INTRODUCTION

Pulmonary hypertension (PH) is defined as an increase in pulmonary systolic and mean pressure greater than 25 mmHg and 15 mmHg respectively. PH is conventionally divided into primary and secondary etiologies. Primary idiopathic PH is rarely diagnosed in the dog. PH is classified by the World Health Organization into pulmonary arterial hypertension, pulmonary venous hypertension, PH associated with disorders of the respiratory system or hypoxemia, PH due to chronic thromboembolic disease, and PH due to disorders directly affecting the pulmonary vasculature. Diseases leading to PH commonly include primary pulmonary disease (chronic bronchitis, interstitial lung disease, chronic exposure to high altitude), cardiovascular disease leading to chronic elevations in left atrial or left ventricular end diastolic pressure (cardiomyopathy, degenerative mitral valve disease, mitral valve stenosis, left to right shunting congenital heart disease), pulmonary thromboembolic disease (thrombus, tumor), and inflammatory disorders directly affecting the pulmonary vasculature (dirofilariasis). The prevalence of heartworm induced PH is thought to be high, however two veterinary studies did not report PH although these were not heartworm endemic areas. Pulmonary venous hypertension secondary to primary cardiovascular disease was the most common underlying clinical diagnosis in both studies occurring in 41-43% of dogs reviewed.

Histopathological findings in affected lung tissue include medial and intimal hypertrophy, fibrosis with muscularization of arterioles, pleuroperitoneal lesions and fresh or recanalized thrombi. PH develops as a result of hypoxia induced vasoconstriction, endothelial dysfunction and vascular remodeling. Endothelial dysfunction results in a progressive decrease in nitric oxide and prostacyclin and increased endothelin (ET) production resulting in reduced vasodilation and pronounces vasoconstriction respectively. ET levels are reportedly increased in dogs with experimentally induced dirofilariasis and PH secondary to cardiac and respiratory disease.

The majority of dogs with mild PH are asymptomatic thus mild PH often goes undiagnosed. The true prevalence of PH is therefore unknown. Dogs with clinical PH often present with a non-specific history of exercise intolerance, cough, dyspnea, and syncope associated with excitement or activity. Syncope occurred in 23% of dogs in one retrospective study of canine PH. Syncope in association with PH is typically attributed to hypoxemia or low cardiac output. Abnormal physical examination findings may include a systolic murmur of tricuspid regurgitation, and extra heart sound (split S2, gallop rhythm), ascites, jugular venous distention, abnormal lung sounds and rarely peripheral edema. Diagnostic tests are required to confirm a diagnosis of PH, determine the severity of PH and identify any underlying causes.

Diagnostic Testing

Routine diagnostic testing may include thoracic radiography, electrocardiography, indirect systemic blood pressure measurement, echocardiography, hematologic, serum biochemistry, urinalysis, and heartworm antigen testing. Atrial blood gas analysis and or pulse oximetry should be performed in dyspneic patients to determine the degree of hypoxemia and acidosis which perpetuate vasoconstriction. Secondary causes of PH are often readily diagnosed with a combination of tests. Thoracic radiographs aid in the identification of underlying primary pulmonary disease and significant left heart disease. The most commonly observed radiographic abnormalities are cardiomegaly, pulmonary infiltrates, and pulmonary artery enlargement. While echocardiographic abnormalities including tall P waves, a right axis shift in the frontal plane, and S waves in leads I, II, III, and aVF may indicate right sided heart enlargement, they are neither sensitive nor specific as a screening test for PH. Indirect systemic blood pressure measurements may identify systemic hypertension secondary to renal or endocrine disease or hypertension secondary to reduced cardiac output, alternatively it may be normal. The identification of systemic hypertension may influence therapeutic treatment choices to avoid further peripheral vasodilation. If thromboembolic disease is suspected, coagulation testing should be performed particularly the quantification of ATIII. Pulmonary perfusion studies may aid in the diagnosis of pulmonary thromboembolic disease (PTE) but are reportedly normal in up to 28% of human patients with PTE. REF Perfusion deficits resulting in a false positive test can occur in the absence of PH if pulmonary venous hypertension, pulmonary masses, loss of pulmonary parenchyma and lung displacement secondary to pleural effusion are present.

Right heart catheterization is invasive and requires general anesthesia in the dog but can provide direct measures of pulmonary artery and right heart pressures, pulmonary capillary wedge pressure and oxygen saturation. Transcranial echocardiography (TTE) is a useful noninvasive test for diagnosing PH. Pulmonary artery pressures can be estimated indirectly with Doppler echocardiography by documenting (color Doppler) and quantitating (spectral Doppler) tricuspid and or pulmonary regurgitation velocities and converting them to a pressure gradient with the modified Bernoulli equation (P=4V²). Patients with PH typically have an abnormal transpulmonary velocity profile that demonstrates a rapid acceleration and rapid or abrupt deceleration pattern with notching. The pulmonary acceleration time (AT) to ejection time (ET) ratio may be useful in the diagnosis of PH in patients without tricuspid or pulmonary regurgitation. An AT:ET ratio >0.32 suggests normal pulmonary artery systolic pressure. In addition to estimating pulmonary pressures and evaluating right heart enlargement, TTE may aid in the identification of underlying cardiac disease including cardiomyopathy, mitral valve endocardiosis or stenosis, congenital defects, heartworms or thrombi. Intravenous saline contrast echocardiography may be useful to rule out congenital heart disease and should be performed in young dogs with suspected PH. TTE is also useful for monitoring disease progression and response to therapeutic management.
INTRODUCTION

This talk will build on the content of the previous talk that focused on the diagnosis of PH. Pulmonary hypertension (PH) is a life-threatening disease characterized by hypoxia-induced vasoconstriction, endothelial dysfunction, and vascular remodeling of the pulmonary arteries. Endothelial dysfunction leads to pathologic increases in endothelin (ET) expression, a potent vasoconstrictor, and decreased synthesis of the vasodilators nitric oxide (NO) and prostacyclin (PGI2). In addition, normal cGMP-mediated vasodilation is diminished by the enzyme family of phosphodiesterases (PDE) which are responsible for the degradation of cGMP and are present as PDE I, II, III, IV, and V in human bronchi and the trachea. Therapeutic management of PH is based on palliation of clinical signs of right heart failure, and forward left heart failure and ultimately by addressing the pathologic mechanisms outline and any underlying etiologies.

THERAPEUTIC STRATEGIES

Hypoxemia is a potent vasoconstrictor and conventional therapy of PH in humans consists of continuous oxygen therapy along with anticoagulation to decrease the propensity for thromboembolic events. During initial diagnostic evaluation of PH in humans, a positive response to inhaled vasodilator therapy with nitric oxide (reduction in pulmonary pressure) is recognized to predict the survival of a patient with a high chance of clinical benefit from high-dose calcium channel blocker therapy (nifedipine, diltiazem). Unfortunately, response to high-dose calcium channel blockade is limited in only a small percentage of people who for the most part have idiopathic or primary familial PH. High-dose calcium channel blockade may not be well tolerated as a result of systemic vasodilation in addition to pulmonary vasodilation as well as the negative inotropic effects. Anecdotal experience in dogs suggests they are not clinically useful in the treatment of PH. Hydralazine, a direct arteriolar dilator, was administered to 7 dogs with experimentally induced chronic heartworm disease and resulted in improvement in pulmonary hemodynamics in 4 (60%) dogs and systemic hypotension in 2 (30%) dogs. Caution should be used when administering any vasodilator in PH, especially in patients with clinical signs suggestive of, or the documentation of systemic hypotension.

Treatment goals are to improve clinical signs and quality of life and to identify and definitively treat any underlying etiologies. As discussed previously, commonly reported diseases leading to PH include primary pulmonary disease (bronchitis, interstitial lung disease, hypertension at high altitude), cardiovascular disease leading to chronic elevations in left atrial or left ventricular end-diastolic pressure also known as pulmonary venous congestion (cardiomyopathy, degenerative mitral valve disease, mitral valve stenosis, left to right shunting congenital heart disease), thromboembolic disease (thrombus, tumor), and inflammatory disorders directly affecting the pulmonary vasculature (dirofilariasis). Dogs with primary pulmonary disease and dirofilariasis may benefit from anti-inflammatory corticosteroid therapy as well as bronchodilators including theophylline. Theophylline is a methylxanthine that has in addition to bronchodilating properties, the ability to vasodilate through non-specific PDE inhibition and subsequent preservation of cAMP and cGMP concentrations leading to a reduction in mean pulmonary artery pressures in humans. Dogs with PH secondary to pulmonary venous hypertension or that have developed right heart failure are treated by managing the underlying cardiac disorder with the use of appropriate heart failure medications including angiotensin converting enzyme inhibitors, diuretics, and positive inotropes or inotropes. Positive inotropic therapy may benefit patients with systemic dysfunction and or clinical evidence of heart failure. While digoxin therapy is considered by many as standard heart failure therapy, its weak inotropic properties and the important adverse effects of digoxin toxicity should be considered carefully when it is initiated in PH patients. Clinical indication for digoxin may be limited to rate control in supraventricular arrhythmias such as atrial fibrillation. Pimobendan, a PDE III inhibitor, may have an important advantage in managing PH patients as a result of its combined positive inotropic and balanced vasodilating properties that are mediated through both PDE III and V inhibition in vascular smooth muscle. Acute or short-term management (days to weeks) in severe symptomatic PH should include heparin or ideally fragment, chronically there are poor therapeutic choices but with the exception of heartworm disease low dose aspirin may be useful.

Novel Therapeutic Agents

New medications have been recognized to alter pathologic vasoconstriction and endothelial dysfunction associated with PH. Prostacyclin is a metabolite of arachidonic acid with potent vasodilatory activity as well as the ability to inhibit platelet aggregation. Prostacyclin analogues have been shown to improve symptoms and short-term survival in human patients. Epoprostenol (Flolan, GlaxoSmithKline, $38 per 1.5mg, $3900/month) was the first available prostacyclin used to treat PH in humans. It is administered via continuous rate intravenous infusion and due to a very short half-life and abrupt withdrawal is associated with increased morbidity and mortality. Adverse effects related to the drug are mild and dose related while sepsis and thrombosis are important adverse effects related to chronic central venous access. Treprostinil (Remodulin, United Therapeutics Corp.) has similar hemodynamic effects as epoprostenol but is administered as a constant rate subcutaneous infusion which lowers the risk of sepsis associated with direct venous access. Intravenous Iloprost (Berlex Labs) has similar hemodynamic effects as epoprostenol with a longer half-life diminishing the adverse effects associated with abrupt withdrawal. Inhaled iloprost is also available and has a shorter half-life of 20-25 minutes requiring administration every 2-3 hours. Beraprost (United Therapeutics Corp), the first orally stable prostacyclin analogue, requires administration 3 times a day to maintain adequate blood levels. It is currently in phase 3 clinical trials in the United States.

Big ET-1 is converted to functional ET by endothelin converting enzyme. ET is a potent vasoconstrictor and smooth-muscle agonist resulting in vascular hypertrophy. ET levels are elevated in humans with PH and dogs with experimentally induced
Two types of ET receptors have been identified, ET<sub>A</sub> and ET<sub>B</sub>. ET<sub>A</sub> receptors are located on vascular smooth muscle cells and mediate vasoconstriction and vascular smooth muscle proliferation while ET<sub>B</sub> receptors are located on both endothelial and vascular smooth muscle cells and mediates vasodilatation and vasoconstriction. ET<sub>B</sub> receptors are up regulated in PH. The ET receptor antagonist bosentan (Tracleer, Actelion Pharmaceuticals US, $49.50 per 125mg tablet, $2970/month) competitively antagonizes the ET receptor types ET<sub>A</sub> and ET<sub>B</sub> with slightly more affinity for ET<sub>A</sub> receptors. Optimal dosage in humans is 125mg every 12 hours. In human studies, bosentan resulted in significant increases in exercise capacity. A potentially important adverse effect of bosentan therapy is elevations in hepatic enzyme activity that typically resolve with discontinuation of the drug but require monthly monitoring of serum biochemistries. The selective ET<sub>A</sub> receptor antagonists, sitaxsentan and ambrisentan, are currently being evaluated in human clinical trials.

PDE V is elevated in humans with hypoxia induced PH. PDE V inhibitors prevent degradation of cGMP resulting in relaxation of pulmonary vascular smooth muscle and, to a lesser degree, systemic vasodilation. PDE V degrades cGMP specifically while PDE III degrade both cAMP and cGMP. Sildenafil (Viagra, Pfizer, $14 per 100mg tablet, $315/month) is currently the most extensively researched of the PDE V inhibitors, and has been shown to improve both exercise tolerance and quality of life in humans with PH resulting in its FDA approval for the treatment of PH. Subsequently Viagra was recently re-released as Revatio (Pfizer, $11 per 20mg tablet, $990/month). Clinical improvement has been documented at multiple dosages ranging from 20mg to 80mg three times a day. Because higher doses did not increase the efficacy, the currently recommended dose in humans is 20mg every 8 hours. Imperially, the authors' start at about 5 mg per dog BID and up titrate (days to weeks) to a target dose of 25 mg per dog BID. This target dose is usually in the range of 2-3 mg/kg BID and is used because it allows for a 100mg tablet to be quartered which helps keep the costs down for the client. The stability of an oral sildenafil liquid dosage form has been reported in people. Alternatively, pimobendan (Vetmedin, Boehringer Ingelheim, $0.70 per capsule, $42/month) is an inodilator (positive inotrope via predominantly calcium sensitizing effects with some PDE III inhibitory activity in cardiomyocytes and balanced vasodilation via PDE III and V inhibition. In addition, it is recognized to have palliative affects on the maladaptive cytokines changes in chronic heart failure and some antiplatelet effects. Thus pimobendan alone or in combination with medications like sildenafil (other PDE V inhibitors) may be useful in the management of both symptomatic and asymptomatic canine PH and are currently used routinely in combination for the management of canine PH by the authors. Studies are in progress to evaluate potential benefits of multidrug therapy including the use of the sildenafil in combination with bosentan and the use of the PDE III & V inhibitor, pimobendan, to enhance prostaglandin analogue activity. Inhaled nitric oxide is a potent vasodilator but an extremely short half-life limits its use to that of a diagnostic tool instead of as a therapeutic agent. Oral sildenafil given as a single dose was found to be as effective a vasodilator as inhaled nitric oxide. Oral supplementation with L-arginine requires further investigation but may prove useful.

Sedation
Cardiac medications 20ug/kg IM. - Do not echo if needed. For maximum effect on contractility.