What to Expect When You're Expecting Pulmonary Hypertension

Presentation Notes

Daniel Newhard, DVM

AUVU Cardiology Seminar 2018

Definition

- Pulmonary arterial systolic pressure > 30 mmHg
- Pulmonary arterial pressure is determined by:
    - Pulmonary blood flow
    - Pulmonary vascular resistance
    - Pulmonary venous pressure

Classification

- Pulmonary hypertension can be classified by anatomic region affected and by disease process
    - Anatomic region
        - Pre-capillary
            - Caused by changes in resistance to flow – active, primary, or secondary
            - This is essentially any condition causing pulmonary hypertension except for left-sided cardiac disease
        - Post-capillary
            - Pulmonary venous hypertension
            - Caused by left-sided cardiac disease
            - This is the most common form of PH due to the high prevalence of myxomatous mitral valve disease in dogs
    - World Health Organization classification – altered for veterinary medicine
        - Class 1 – pulmonary arterial hypertension
            - Idiopathic, familial, left-to-right shunts (PDA, VSD), heartworm disease
        - Class 2 – pulmonary venous hypertension
            - Left-sided cardiac disease
        - Class 3 – pulmonary disease and/or hypoxia
            - COPD, pulmonary fibrosis, neoplasia, high-altitude disease, reactive, heartworm disease
        - Class 4 – thrombotic/thromboembolic disease
            - Heartworm disease, Cushing's, IMHA, etc.
        - Class 5 – miscellaneous
            - Compressive mass lesions, granulomas, heartworm disease

Clinical signs

- Exercise intolerance is most common based on retrospective studies
- **Syncope**
    - The two most common causes of syncope in dogs are pulmonary hypertension and arrhythmias
- Weakness
- Lethargy
- Cough

    - Cough can be due to the pulmonary hypertension itself or from the underlying disease causing the pulmonary hypertension
- Tachypnea
- Dyspnea

Physical Examination

- Heart murmurs
    - PH may not necessarily cause heart murmurs by itself, but can exacerbate the amount of tricuspid regurgitation already present – this is usually a right apical systolic heart murmur
- Crackles +/- increased bronchovesicular sounds if underlying pulmonary parenchymal disease is present
- Split S2 sound – delayed closure of pulmonic valve after closure of aortic valve is exacerbated
- Cyanosis
- Ascites
- Normal – patients can have significant pulmonary hypertension but also have an unremarkable physical examination

Diagnosis

- Right heart catheterization
    - Placing pressure monitoring catheters in the right ventricle and main pulmonary artery is the gold standard method, but more invasive than other tests
    - Avoiding general anesthesia is ideal in patients with significant pulmonary hypertension since they are usually horrible anesthetic candidates
- Echocardiography
    - This is the gold standard and most sensitive test out of the non-invasive methods
    - Findings:
        - Dilated main pulmonary artery +/- dilated right and left pulmonary arteries
        - Right atrial and right ventricular dilation
        - Right ventricular concentric hypertrophy
        - Increased velocity of tricuspid valve regurgitation velocity, if present (in the absence of outflow obstruction, such as pulmonic stenosis)
            - Tricuspid regurgitant velocity > 2.8 m/sec = pulmonary arterial hypertension
- Thoracic Radiographs
    - Dilated main pulmonary artery +/- dilated cranial and caudal lobar arteries
    - Right-sided cardiomegaly
    - Pulmonary parenchymal disease, depending on the underlying cause of the PH
    - Some patients with significant PH have normal thoracic radiographs
    - Acute tachypnea and dyspnea with no evidence of parenchymal disease on thoracic radiographs suggests acute pulmonary thromboembolic events
- Electrocardiography
    - Significant right-sided cardiac remodeling can cause deep S waves in lead II on the ECG, as well as potentially right bundle branch block and a right-axis shift for the MEA calculation
    - This is not the most sensitive test, as many dogs with PH will lack these ECG findings
- Biomarkers
    - NT-proBNP has been shown to be increased in dogs with PH, but it doesn't tell you the specific cause of PH and it can't rule out that there aren't other cardiac disease present concurrently with the PH
    - Cardiac troponin I levels have been shown to NOT be increased in dogs with PH

Diagnostic algorithm if PH is suspected

- The two easiest diseases to rule out (most of the time) are heartworm disease and left-sided cardiac disease, so these are usually excluded first
- Chronic lower airway disease is a common cause, which can sometimes be ruled out by evaluating thoracic radiographs +/- obtaining a history of respiratory signs (coughing, etc.)
    - Bronchoscopy/BAL can also be performed for some of these cases with odd respiratory signs and changes on thoracic radiographs
- Other causes of PH are more difficult to rule out, such as pulmonary thromboembolic events (PTEs)
        - For PTEs,
            - CT angiography is the gold standard
            - Angiography can also be used to determine if large thrombi are present in the large pulmonary arteries
            - Coagulation panel can be helpful ***sometimes***
                - Increased D-dimer concentrations suggest recent fibrinolysis
                - Increased fibrinogen
                - Low antithrombin III levels
            - Evaluate for systemic conditions that can lead to a hypercoagulable state
                - Cushing's
                - IMHA
                - Pancreatitis
                - Sepsis

Underlying vascular pathology

- The development of PH is all about an imbalance between vasoconstrictors and vasodilators
    - Vasoconstrictors predominate – endothelin-1, thromboxane A2, serotonin
        - Leads to smooth muscle proliferation, platelet activation, and vascular remodeling
    - Vasodilators are decreased or the endothelium no longer responds appropriately – nitric oxide, prostacyclin (PGI2)
        - Nitric oxide signals a cascade within the endothelial cells to increased cyclic GMP levels → cyclic GMP then prevents vasoconstriction of smooth muscle → dilation
        - These peptides also inhibit smooth muscle cell proliferation and inhibit platelet activation
- The question becomes – What comes first? (classic chicken or the egg scenario)
    - Idiopathic/familial pulmonary arterial hypertension is common in people
        - Genetic mutations resulting in smooth muscle cell proliferation and vasoconstriction
        - Reports of this in veterinary medicine, but it requires histopathology (usually done at necropsy – a little too late)
        - Diagnosis of exclusion in vet med, but we may just be missing other diagnoses
    - Pathology to the vessels, from whatever the cause, is usually irreversible
    - Vicious cycle - pathology leads to decreased arterial compliance in the lungs, which then signals the endothelial cells to undergo change → fibrosis, vascular remodeling, vasoconstriction, inappropriate responses to vasodilators and certain medications
    - Local thrombotic events can occur with pulmonary hypertension – raises the question "should all patients with significant PH be on anti-platelet +/- anti-coagulant therapy?"
        - Warfarin or other anti-coagulants are standard of care in humans with significant PH

Right-sided cardiac remodeling

- Increased pulmonary arterial pressure increases wall stress on the right ventricle

- Increased wall stress increases myocardial oxygen consumption, which becomes detrimental to the heart
- RV undergoes concentric hypertrophy to lower the wall stress
- This process continues until the RV wall cannot hypertrophy any more, then it begins to dilate
- Once the RV dilates, wall stress increases again and makes the myocardium unhealthy
- Over time, this chronic pressure, and then usually volume, overload leads to right-sided congestive heart failure
- If significant enough, right-sided disease can impact left-sided function
    - This is more common in people, but can occur in dogs

Importance of PH

- The presence of PH significantly reduces survival time in dogs with myxomatous mitral valve disease
    - Median survival is 758 days without PH vs. 456 days in dogs with PH
    - Estimated pressure > 55 mmHg (which is most of the patients we see with PH) has a worse outcome
    - Pressures > 48 mmHg have been shown to be correlated with a lack of response even if you decrease the left-sided cardiac load

Treatments

- Pharmacologic targets
    - Endothelin
    - Prostacyclin
    - Nitric oxide pathway
- Pharmaceutical classes
    - Phosphodiesterase V inhibitors
    - Prostacyclin analogs
    - Non-prostanoid receptor agonists
    - Endothelin receptor antagonists
    - Guanylyl cyclase stimulators

- Phosphodiesterase V inhibitors (PDE5 inhibitors)
    - This is the most commonly used class of drugs to treat PH (and the most cost effective)
    - Sildenafil (Viagra)
        - Sildenafil inhibits PDE5, so cGMP levels are increased → vasodilation
        - PDE5 in higher concentrations in larger pulmonary arteries
        - 2 mg/kg PO TID
        - Reduces pressure gradient in some studies
        - Most beneficial clinical result is often improvement +/- resolution of the clinical signs
        - May or may not slow the progression of the disease
        - When do we start sildenafil?
            - Moderate to severe PH
            - If right-sided cardiac remodeling is present
            - If right-sided CHF is present
            - If clinical signs are suspected to be due to the PH
        - PDE5 polymorphisms
            - Genetic mutations in PDE5 are present in people – alters how they respond to sildenafil and how cGMP levels change

            - Genetic polymorphism found in dogs – does this change how our patients respond to sildenafil?
    - Tadalafil (Cialis)
        - Same mechanism as sildenafil, but dosed once daily – easier for owner administration?
        - No large clinical studies evaluating it in dogs, but is efficacious in case reports
    - Theophylline
        - Non-specific PDE inhibitor
        - Not often started for PH itself, but can be helpful with lower airway disease
    - Pimobendan
        - PDE3 inhibitor
        - PDE3 is in higher concentrations in the small arteries in the lungs
        - Pimobendan has been shown to lower NT-proBNP in dogs with PH
- L-arginine supplementation
    - L-arginine is a precursor necessary for nitric oxide production
    - Shown to increase nitric oxide concentrations in dogs, but is only beneficial to the downstream cascade if sildenafil is used concurrently
    - No obvious benefit clinically in dogs, but it is inexpensive and won't hurt
- Endothelin-1 antagonists
    - Standard of care in people with significant PH
    - Bosentan, sitaxsentan, ambrisentan
    - No studies evaluating their use in dogs with PH, just anecdotal reports
    - Usually financially limiting
- Prostacyclin pathway
    - PH leads to decreased prostacyclin and increased thromboxane A2
    - Epoprostanol – must be given as a CRI through a central line
    - Iloprost – inhaled 6-12 times per day
    - Usually financially and logistically limiting
    - Non-prostanoid prostacyclin receptor agonists
        - Selexipag – PGI2 receptor agonist
        - Not evaluated in dogs, financially limiting
- Guanylyl cyclase stimulators (GCSs)
    - Nitric oxide pathways are down-regulated or not efficient in PH
    - GCSs bypass the need for nitric oxide and stimulate the pathway by triggering guanylyl cyclase activity to increase cGMP levels
    - Riociguat

Surgical intervention for PH

- Atrial septostomy
    - Catheter and balloon placed across the interatrial septum to form a permanent 'atrial septal defect'
    - Acts as a pop-off valve to release right-sided pressures
    - Invasive – not common in vet med
- Potts procedure
    - Anastomosis of the left pulmonary artery to the descending aorta
    - Reduces pressure in the pulmonary arterial system and translates it to the systemic pressures – pulmonary and systemic pressures equalize
    - Usually used in children with severe PH
    - Invasive – not used in vet med

- Transplantation
    - If our patients with significant PH were people, they would all have lung or heart-lung transplants

Summary

- Pulmonary hypertension isn't *too* difficult to diagnose – finding the cause is a different story
- We have medications to improve clinical signs, but by the time we diagnose it, it's significant and we can't do anything to reverse the remodeling
    - We can only try to slow down the progression
    - We often improve clinical signs – this is usually temporary
    - Our treatments are essentially Band-Aids®
- There are many medical therapy options for people, but we are limited by the financial cost of these medications in vet med