PULMONARY HYPERTENSION AND NON-CARDIOGENIC PULMONARY EDEMA

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PULMONARY HYPERTENSION

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- PH is defined by increased pressure within the pulmonary vasculature
- This is a hemodynamic and pathophysiologic state present in a wide variety of cardiovascular, respiratory, and systemic diseases
- Increased PAP is not a defining characteristic of a specific clinical condition but rather an abnormal hemodynamic state associated with numerous, diverse disorders
- In humans, PH is defined as a mean PAP ≥25 mm Hg at rest

DIAGNOSIS OF PH

- The standard method for diagnosis of PH is direct assessment of pulmonary arterial pressure (PAP) by right heart catheterization (RHC)
  - RHC is required for definitive diagnosis of PH but seldom practical
- Echocardiographic assessment is based on characteristic cardiac changes that occur secondary to PH and by estimating PAP from spectral Doppler tracings

ECHOCARDIOGRAPHIC FINDINGS OF PH

- In absence of RV outflow tract obstruction, estimation of PAP involves quantifying peak tricuspid regurgitation velocity (TRV), and then derivation of the pressure gradient (PG) between the RV and right atrium using the simplified Bernoulli Equation:
  - Bernoulli equations: PG = 4 × velocity [m/s]2
- An estimate of right atrial (RA) pressure is added to the calculated PG to yield estimated systolic PAP. Validated methods to estimate RA pressure are unavailable in dogs, and therefore estimates of RA pressure are arbitrary and potentially flawed
- It is instead recommended to use only continuous wave Doppler measurement of tricuspid regurgitation velocity (TRV) (versus estimated systolic PAP) as a key metric in determining PH probability as long as clinicians are aware that systolic PAP might be underestimated when severe RA hypertension is present.

ACVIM ECHOCARDIOGRAPHIC PROBABILITY OF PH

TABLE 2 Echocardiographic probability of PH in dogs

Peak tricuspid regurgitation velocity (m/s)	Number of different anatomic sites of echo signs of PH[a]	Probability of PH
≤3.0 or not measurable	0 or 1	Low
≤3.0 or not measurable	2	Intermediate
3.0 to 3.4	0 or 1	Intermediate
>3.4	0	Intermediate
≤3.0 or not measurable	3	High
3.0 to 3.4	≥2	High
>3.4	≥1	High

RADIOGRAPHIC FINDINGS

- Tortuous, blunted, or dilated pulmonary arteries
- Asymmetric radiolucent lung fields on dorsoventral or ventrodorsal views
- Patchy, diffuse alveolar infiltrates
- Bulge in the region of the pulmonary trunk or right- sided cardiac enlargement

CLINICAL DEFINITION OF PH

- Severity of PH is often divided into mild, moderate, or severe
  - This is based on the pressure gradient derived from TRV (also called the tricuspid regurgitation PG) or estimated systolic PAP
  - Argued that this is arbitrary and misleading
- Instead proposed by ACVIM, that the "clinical definition of PH should include dogs with intermediate or high probability of PH and a tricuspid regurgitation PG cutoff of >46 mmHg"

PROPOSED CLINICAL CLASSIFICATION OF PH

- ACVIM clinical classification of PH in dogs:
  - Group 1: pulmonary arterial hypertension
  - Group 2: Left sided heart disease
  - Group 3: Respiratory disease/hypoxia
  - Group 4: Pulmonary emboli/pulmonary thrombi/pulmonary thromboemboli
  - Group 5: Parasitic disease (Dirofilaria and Angiostrongylus)
  - Group 6: Disorders that are multifactorial or with unclear mechanisms.

TABLE 5 Terminology, hemodynamic definitions, and echocardiographic findings of PH together with the proposed clinical classification groups of pulmonary hypertension

Terminology	Hemodynamic definition by right heart catheterization used in humans	Echocardiographic findings	Clinical classification group
Precapillary PH	Mean PAP ≥25 mm Hg	No left atrial enlargement	Group 1. Pulmonary arterial hypertension[a]
	PAWP ≤15 mm Hg	At least some findings listed in Table 3 are expected	Group 3. PH due to respiratory disease/ hypoxia
	Increased PVR		Group 4. Thromboembolic PH
			Group 5. Parasitic disease
			Group 6. PH with multifactorial and/or unclear mechanisms
Postcapillary PH	Mean PAP ≥25 mm Hg	Left atrial enlargement	Group 2. PH due to left heart disease
	PAWP >15 mm Hg		Group 6. PH with multifactorial and/or unclear mechanisms
Isolated postcapillary PH	DPG <7 mm Hg	Left atrial enlargement	
	PVR not increased		
Combined postcapillary & precapillary PH	DPG ≥7 mm Hg	Left atrial enlargement	
	Increased PVR	At least some findings listed in Table 3 are expected	

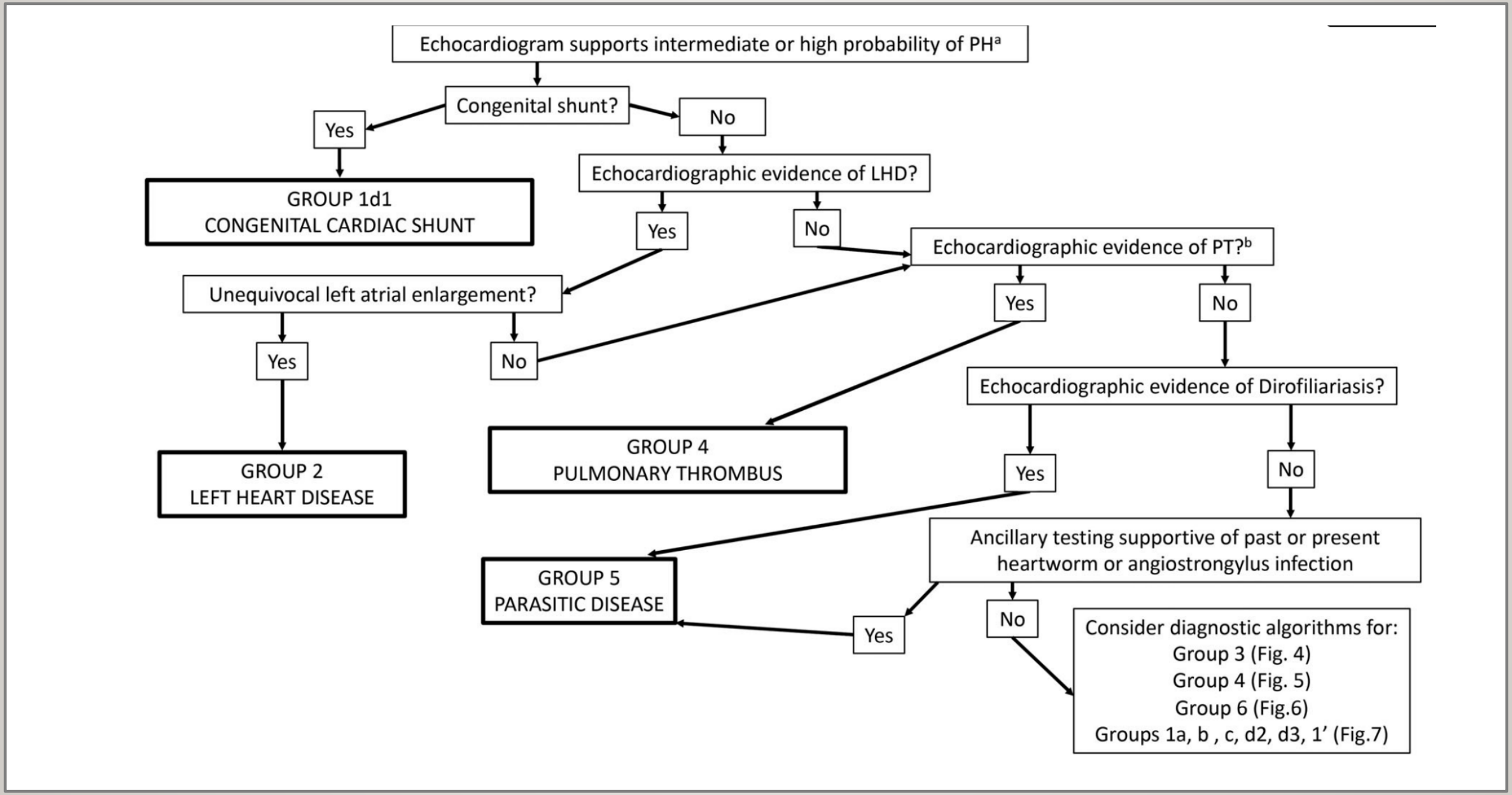
Abbreviations: DPG, diastolic pressure gradient (diastolic PAP − mean PAWP); PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

[a]Congenital cardiac shunts (group 1d1) exhibiting left-to-right shunting represents an exception. The PH may be primarily due to increased right heart cardiac output and not increased PVR.

CLINICAL PRESENTATION

- Generally older small breed dogs with acquired cardiac, respiratory, and systemic diseases
- Can be seen in puppies with congenital cardiac shunts and developmental lung disease

Findings strongly suggestive of PH	Findings possibly suggestive of PH
Syncope (especially with exertion or activity) without another identifiable cause	Tachypnea at rest
Respiratory distress at rest	Increased respiratory effort at rest
Activity or exercise terminating in respiratory distress	Prolonged postexercise or post-activity tachypnea
Right-sided heart failure (cardiogenic ascites)	Cyanotic or pale mucous membranes


Echocardiogram supports intermediate or high probability of PH[a]
Congenital shunt?
Yes
No
GROUP 1d1
CONGENITAL CARDIAC SHUNT
Echocardiographic evidence of LHD?
Yes
No
Unequivocal left atrial enlargement?
Yes
No
GROUP 2
LEFT HEART DISEASE
Echocardiographic evidence of PT?[b]
Yes
No
GROUP 4
PULMONARY THROMBUS
Echocardiographic evidence of Dirofiliariasis?
Yes
No
GROUP 5
PARASITIC DISEASE
Ancillary testing supportive of past or present heartworm or angiostrongylus infection
Yes
No
Consider diagnostic algorithms for:
Group 3 (Fig. 4)
Group 4 (Fig. 5)
Group 6 (Fig.6)
Groups 1a, b , c, d2, d3, 1' (Fig.7)

TREATMENT OF PH

- Goals should be to:
  - Treat underlying disease(s) contributing to PH
  - Decrease risk of progression or complications of PH
  - Specific treatment to treat the PH

PH SPECIFIC TREATMENT

- Sildenafil
  - PDE5 inhibitor that targets and augments vascular nitric oxide pathway
  - Intended to target pre-PH by decreasing PVR. Acts as a pulmonary arterial vasodilator
  - Studies show improvement of clinical signs, quality of life, exercise capacity and decreased echocardiographically estimated PAP
  - Short half life- needs q8h dosing
  - Can lead to acute pulmonary edema-> use in caution in dogs with congenital cardiac shunt

BOX 1 Unproven alternative or adjunct therapies that might be considered for use in dogs with pulmonary hypertension

Pimobendan: Pimobendan is an oral PDE3i with positive inotropic and systemic vasodilatory properties. It has been shown to improve RV systolic function following a single oral dose in healthy dogs.[26] Although pimobendan has been suggested as a treatment for PH in general,[24,83,105,205,220] to date, there is no direct or clear evidence of its beneficial effects on pre-PH. Previously reported improvements in estimated PAPs in dogs with MMVD might be related to its beneficial effect on lowering LA pressure[221] and thus targeting postcapillary PH. Further study is needed to help clarify pimobendan's role in pre-PH. Thus, the panel does not advocate for or against the use of pimobendan as adjunct treatment in dogs with pre-PH.

Milrinone: Milrinone is an IV PDE3i. It has both PA vasodilating and positive inotropic properties. In experimental canine PH, milrinone improved RV function[222] and decreased mean PAP.[223]

Tyrosine kinase inhibitors (eg, toceranib, imatinib): Tyrosine kinase inhibitors (TKI) result in PA vasodilation by inhibiting the activation of platelet derived growth factor by impeding phosphorylation of the platelet-derived growth factor receptor tyrosine kinase. In people, specific TKI are effective at improving refractory PH[224-228] but serious adverse events are common.[228] In dogs, a single study demonstrated imatinib reduced PAP in dogs diagnosed with PH secondary to LHD.[229] Paradoxically, some TKI can induce PH in humans.[230] Consideration of and monitoring for contraindications and adverse events are indicated.

L-arginine: L-arginine is an amino acid that is essential, in conjunction with oxygen, to the production of NO. Oral administration increases surrogate markers of NO in healthy dogs.[231] Although no clinical studies in dogs have demonstrated the benefits of L-arginine in clinical patients, 1 study in experimental canine acute PTE showed L-arginine and sildenafil together were not more beneficial than sildenafil alone.[232]

In dogs, there is insufficient information in the literature and anecdotal experience with other PH-specific therapies used in humans (eg, calcium channel blockers, endothelin antagonists, prostanoids, soluble guanylate cyclase stimulators, etc). No recommendations on the use of these medications can be made at the current time.

LONG TERM MANAGEMENT OF PH

- Prognosis of dogs with PH is variable and related to the cause of PH
- Unless a reversible cause of PH is identified, dogs with a high probability of PH experience a worse prognosis than dogs with same disease but with a low probability of PH
- Right-sided heart failure secondary to PH has a worse prognosis
- Need frequent monitoring at home, general recheck exams, serial echocardiograms

NON CARDIOGENIC PULMONARY EDEMA

QUESTION

- List the general categories of pulmonary edema

PULMONARY EDEMA

- The accumulation of extravascular fluid within the pulmonary parenchyma or alveoli
- Two main physiologic forms:
  - High-pressure edema: caused by increased pulmonary capillary hydrostatic pressure
  - Increased-permeability edema: caused by damage of the microvascular barrier and alveolar epithelium in more severe cases
- Initial diagnostic approach is to differentiate cardiogenic (caused by left-sided, backward heart failure) from non-cardiogenic edema (all causes other than left-sided heart failure)

PATHOPHYSIOLOGY OF PE

- High-pressure edema (cardiogenic)
  - High pulmonary capillary pressures cause fluid extravasation that overwhelms lymphatic removal. Fluid initially flows toward the peribronchovascular interstitium, then distends all parts of the pulmonary interstitium, then eventually spills into the airspaces at the junction of the alveolar and airway epithelia
  - Often the pressure increase is gradual and edema forms over time, but if there is an acute increase in hydrostatic pressure (e.g., chordae tendineae rupture), then edema can form peracutely

PATHOPHYSIOLOGY OF PE

- Increased permeability edema:
  - Injury occurs to the microvascular barrier (and sometimes alveolar epithelium) allowing leakage of fluid with a high protein content.
  - Inciting cause may be hematogenous (to the capillary and then the alveolar epithelial cell), or aerogenous (alveolar cell is damaged and then the capillary)
  - Because of the increased permeability, the protective fall in interstitial colloid osmotic pressure is diminished so that hydrostatic pressure becomes the main determinant of edema formation
  - Interstitial fluid accumulation can then occur at lower hydrostatic pressures, and relatively small rises in pressure result in greater edema formation
  - In more severe cases, with concurrent endothelial and epithelial injury, there is a direct conduit between the intravascular space and the alveoli

PATHOPHYSIOLOGY OF PE

- Mixed cause edema
  - Pathophysiology is not completely understood
  - Probably d/t combination of hydrostatic and increased permeability PE
  - Includes neurogenic PE (NPE), negative pressure PE (NPPE) and re-expansion

NEUROGENIC PULMONARY EDEMA

- Seen acutely after a neurologic event (seizure, head trauma, electric cord bite)
- Blast theory:
  - Massive, neuronal, sympathetic activity results in a sequence of events causing both hydrostatic and increased permeability edema
- Initially hydrostatic pressure edema occurs, but at very high pulmonary hydrostatic pressures, endothelial cell injury and vascular leak result in RBC and protein leakage into the alveolus
- Sympathetic stimulation also causes vascular effects that can result in acute cardiac insufficiency
- Clinical signs generally resolve within 24-48hrs
- Prognosis is good but depends on underlying cause

NEGATIVE PRESSURE PULMONARY EDEMA

- Occurs after upper airway obstruction (strangulation, sharp pull on lead, etc)
- During upper airway obstruction, extreme subatmospheric, intrathoracic pressures are generated that then causes pulmonary vascular pressure overload, an increase in vascular return, and preload
- This is thought to be exacerbated by sympathetic stimulation associated with hypoxia causing an increase in afterload
- As with NPE there is both hydrostatic pressure edema and resultant microvascular damage.
- Endothelial cell injury and vascular leak cause the permeability edema
- Clinical signs generally resolve within 24-48hrs
- Prognosis is good but depends on underlying cause

RE-EXPANSION PULMONARY EDEMA

- Relatively rare cause of pulmonary edema
- Reported in dogs and cats after acute re-expansion of chronically collapsed lung lobes
- May be due to decreased surfactant, negative interstitial pressure, mechanical disruption of the parenchyma, ROS formation, or reperfusion injury

ACUTE LUNG INJURY/ACUTE RESPIRATORY DISTRESS SYNDROME

- Increased permeability edema is synonymous with ALI
- ALI/ARDS was first described in WWI with men able to be resuscitated in field, but later died several days later from multiorgan failure
- Initially defined as severe respiratory failure after a "catastrophic event"
- ARDS is the most severe form of increased permeability edema
- Can be caused by inflammation, infection, sepsis, SIRS, severe trauma, multiple transfusions, smoke inhalation, submersion injury, aspiration, and ingestion of drugs and toxins

QUESTION

- Of the five causes of hypoxemia, which are commonly seen in patients with ARDS?

BERLIN DEFINITION OF ARDS

- Timing
  - Within one week of a known insult or new or worsening respiratory symptoms
- Chest imaging (CT or CXR)
  - Bilateral opacities on imaging not fully explained by effusions, lobar/lung collapse, or nodules
- Origin of edema
  - Respiratory failure not fully explained by cardiac failure or fluid overload
- Oxygenation
  - Mild: P:F 200-300 with PEEP or CPAP at least 5 cmH2O
  - Moderate: P:F 100-200 with PEEP at least 5 cmH2O
  - Severe: P:F<100 with PEEP at least 5 cmH2O

VET ALI AND ARDS CRITERIA

- <72 hours of tachypnea and labored breathing at rest
- Known risk factors
- Evidence of pulmonary capillary leak without increased pulmonary capillary pressure (one of the following)
  - Bilateral/diffuse infiltrates on CXR
  - Bilateral dependent density gradient on CT
  - Proteinaceous fluid within the conducting airways
    - ARDS: edema protein content >60% of peripheral protein concentration (E:F ratio >0.6)
    - Non-ARDS: edema protein content <45% of peripheral protein concentration (E:F ratio <0.45)
  - Increased extravascular lung water

VET ALI AND ARDS CRITERIA

- Evidence of inefficient gas exchange (at least one)
  - Hypoxemia without PEEP or CPAP and known FiO2
    - P:F
      - P:F <300 = VetALI
      - P:F <200 = VetARDS
    - Increased A-a gradient
    - Venous admixture
  - Increased dead space ventilation
- Evidence of diffuse pulmonary inflammation
  - TTW/ETW/BAL
    - Neutrophilia
    - Biomarkers of inflammation
    - Molecular imaging (PET)

STAGES OF ARDS

- Exudative
  - Days 0-6
  - Protein-rich edema, presence of eosinophilic hyaline membranes in the walls of the alveolar ducts
- Proliferative
  - Days 4-10
  - Decreased edema and hyaline membranes, increased interstitial fibrosis
- Fibrotic
  - Day 8 onward
- Fibrosis that may obliterate areas of the lungs

RECOVERY FROM ARDS

- Excessive fluid and proteins removed from the airways and alveoli -> type II pneumocytes repopulate the epithelial lining -> abnormal interstitium restores its normal matrix -> damaged endothelium is repaired -> blood flow restored -> residual cellular components removed
- May be incomplete
- Majority occurs in the first three months after extubation, with additional recovery over the first year

RETROSPECTIVE EVALUATION OF THE PREVALENCE, RISK FACTORS, MANAGEMENT, OUTCOME, AND NECROPSY FINDINGS OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME IN DOGS AND CATS: 29 CASES (2011-2013)

- Prevalence of ARDS: Dogs: 3.2%; cats: 1.3%
- Inciting causes: SIRS, aspiration, sepsis, multiple transfusions, trauma, adverse drug reaction
  - None associated with an increased risk of ALI/ARDS compared to controls
- Survival: 2/24 dogs, 1/5 cats
  - Dogs: 92% mortality; 18% died, 82% euthanized
  - Cats: 80% mortality; 75% died, 25% euthanized

GENERAL DIAGNOSTICS FOR PULMONARY EDEMA

- Give supplemental 02 first!
- POCUS (B lines, can assess LA size)
- CXR (best delayed until have started empirical therapy and more stable)
- Consider art gas and pulse ox to assess hypoxemia but probably not necessary on initial presentation
- Echocardiogram eventually if concerned for cardiogenic PE

RADIOGRAPHIC FINDINGS OF PULMONARY EDEMA

- Nearly all causes of PE can produce a diffuse alveolar pattern so can be difficult to discern cardiogenic vs NCPE
- Cardiogenic edema:
  - Typically perihilar but in cats can be patchy alveolar or even nodular
  - Pulmonary veins more distended than pulmonary arteries
  - Cardiomegaly, specifically enlarged LA
- NPE, NPPE
  - Typically dorsocaudal alveolar pattern

TREATMENT OF NCPE

- Oxygen supplementation
- Minimize stress
- Consider body position- try to keep sternal
- Positive pressure ventilation (PPV) may be required if:
  - Hemoglobin saturation <90%
  - PaO2 >60 mm Hg with noninvasive methods
  - Hypoventilation (PaCO2 >60 mm Hg)
  - Concern for respiratory fatigue

LUNG PROTECTIVE VENTILATION

- Low Vt and airway pressures to prevent further lung damage
  - Vt 4-6 ml/kg
  - PEEP of at least 5 cmH2O to prevent derecruitment
    - Mortality is increased when PEEP is kept low
  - Low driving pressure (<15 cmH2O)
    - Driving pressure = Pplat – PEEP
    - Adjust PEEP to minimize driving pressure

TREATMENT OF NCPE

- Limited evidence supportive of use of furosemide
- Vasodilators are used in acute high-pressure edema situations
  - Nitric oxide donors (nitroprusside, isosorbide dinitrate, and glycerol trinitrate/nitroglycerin)
  - Nitroprusside causes arteriodilation and venodilation, whereas nitroglycerin is mainly a venodilator
- α-adrenergic antagonists in experimental and human NPE
- β2 agonism in toxic lung injury
  - Act via cAMP to increase fluid reabsorption by alveolar epithelial cells from the alveolar space

REFERENCES

Balakrishnan et al. 2017. Retrospective evaluation of the prevalence, risk factors, management, outcome, and necropsy findings of acute lung injury and acute respiratory distress syndrome in dogs and cats: 29 cases (2011-2013). Journal of Veterinary Emergency and Critical Care. (6):662-673. doi: 10.1111/vec.12648

Pfeilsticker and Neil. 2017. 'Lung-protective' ventilation in acute respiratory distress syndrome: still a challenge? Journal of Thoracic Disease; 9(8): 2238–2241. 10.21037/jtd.2017.06.145

Reinero et al. 2020. ACVIM consensus statement guidelines for the diagnosis, classification, treatment, and monitoring of pulmonary hypertension in dogs. Journal of Veterinary Internal Medicine. https://doi.org/10.1111/jvim.15725

Silverstein and Hopper. 2015. Small Animal Critical Care Medicine. Pulmonary Edema. Elsevier.

Wilkens et al. 2007. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: The Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. Journal of Veterinary Emergency and Critical Care. https://doi.org/10.1111/j.1476-4431.2007.00238.x