Pulmonary Hypertension
The cardiopulmonary “Great Pretender”

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Introduction

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Introduction

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Introduction

Gordon D. Peddle
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Goals

- Define pulmonary hypertension (PH)
- Discuss pathophysiology of pulmonary hypertension
- Describe etiologies of PH in veterinary medicine
- Understand the method of diagnosis of PH in veterinary medicine
- Treatment modalities

Goals

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Pulmonary vein:

Pulmonary hypertension (PH):

What are normal pulmonary artery pressures?

- Sys/dia: 25/10 mm Hg
- Mean PAP: 15 mm Hg

Nonspecific definition:
Elevated pressures in the arteries of the lungs

Let’s get elementary!

• Simple equation that governs the laws of pressure (P), resistance (R), and flow (Q):
  - $\Delta P = Q \times R$
  - Via $Q = \frac{\Delta P}{R}$

Key Point:

• Pulmonary Arterial Hypertension (PAH) & Pulmonary Hypertension (PH) ≠ NOT the exact same entity
  - Ideally not be used interchangeably

• In humans PAH is a distinct entity (and subcategory of PH) separate from other causes of pulmonary hypertension

World Health Organization (WHO) Classifications of Pulmonary Hypertension (PH): (1-5)

• Group 1: Pulmonary arterial hypertension (PAH)
  - Idiopathic
  - Heritable (familial)
  - BMPR2, ALK1, endoglin
  - Drug- and toxin-induced
  - Associated with (APAH):
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Congenital heart disease (systemic-to-pulmonary shunts)
    - Schistosomiasis
    - Persistent pulmonary hypertension of the newborn
  - Group 1': Pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis
Health impact: humans

- Survival rates, pulmonary arterial hypertension (PAH)
  - 1 year: 85%
  - 3 year: 68%
  - 5 year: 57%
  - 7 year: 49%

Group 2: Pulmonary hypertension with left heart disease (PH-LHD)

- Systolic dysfunction
- Diastolic dysfunction
- Valvular heart disease

“Irrespective of the origin of left heart disease, the first event leading to PH is a passive backward transmission of filling pressures...”

Vachery et al. J Am Coll Cardiol 2013;62:D100-

Group 3: Pulmonary hypertension due to lung disease and/or hypoxemia

- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease
- Mixed restrictive/obstructive pulmonary disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic high altitude exposure*
- Developmental abnormalities

*Veterinary correlate: Bovine High Mountain Disease (BHMD, or Brisket disease)

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)

- Thromboembolic obstruction of proximal PA(s) (massive embolus)
- Thromboembolic obstruction of distal PA(s) (nonmassive)
- Non thrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5: PH with unclear multifactorial mechanisms

- Haematological disorders
- Systemic disorders
  - Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, vasculities, other
- Metabolic disorders
  - Glycogen storage disease, thyroid disorders, Gaucher disease
- Other
  - Tumoral obstruction, compression, chronic renal failure (dialysis)

Pulmonary arterial hypertension (PAH, WHO Group 1): Definition

1. Mean pulmonary artery pressure (MPAP):
   - ≥ 25 mm Hg at rest
   - ≥ 30 mm Hg with exercise
2. Pulmonary vascular resistance (PVR):
   - > 3 Wood units
   - Wood unit = mm Hg·L/min
3. Pulmonary capillary wedge pressure (PCWP):
   - < 15 mm Hg

*PCWP estimates left atrial pressure
Pulmonary hypertension due to left heart disease (PH-LHD, WHO Group 2): Definition

• 1. Mean pulmonary artery pressure (MPAP):
  ▫ ≥ 25 mm Hg at rest
  ▫ ≥ 30 mm Hg with exercise

• 2. Pulmonary vascular resistance (PVR):
  ▫ > 3 Wood units
    - Wood unit = mm Hg/L/min

• 3. Pulmonary capillary wedge pressure (PCWP):
  ▫ > 15 mm Hg

Pulmonary hypertension: Additional terminology

• Precapillary: Pulmonary arterial hypertension (PAH)
  ▫ Normal pulmonary venous pressures
  ▫ unusually high mPAP-PCWP
  ▫ ↓ PVR

• Postcapillary: elevated pulmonary capillary wedge pressure (PCWP)
  ▫ High cardiac output PH
    - Rarely attributable to output alone

Transpulmonary gradient (TPG)

• TPG = mPAP – PCWP

• mPAP = mean pulmonary artery pressure

• PCWP = pulmonary capillary wedge pressure

Post-capillary PH (PH-LHD): Additional terminology

• “Passive” vs “Reactive” PH
  ▫ “Passive” = transpulmonary gradient ≤ 12 mm Hg
  ▫ “Reactive” = transpulmonary gradient > 12 mm Hg

“Out of Proportion” PH

• Better way to describe reactive PH?

How best to characterize the pulmonary vascular component?

• Diastolic pressure difference?
  ▫ Diastolic PAP – mean PCWP
    ▫ Diastolic PAP less influenced by PCWP

• PAP = pulmonary artery pressure
  ▫ PCWP = pulmonary capillary wedge pressure

1) Isolated post-capillary PH
2) Combined post-capillary and pre-capillary PH
Diagnosis of PH in humans

- Cardiac catheterization: Gold standard  
  - Pulmonary artery pressure, resistance measurements
- CT/MRI evaluation for PTE
- Echocardiography  
  - Considered less than ideal method in humans  
  - Nonetheless remains an effective screening tool  
  - 83% sensitivity, 72% specificity  
  - Janda et al, Heart 2011;97:612-622

WHO Classifications:
- Group 1: PAH  
  - Idiopathic, heritable, toxic  
  - APAH conditions  
  - Congenital heart disease (shunts)
- Group 2:  
  - PH-Left sided heart disease
- Group 3:  
  - Lung disease, hypoxemia
- Group 4:  
  - Thromboembolic disease  
  - Parasitic disease
- Group 5:  
  - Multifactorial  
  - Storage diseases  
  - Systemic diseases

Pathophysiology:
Chronic lung disease-induced PH

- Hypoxic pulmonary vasoconstriction
- Acidemia, hypercarbia
- Distortion of pulmonary vessels by parenchymal changes
- Cardiac output, viscosity from secondary polycythemia

P = QR

Pulmonary hypertension due to left heart disease (post-capillary PH)

- Passive congestion leads to PH  
- Can develop “reactive” or “out of proportion” component
- Secondary vascular remodeling
- Can be chronic and/or acute
- Cats: Acute PH contributing to pleural effusion with L-CHF?

P = QR

Pulmonary thromboembolism (PTE)

- Direct obstruction of pulmonary artery or arteries  
  - Massive PE vs non-massive PE  
  - Acute vs chronic  
  - Secondary arteritis, parenchymal inflammation

\[ P = QR \]

Pulmonary artery parasitic disease

- Heartworm = misnomer  
  - Immature D. immitis larvae migrate to main PA by day 90 and mature to adults
  - Primary agents of vascular disease  
    - Intimal proliferation, narrowing of small vessel lumens  
    - Endarteritis of small peripheral branches  
    - Thrombosis, thromboembolism

P = QR
L->R systemic-to-pulmonary shunts

- Intracardiac
  - Ventricular septal defect
  - Atrial septal defect
- Extracardiac
  - Patent ductus arteriosus
  - Aortopulmonary window
  - Peripheral AV fistula

Key:
- Large shunts = PH likely
- Small shunts = PH unlikely

P = QR

L->R systemic-to-pulmonary shunts

- Flow-mediated PH
  - Flow alone causes pressure, not resistance
  - Resistance via:
    - Enhanced smooth mm cell proliferation
    - Increased deposition of matrix glycoproteins

P = QR

Plexiform lesions in precapillary arterioles

- Hallmark of PAH
  - Obliterative endothelial cell proliferation
  - Vascular smooth muscle cell hypertrophy

P = QR

Idiopathic

- Difficult to be certain
  - Subclinical radiographic lung disease?
  - Not routinely performing pulmonary CT (emboli?)
- Familial?

Pulmonary Hypertension in Vet Med

- Demographics
  - Dogs >> cats (with current detection methods)
  - Male = Female
  - All ages represented
    - Middle age to older dogs
    - Chronic lung disease
    - Chronic left sided heart disease
  - Parasitic disease: All ages; geographic and socioeconomic components
    - D. immitis: Southeast US
    - Angiostrongylus vasorum (Europe)
Presenting complaints

• Coughing
• Dyspnea/tachypnea
• Wheezing
• Syncope
• Collapse
• Exertional intolerance
• Weakness/lethargy
• Asymptomatic

Physical examination

• Related to the disease process
  - Cyanosis (generalized)
  - Pulmonary crackles
  - Right sided cardiac murmur (tricuspid)
  - Split second heart sound (Split S2)
  - Jugular vein pulsation**
  - Signs of R-CHF
    - Abdominal distension/ascites
    - Muffled heart/lung sounds (pleural effusion)
  - Tachycardia vs profound sinus arrhythmia
  - Left sided cardiac murmur (mitral)
    - May be unrelated
    - Many patients likely to have concurrent mitral valve disease simply based on signalment

PH: Diagnosis

• Thoracic radiographs (nonspecific)
  - Critical in any dyspnea patient
    - +/- Right heart enlargement
    - +/- Enlarged main, peripheral PAs
    - +/- Pleural effusion, ascites if R-CHF
    - +/- Bronchial/pulmonary disease
    - +/- Tortuous peripheral PAs (heartworm)
    - +/- Left heart enlargement
    - +/- “Westermark sign” (PTE)
      - Focal pulmonary oligemia

2 YO Mastiff MC: Idiopathic PH

Heartworm dz
5YO MC Lab mix

5YO Jack Russell Terrier
Coughing, tachypnea, cyanosis
PH with chronic pulmonary disease
VHS11.8
PH, chronic pulmonary disease
10 YO FS Corgi

PDA, overcirculation
8 MO Toy Poodle

Electrocardiography
- Evidence of right axis deviation (deep S wave in lead II)
- Not likely to be evident until disease moderate or severe
- Not very sensitive, but highly specific for right ventricular hypertrophy

Diagnosis: Veterinary patients
- Cardiac catheterization: Gold standard
  - Not practical in veterinary patients
- CT/MRI eval for PTE (humans)
  - Not practical in veterinary patients with dyspnea
- Echocardiography
  - Has become cornerstone of diagnosis in vet med

Echocardiography:
  Nonspecific findings
  - RV dilation/hypertrophy
    - Acute vs chronic?
  - Dilated PA
  - Prolapse of TV, PV
  - IVS flattening, paradoxical septal motion
    - Septum moves towards LV during diastole/systole due to high RV pressure
Normal dog

Severe PH

Suspect acute PTE

Dilated pulmonary arteries

Diagnosis: Doppler

- Color
  - Tricuspid regurgitation (TR)
  - Pulmonic insufficiency (PI)

- Spectral – Definitive diagnosis
  - Peak tricuspid regurgitation velocity
  - Peak and/or end-diastolic PI velocity

TR velocity

- Pressure gradient (PG) across tricuspid valve (TV) during systole (RV-RA gradient)
  - ≈ Systolic RV pressure
  - ≈ Systolic PA pressure
  - Only accurate in the absence of right sided outflow obstruction

\[ \Delta P = 4V^2 \] where V = peak tricuspid regurgitation velocity
TR velocity: Downsides

- Trivial jet
- Respiratory variation: peak TR velocity lower on expiration, can lead to underestimation
- May overestimate TR velocity if Doppler gain set too high
- Effect of catecholamines, volume load on RV systolic pressure
- MR or SAS may be confused with TR jet
  - Differentiate based on transducer angle, flow duration

PH severity (veterinary patients)

- Based on TR velocity (RV-RA pressure gradient)
  - Normal:
    - $< 2.8 \text{ m/s}$, $< 3.0 \text{ m/s}$, $< 3.2 \text{ m/s}^2$
  - PG ≤ 35 mm Hg: Normal
  - PG 35-50 mm Hg: Mild
  - PG 50-75 mm Hg: Moderate
  - PG ≥ 75 mm Hg: Severe

PI velocity

- End-diastolic velocity estimates end-diastolic PA pressure
  - Normally $< 5 \text{mmHg}$
- Peak early diastolic PI estimates mean PA pressure
  - Masuyama: $\text{MPAP} = 4 \times \text{peak PI}^2$

RVOT flow acceleration

- As pressure in the PA increases, acceleration becomes shorter

$\text{PG} = 4v^2$

Peak PI = Mean PA pressure
64 mm Hg

End-diastolic PI = end-diastolic PA pressure
36 mm Hg

Mahan’s equation: $\text{MPAP} = 79 - 0.45(AcT)$
- AcT is dependent on HR and CO
- If inc RV output (due to ASD), AcT may be normal even if PAH present
- Must correct AcT for fast or slow HR
Determining etiology of PH

- Radiographs
- Echocardiogram
  - Left heart disease, heartworms, massive PTE
- Heartworm testing
- Plasma D-dimer: evaluation for likelihood of PTE
  - Sensitive, not generally specific
- Arterial blood gas, A-a gradient do not help differentiate PTE from other causes
- Endotracheal wash
  - Not generally advised once PH identified
  - Bacterial component not likely
  - High risk anesthesia

Diagnostic Utility of D-Dimer Concentrations in Dogs with Pulmonary Embolism (Epstein et al., J Vet Intern Med 2013)

- D-dimer cutoff: 250 ng/mL
  - 80% sensitivity, 30% specificity
  - No value was 100% specific
- Elevated D-dimer also has been documented in dogs with
  - DIC
  - Internal hemorrhage
  - Neoplasia
  - Renal disease
  - Liver disease
  - Post-operatively

12 YO Cavalier King Charles Spaniel

Mitrval valve disease, subsequent rupture of atrial septum
- Acquired L \( \rightarrow \) R atrial septal defect (ASD)

Massive pulmonary embolus (right pulmonary artery)

Flow-mediated PH (left-to-right shunting)

- 9 month old Cocker Spaniel

Primus atrial septal defect (ASD)
Mild to moderate PH
Practical guide to PH (not associated with left sided heart disease)

- The cardiopulmonary "Great Pretender"
  - Be aware of overrepresented breeds when they walk in the door
  - Heartworm status? On preventative?
  - Syncope?
    - Description of episodes critical re: syncope vs seizure!

- Signs of PH:
  - Coughing
  - Dyspnea/tachypnea
  - Wheezing
  - Syncope
  - Collapse
  - Exercise intolerance
  - Weakness/lethargy
  - Asymptomatic

Practical guide to PH

- Key physical examination findings:
  - Dyspneic, small breed dog with absence of heart murmur
  - Does NOT mean if there is a murmur that PH is NOT present....
  - Means that with clinical respiratory signs, but no murmur identified, likelihood of PH >> L-CHF
  - Split second heart sound
  - R-CHF

- Deep S-wave in lead II ECG in dyspneic dog
  - (General practice/emergency setting)

Practical guide to PH

- Thoracic radiographs
  - Right sided cardiomegaly, PA enlargement
  - Pulmonary pattern more consistent with chronic airway disease than pulmonary edema

- Clinical progression
  - Marked responsiveness to oxygen therapy
  - Pulse oximetry readings < 90% even with significant clinical improvement
  - Lack of continued improvement over 12-24 hour period with CHF therapy (have I been fooled...?)

Just when you thought you were safe...

- Many dogs with pulmonary hypertension (regardless of etiology) will show some improvement with common CHF therapies:
  - Oxygen
  - Furosemide
    - Pulmonary vasodilatory effects
  - Pimobendan
    - Phosphodiesterase inhibition

Pulmonary hypertension: Treatment

- Treat underlying etiology
  - Chronic/inflammatory lung disease
  - Bronchodilators (theo-, aminophylline, terbutaline)
  - Corticosteroids
  - +/- Antibiotics
  - Heartworm disease
    - Manual worm extraction
    - Bronchodilators
    - Corticosteroids
    - Doxycycline
    - Immiticide....eventually

- Pulmonary thromboembolism
  - Hypercoagulable?
    - Underlying systemic disease (IMHA, liver disease, PLE)
    - D-dimer
    - Thromboelastography (TEG)
  - Antithrombotics
    - Heparin products
    - Plavix
    - Aspirin
• Left heart disease
  ▫ Adjust L-CHF therapy first

  "The primary goal of therapy of PH-LHD must be to improve global management of the underlying condition before considering specific measures to treat PH" - Vuchay et al, J Am Coll Cardiol 2013;62:D100-8

• L-R shunts
  ▫ Correct/close shunt if PH not severe

PH-specific therapies

PH-specific therapy

• Pulmonary vasoreactivity testing (humans)
  ▫ ↓ PAP, ↓CO, ↓PVR

• Bronchodilators
  ▫ Theophylline
  ▫ Aminophylline
  ▫ Terbutaline

Pulmonary vasodilators

• OXYGEN!
• Calcium channel blockers (amlodipine)
  ▫ Less effective in animals
• PAH-specific therapies
  ▫ Endothelin receptor antagonists
  ▫ Prostanoids
  ▫ Phosphodiesterase type-5 inhibitors
  ▫ Guanylate-cyclase stimulators

Endothelin receptor antagonists

• Endothelin-1: Cause or effect?
  ▫ ET$_A$: Vasoconstriction, proliferation
  ▫ ET$_B$: ET-1 clearance, 2NO, prostacyclin
  ▫ No difference in efficacy of selective vs nonselective ET-1 antagonists (humans)
  ▫ Bosentan, ambrisentan, macitentan
  ▫ Cost prohibitive in veterinary patients
  ▫ Good Rx.com: $8400.00 for 60 tablets (125 mg bosentan)
Prostanoids

- Prostacyclin
  - Relaxes vascular smooth muscle
  - Inhibits smooth muscle cell growth
  - Most potent endogenous inhibitor of platelet aggregation
- Epoprostenol (IV infusion)
- Iloprost (inhaled)
- Treprostinil (inhaled, IV, SQ)
- Cost prohibitive in veterinary patients
  - GoodRx.com: $3300.00 for 1 carton (30 ampules) of 10 mcg/mL Iloprost

Phosphodiesterase type 5 (PDE5) inhibitors

- Enhance NO-dependent, cGMP-mediated pulmonary vasodilation
  - via inhibition of cGMP breakdown
- Sildenafil (Viagra) 1-2 mg/kg PO q8h
- Tadalafil (Cialis) 1 mg/kg PO q24h
- Vardenafil (Levitra)
- Cornerstone of therapy in veterinary medicine
- Selective pulmonary vasodilators
- Preferentially vasodilate within aerated lung
  - Side effects: hyperactivity, disturbed color vision (humans)
- Pimobendan (PDE3 >> PDE5)

PDE5 inhibitors: Mechanism of action

- Hypoxia
- Vessel shear stress
- Vascular injury
- Thrombosis

Guanylate-cyclase Stimulators

- Directly stimulate guanylate cyclase (cGMP production) independently of nitric oxide
- Riociguat

Corticosteroids: to give or not to give?

- Dogs with PH associated with primary pulmonary infiltrates on radiographs (non-cardiogenic)
- If previously documented chronic pulmonary disease, corticosteroids likely indicated
- What if not previously documented?

Kellihan HB, et al

  - Localized noncardiogenic pulmonary edema?
Ancillary therapy
Non-cardiogenic PH in animals

- Therapy for right sided CHF if present
  - Diuretics
  - ACEI, Aldosterone antagonists
  - +/- Pimobendan
  - Caution combining sildenafil, pimobendan, theophylline (agitation, hyperactivity)

- HOWEVER....
  - If highly responsive to PH-specific therapy (Sildenafil), it is possible patient may be temporarily or permanently weaned off of R-CHF therapy (in patients with non-cardiogenic PH)!!

Sildenafil for PH secondary to left sided heart disease: when to use?

- Specific guidelines in animals not well established
- Syncope
- Right sided congestive heart failure
- Dyspnea, exertional intolerance in the absence of recurrent pulmonary edema?
- Stable L-CHF patients with moderate-severe PH?
  - Not investigated to date

Transpulmonary gradient (TPG)

- Estimated systolic pulmonary artery pressure
  - >55 mm Hg?
  - >75 mm Hg?
  - higher?

- It’s all about the transpulmonary gradient...which we can’t truly effectively measure via echocardiography

Dangers of sildenafil use with chronic left sided heart failure

- Again, it’s all about the transpulmonary gradient...

- Risk of inadequate pressure gradient to drive blood flow from pulmonary arteries into pulmonary capillaries with sildenafil use = cardiovascular collapse

PH: Prognosis

- Long-term: Poor
- Short-term: Guarded
  - Many patients will respond positively to therapy
  - Quality of life may be dramatically improved
  - Improvement may be delayed and/or gradual
  - May require prolonged hospitalization (2-5 days)
  - Medication cost $$
    - Sildenafil, Cialis
    - Fluticasone
What’s new: Etiology/therapy

• Role of iron?
  ▫ Important cofactor in inhibition of hypoxic pulmonary vasoconstriction
  ▫ Iron deficiency (in absence of anemia) has been documented in subset of human patients with PH
  ▫ Clinical improvement reported with iron supplementation in PH patients (with and without deficiency)

What’s new: Therapeutic targets in humans

• Prostaglandin receptor agonists
• Tyrosine kinase inhibitors
• Rho-kinase inhibitors
• Vasoactive intestinal peptide
• Endothelial progenitor cell transplantation

  ▫ Percutaneous balloon atrial septostomy
  ▫ Percutaneous pulmonary artery denervation
  ▫ Focal blunting of adrenergic nervous system

• Thank you kindly for your time and attention!
• Q & A

#CPRwheel

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