided CHF is present, jugular distention may be noted.

### DIAGNOSIS

#### Cardiac catheterisation

Right-sided cardiac catheterisation has long been considered the gold standard for diagnosis of PAH in people. Although the procedure itself is relatively straightforward, expertise and equipment to routinely catheterise cardiac patients is typically not available in veterinary clinical situations and the procedure can be difficult in conscious and fragile patients. As a result, Doppler echocardiography has become the standard for clinical diagnosis of PAH in veterinary patients. In cases of PAH due to left-sided heart disease, however, Doppler echocardiography has several drawbacks when compared with cardiac catheterisation (see the section Echocardiographic Diagnosis).

In a typical right-sided cardiac catheterisation, performed in a conscious patient, multiple haemodynamic parameters may be recorded (Table 2). Although systolic PAP is typically used in clinical definitions (and echocardiographic diagnosis) of PAH, the mean PAP is also measured during cardiac catheterisation in order to derive PVR, a measure of the interaction of flow and resistance in the pulmonary circuit that can be used to quantitate primary or secondary PAH.

Pulmonary vascular resistance is typically calculated as an index (per m² or per kg): PVRI = (PAPm – PCWP) × 80/CI (if CI is expressed per m²) or PVRI = (PAPm – PCWP)/CI (if CI is expressed per kg)

where PVRI = pulmonary vascular resistance index (dynes *sec* cm⁻¹/m² or mmHg/ml/min/kg), PAPm = mean pulmonary arterial pressure (mmHg), PCWP = pulmonary capillary wedge pressure (mmHg) and CI = cardiac index.

An important implication of this formula is that elevated PAPm does not necessarily imply elevated PVR. In the case of PVH, both PAPm and PCWP are elevated to a similar degree and if CI remains the same, PVRI will be unchanged. If PAPm increases exceed those of PCWP, even if PCWP is elevated, PVRI will be increased and a reactive PAH component is likely present in addition to PVH.

#### Echocardiographic diagnosis

Two-dimensional, Doppler echocardiographic examinations have largely replaced cardiac catheterisation as a diagnostic tool for PAH in clinical veterinary medicine. In most cases, echocardiography can provide “surrogate” values for many invasively measured parameters (Table 2) and in conjunction with other clinical testing, is used to diagnose the presence and possible causes of PAH (Fig. 3).

### Two-dimensional findings

When pursuing a diagnosis of PAH secondary to left atrial hypertension, evidence of significant left-sided valvular (Fig. 3a) or myocardial dysfunction (systolic, diastolic or both) should be documented. In particular, in the absence of pericardial disease, significant LA enlargement should be present to support a diagnosis of significantly elevated LA pressure.

Two-dimensional findings may be suggestive of or consistent with increased PAP but are neither diagnostic nor quantitative (Table 3). Findings consistent with increased PAP that have been documented in naturally occurring PAH include main pulmonary artery enlargement (Fig. 3c), flattening or abnormal motion of the interventricular septum, and variable degrees of RV dilation and wall thickening, the degree of which is likely related to the functional status of the RV and chronicity of loading conditions (Ghio and others 2001).

![FIG 2. Development of ascites in a dog previously diagnosed with congestive heart failure secondary to degenerative mitral disease with severe mitral regurgitation reflects the presence of pulmonary hypertension leading to right ventricular failure](image-url)
Each of these findings is additive in support of a diagnosis of PAH in a patient at risk, but none alone is definitive.

Doppler echocardiographic findings
The presence of tricuspid regurgitation (TR) or pulmonary insufficiency (PI) in the absence of pulmonic stenosis or RV failure allows reasonably accurate estimation of PAPs and PAPd, respectively (Figs 3b, 3c, 3d). The tricuspid transvalvular pressure gradient may be estimated using peak TR velocity in the modified Bernoulli equation (pressure gradient = 4 × (peak velocity of TR)^2). Abnormal RV-RA and PA-RV gradients provide a reliable indication of abnormality and can be used to categorise severity of PAH (Johnson and others 1999, Pyle and others 2004, Serres and others 2006, Kellum and Stepien 2007), but these measurements may not be sensitive enough to use to follow therapy (Kellum and Stepien 2007). The tricuspid systolic gradient can be added to the estimated or measured RA pressure to provide an approximation of systolic pulmonary artery pressure (PAPs).

The shape of the pulmonary outflow velocity profile has also been scrutinised as an indicator of the presence of PAH with variable results (Johnson and others 1999, Kellum and Stepien 2007). Lastly, systolic time intervals have been shown to be sensitive predictors of PAH in dogs; shortened acceleration time and decreased acceleration time/ejection time ratio was originally documented using the pulmonary valve flow profile in dogs with PAH due to pulmonary disease (Schober and Baade 2006) but similar findings were present in dogs with PAH related to heart failure (Serres and others 2007). Tissue Doppler measurements involving the basal RV myocardium have also proved valuable in identifying changes in RV systolic and diastolic function associated with PAH in dogs (Serres and others 2007) but do not indicate pulmonary arterial pressure. Detailed explanation of Doppler measurements and equations is beyond the scope of this review, and the interested reader is directed to the references for further explanation (Johnson and others 1999, Baumwart and others 2005, Schober and Baade 2006, Serres and others 2006, Kellum and Stepien 2007, Serres and others 2007).

Table 2. Haemodynamic values obtained by right heart catheterisation and comparable echocardiographic values

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Value*</th>
<th>Echo surrogate</th>
</tr>
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<tbody>
<tr>
<td>RAPm</td>
<td>Mean right atrial pressure (mmHg)</td>
<td>None</td>
</tr>
<tr>
<td>PAPs</td>
<td>Pulmonary arterial pressure in systole (mmHg)</td>
<td>Estimated by adding RAP to TR systolic pressure gradient. Pressure gradient = 4 × (peak velocity of TR)^2</td>
</tr>
<tr>
<td>PAPd</td>
<td>Pulmonary arterial pressure in diastole (mmHg)</td>
<td>Estimated by pulmonary insufficiency diastolic pressure gradient</td>
</tr>
<tr>
<td>PAPm</td>
<td>Mean pulmonary arterial pressure (mmHg)</td>
<td>Estimated as PAPm = (0.69 × estimated PAPs)−0.22</td>
</tr>
<tr>
<td>PCWP (PAW)</td>
<td>Pulmonary capillary wedge pressure, also called pulmonary arterial wedge (mmHg)</td>
<td>Accuracy unknown in veterinary patients</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac output (L/min)</td>
<td>Can be estimated as CO = pulmonary FVI × π × (pulmonary valve radius)^2 × HR</td>
</tr>
<tr>
<td>CI</td>
<td>Cardiac index (L/min/m^2) estimated by thermodilution or angiography</td>
<td>CI = CO/m^2</td>
</tr>
<tr>
<td>PAPm – PCWP</td>
<td>Gradient across pulmonary vascular bed (mmHg)</td>
<td>Accuracy of calculation of CO in this setting unknown in veterinary patients</td>
</tr>
<tr>
<td>PVRI</td>
<td>Pulmonary vascular resistance index (dynes/s/cm^5/m^2)</td>
<td>None, cannot estimate component parts</td>
</tr>
</tbody>
</table>

RAE, right atrial enlargement; HF, heart failure; PAH, pulmonary arterial hypertension; TR, tricuspid regurgitation; PI, pulmonary insufficiency; FVI, flow velocity integral; HR, heart rate.

*Cut-off values may vary slightly based on reference used.
the tricuspid systolic gradient may underestimate PAPs, whereas improvement in RV function in response to therapy may lead to increased TR gradients. Doppler measurements do not indicate aetiology and must be considered in light of other findings. If Doppler evidence of PAH is present without evidence of a significant left-sided heart disease and LA enlargement, other causes of PAH should be investigated. When TR or PI is not present, supportive two-dimensional findings can be used in conjunction with systolic time intervals to indicate the probability of PAH; tissue Doppler measures may reflect abnormalities in RV function. As in the case of two-dimensional echocardiographic changes, these measures do not, in themselves, indicate aetiology or accurately reflect severity. Current methods of echocardiographic PAH assessment may not be precise enough to detect small changes that may occur in response to therapy.

**APPROACH TO THERAPY**

Responses to therapy for PAH due to left-heart disease ideally include improved haemodynamic measures and improvement in clinical signs. Effective control of clinical signs may improve survival.

In patients with left-sided CHF-related PAH, treatment includes relief of PVH through optimal therapy of left atrial hypertension as well as therapy of reactive PAH that may be present in addition to PVH. Since development of RV failure is a poor prognostic sign, off-loading the RV with optimal left atrial pressure management and pulmonary vasodilators is likely to confer benefit in this respect as well. It is likely that patient variability will dictate any individual’s response to different modes of therapy.

**Relieve elevated LA pressures**

Optimal chronic management of left atrial pressure is a mandatory part of therapy for patients with PAH related to left-heart dysfunction. Left ventricular end-diastolic and therefore, left atrial pressures may be reduced with combinations of loop
of left-sided CHF; the most promising pulmonarv vasoconstriction in the setting of left-sided heart failure, reduction of left atrial pressure. 

Treat reactive PAH with pulmonary vasodilators

In the setting of left-sided heart failure, use of pulmonary vasodilators is coupled with reduction of left atrial pressure through other methods (see earlier text). Numerous medications have been investigated for use as chronic therapy of reactive pulmonary vasoconstriction in the setting of left-sided CHF; the most promising medications have effects that are relatively specific for the pulmonary vasculature: endothelin antagonists, PDE 5 inhibitors and calcium sensitising agents.

Phosphodiesterase 5 inhibitors
Sildenafil is a selective inhibitor of cGMP-specific PDE 5. Use of PDE 5 inhibitors to treat PAH is a recent development and appears to be effective. Numerous publications have documented haemodynamic and symptomatic benefit from use of sildenafil (related drugs: tadalafil, vardenafil) in many types of PAH, but fewer references are available for clinical use of PDE 5 inhibitors in the setting of PAH with heart failure. In studies of human beings with heart failure and PAH, chronic therapy with sildenafil resulted in decreased PVR and PAPs without altering PCWP with variable effects on CI. These effects are also present during exercise (Guazzi and others 2004, Lewis and others 2007a). In another study, these findings were confirmed and exercise tolerance and quality-of-life indices were improved in heart failure patients with PAH after sildenafil therapy (Lewis and others 2007b). Acute PDE 5 inhibition in dogs with experimental heart failure and PAH appears to “unload” both LV and RV by causing both systemic and pulmonary vasodilatation and has effects similar and additive to BNP (Forfi a and others 2007a). Similarly, sildenafil added to

Table 3. Selected echocardiographic findings consistent with pulmonary hypertension*

<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>Suggested values considered consistent with PAH</th>
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<tbody>
<tr>
<td>Two-dimensional findings</td>
<td></td>
</tr>
<tr>
<td>Interventricular septal motion</td>
<td>Flattening of septum in end-diastole or peak systole, paradoxical septal motion</td>
</tr>
<tr>
<td>Right ventricular size/appearance</td>
<td>Subjective: dilation and/or wall thickening</td>
</tr>
<tr>
<td>Main pulmonary artery size</td>
<td>Pulmonary artery diameter exceeds aortic root diameter in the same echo plane (right parasternal short axis view)</td>
</tr>
<tr>
<td>Doppler flow variables</td>
<td></td>
</tr>
<tr>
<td>TR peak systolic velocity</td>
<td>Peak systolic velocity &gt; 2.5–3.1 m/sec</td>
</tr>
<tr>
<td>TR peak diastolic gradient</td>
<td>Gradient &gt; 25–38 mmHg based on peak TR velocity</td>
</tr>
<tr>
<td>PI peak diastolic velocity</td>
<td>Peak diastolic velocity &gt; 2–2.2 m/sec</td>
</tr>
<tr>
<td>PI peak diastolic gradient</td>
<td>Peak diastolic gradient &gt; 16–20 mmHg</td>
</tr>
<tr>
<td>Systolic time intervals</td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>AT ≤ 58 ms</td>
</tr>
<tr>
<td>ET</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery velocity flow profile</td>
<td>Type II or type III profiles are consistent with PAH</td>
</tr>
<tr>
<td>Tissue Doppler variables</td>
<td></td>
</tr>
<tr>
<td>RV wall S-wave velocity (tdi)</td>
<td>S-wave velocity &lt; 10.5 cm/s</td>
</tr>
<tr>
<td>RV wall E/A ratio (tdi)</td>
<td>E/A ratio &lt; 1.12</td>
</tr>
<tr>
<td>Global tissue Doppler index</td>
<td>G-TDI &lt; 1.8 cm/s</td>
</tr>
<tr>
<td>G-TDI=Stdi×E/Atdi</td>
<td></td>
</tr>
</tbody>
</table>

PI pulmonary insufficiency, PAH pulmonary arterial hypertension, AT acceleration time, ET ejection time, RV right ventricle, tdi (tissue Doppler imaging).

†Accuracy of measurements variable, see References.
the vasodilator effect of ANP (atrial natriuretic peptide) and increased cGMP concentrations in dogs with experimental heart failure (Ishikura and others 2007). In people and dogs, the long-term effects of sildenafil therapy in this setting are unknown.

**Calcium sensitising agents**

PDE 3 differs from PDE 5 in that PDE 3 has activity mainly in large pulmonary arteries, whereas PDE 5 has activity mainly in large pulmonary arteries. PDE 3 inhibitors enhance adrenergic relaxation mechanisms in the pulmonary arteries, whereas PDE 5 inhibitors enhance non-adrenergic and non-cholinergic relaxation mediated by nitric oxide. PDE 3 inhibition provided by the calcium sensitizer pimobendan may provide an additional benefit to heart failure patients with PAH when added to the PDE 5 inhibitor effect of sildenafil. The positive inotropic effects of calcium sensitizers on cardiac output may also improve the haemodynamic status (Kerbau and others 2006). Pimobendan has been reported to be of benefit in PAH in humans in sparse reports (Saara and others 2006, Kellum and Stepien 2007) and has been shown to decrease PAH and increase CO in clinical trials of human beings with heart failure (Nieminen and others 2000, Slawsky and others 2000). Levosimendan, which has not yet seen extensive veterinary use, causes vasodilation by opening ATP-dependent potassium channels in vascular smooth muscle as well as inhibiting PDE 3.

**Veterinary literature**

In veterinary medicine, pimobendan and sildenafil, either separately or in combination, are currently showing the most promise for therapy of PAH associated with left heart dysfunction.

Use of sildenafil to treat naturally occurring PAH in dogs has been reported (Bach and others 2006, Kellum and Stepien 2007, Toyoshima and others 2007). In the two case series reports, a subset of the dogs studied had heart failure as the probable aetiology of the PAH. Both studies found that the sildenafil was well tolerated in the general PAH clinical population, and that clinical signs improved without significant changes in systemic blood pressure (Bach and others 2006, Kellum and Stepien 2007). Bach and others (2006) found that there was a measurable decrease (~18 per cent) in PAP in six of the seven dogs evaluated for PAP change, in contrast to the findings of Kellum and Stepien (2007) that no change in estimated PAP (by Doppler echocardiography) with sildenafil treatment could be documented, despite significant improvements in the clinical status. Improvements in systolic time intervals were noted (Kellum and Stepien 2007). In both the papers, doses of 1 mg/kg PO every 8 hours appeared to be safe and effective. Organised safety data for the use of sildenafil in this situation is not available, but patients with severely reduced renal function may have impaired clearance of sildenafil and drug effects may be prolonged. In chronic CHF patients, cachexia may falsely lower serum creatinine concentrations and cause underestimation of renal impairment. Sildenafil as a single drug has shown minimal systemic hypertensive effects in veterinary patients but caution should be used in fragile patients receiving multiple vasodilators, especially because dehydration may be present.

Anecdotal information supports the use of pimobendan with or without concurrent sildenafil to treat PAH due to left heart dysfunction in dogs, but no clinical trials have been published at the time of writing. Studies are currently ongoing regarding the use of pimobendan in this group of patients.

**SUMMARY**

Pulmonary arterial hypertension secondary to chronic left-sided heart disease and heart failure may be a relatively subtle cause of decreased quality of life and persistent clinical signs in dogs receiving chronic therapy for CHF. Introduction of Doppler methods for the diagnosis of PAH has increased the awareness of the prevalence and importance of PAH in these patients. Increasing understanding of the mechanism of development of PVH and reactive PAH in dogs with left-heart disease has led to the development of successful additive therapies for progressive clinical signs in the setting of chronic therapy for CHF due to left-sided valvular and myocardial dysfunction. Because effective therapies for PAH secondary to chronic left-sided cardiac dysfunction are now available, screening for PAH should be a regular part of the Doppler echocardiographic examination in a clinical setting of chronic therapy for left-sided CHF due to valvular or myocardial disease. In addition, detection of PAH secondary to LA hypertension in clinical veterinary patients should be viewed as an indication that the patient is not yet receiving optimal therapy for left-sided heart failure. In patients with PAH and signs of right heart failure, therapy may be directed at both of these conditions in order to relieve clinical signs and improve haemodynamic status.

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