PULMONARY HYPERTENSION

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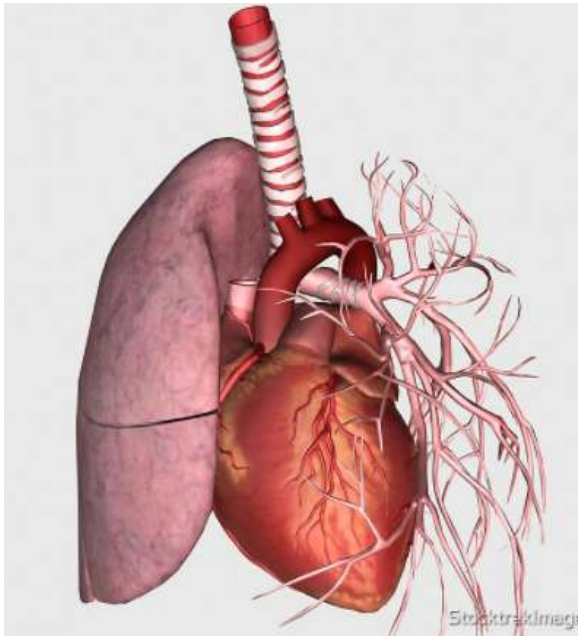
OUTLINE

- Anatomy and physiology – pulmonary vasculature and RV
- PH pathophysiology
- Classification
- Diagnosis
- Treatment

PULMONARY HYPERTENSION

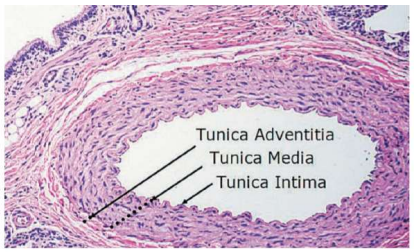


- Underrecognized disease in human and veterinary medicine
- Complex syndrome associated with severe underlying disease

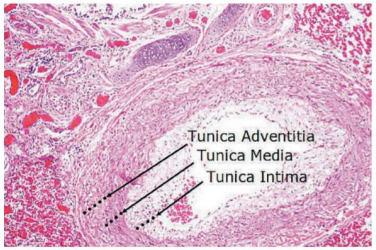
- Pulmonary circulation is:
  - Low pressure
  - Low resistance
  - High capacitance
    - Minimize RV workload
- High pulmonary blood flow accommodated with minimal increase in PA pressure due to:
  - 1) highly distensible thin-walled pulmonary vasculature
  - 2) a large pulmonary capillary surface area with large reserve of unperfused vessels
  - 3) recruitment of under-perfused vessels

- Normal PA pressure 25/8 (12-15) mmHg
  - Determined by: pulmonary artery blood flow, pulmonary vascular resistance, pulmonary venous pressure

PULMONARY VASCULAR ANATOMY



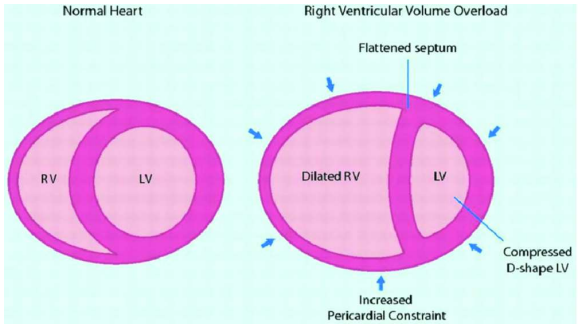
1. A photograph of a cross section of a normal canine pulmonary artery. The tunica adventitia, media, and intima layers are all normal in thickness and cell structure (hematoxylin-eosin stain; 10X magnification). (*Image courtesy of Pam Mouser, DVM, MS, DACVP, Angell Animal Medical Center's Department of Pathology.*)



2. A photograph of a cross section of a canine pulmonary artery in a patient with documented pulmonary hypertension. The tunica adventitia and intima layers are both thickened, supporting the clinical diagnosis of pulmonary hypertension (hematoxylin-eosin stain; 10X magnification). (*Image courtesy of Pam Mouser, DVM, MS, DACVP, Angell Animal Medical Center's Department of Pathology.*)

- In health:
  - Inner tunica intima: single layer endothelial cells, collagen, occasional fibroblast
  - Middle tunica media: elastin, collagen, smooth muscle fibers
  - Outer tunica adventitia: collagen
- In pulmonary hypertension:
  - Concentric thickening and muscularization of the tunica intima
  - Hypertrophy with fibrosis and proliferation of smooth muscle of the tunica media
  - Severe cases – plexiform lesions (irregularly shaped outgrowths that project from the intimal layer into the lumen of the blood vessel)
  - Vessel wall necrosis
- Interdependence of the pulmonary parenchyma and vasculature
- Up to 60% of the pulmonary vascular bed can be lost before pulmonary hypertension develops

RIGHT VENTRICLE



- Thin walled
- Compliant – can accommodate large changes in volume/preload
- Little contractile reserve to overcome increased afterload
  - Takes 96 hours to adapt (become stiffer – reduce wall stress and maintain adequate SV)
  - Acute setting – RV cannot generate pressure >40mmHg = decrease in SV; hemodynamic collapse

Ventricular interdependence – RV, LV are dependent on one another

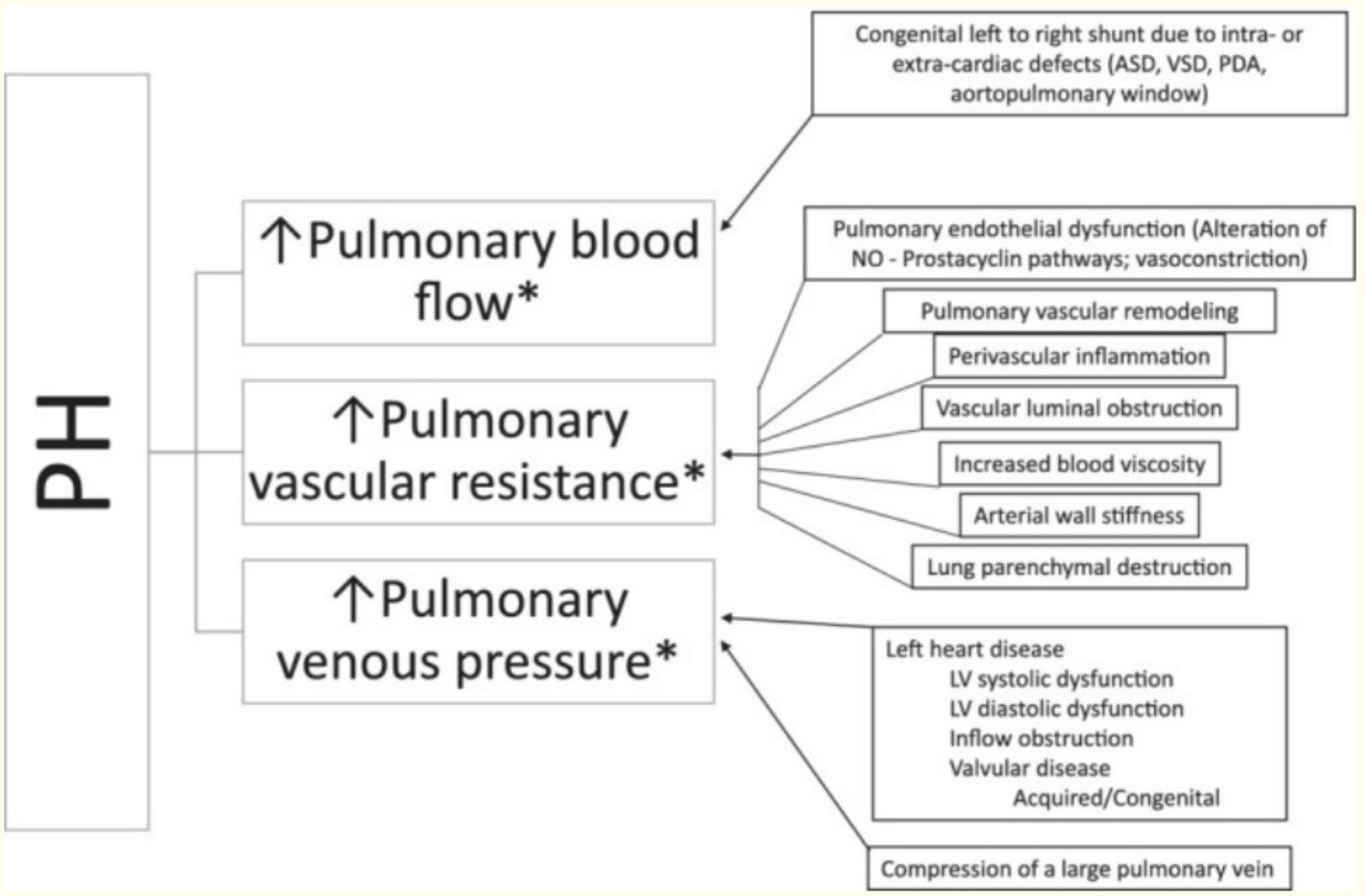
- RV stroke volume determines LV preload
  - Failing RV = decreased LV preload
- RV and LV share muscular septum (interventricular septum) – contributes 20-40% of work of RV contraction when LV contracts
  - LV contraction in spiral motion
  - RV contracts in longitudinal motion and compresses medially against the septum
- Dilated failing RV pushes IV septum into LV → impairs LV filling/contractility
- Impairs role of septum and RV contractility

PULMONARY HYPERTENSION

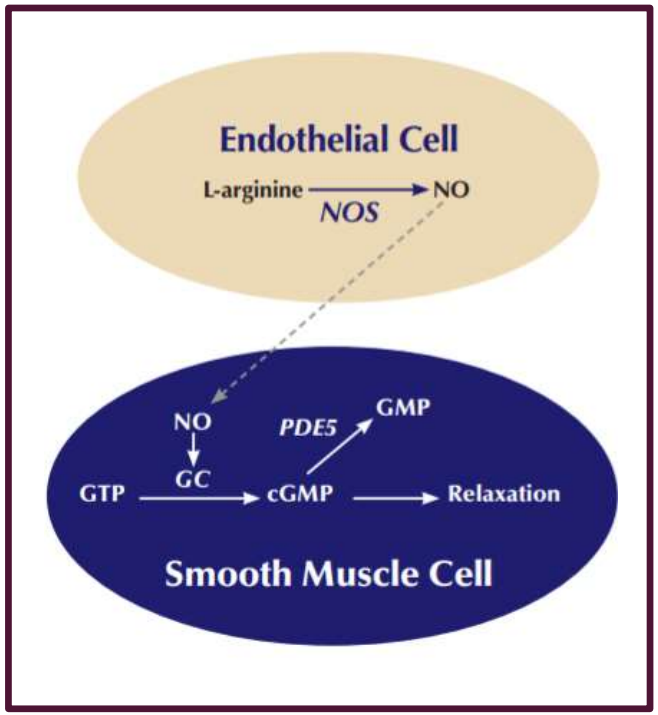
- Defined:
  - Abnormally increased pressure within the pulmonary vasculature
  - Pulmonary artery systolic pressure >30mmHg
  - Mean pulmonary artery pressure >25mmHg at rest

PH PATHOPHYSIOLOGY

- Multifactorial, heterogenous condition – 6 categories
- Results from increased pulmonary blood flow, increased pulmonary vascular resistance, increased pulmonary venous pressure, or some combo
- Imbalance of factors controlling:
  - Pulmonary arterial vasoconstriction / vasodilation
  - Smooth muscle proliferation / vascular remodeling
  - Platelet activation
    - = Abnormal proliferation of the vascular smooth muscles and endothelial cells, inflammation, fibrosis
- Function of the RV determines much of the morbidity and mortality in PH
  - Over time RV works harder, undergoes structural alterations → RV dysfunction/failure → R CHF – ascites, low CO signs, death


PH
↑Pulmonary blood flow*
↑Pulmonary vascular resistance*
↑Pulmonary venous pressure*
Congenital left to right shunt due to intra- or extra-cardiac defects (ASD, VSD, PDA, aortopulmonary window)
Pulmonary endothelial dysfunction (Alteration of NO - Prostacyclin pathways; vasoconstriction)
Pulmonary vascular remodeling
Perivascular inflammation
Vascular luminal obstruction
Increased blood viscosity
Arterial wall stiffness
Lung parenchymal destruction
Left heart disease
LV systolic dysfunction
LV diastolic dysfunction
Inflow obstruction
Valvular disease
Acquired/Congenital
Compression of a large pulmonary vein

CELLULAR LEVEL - VASODILATORS



- Nitric oxide (NO)
  - Synthesized in endothelial cells
  - Produced from L-arginine + O2 by NOS enzyme → NO released from vascular endothelium → travels to smooth muscle → stimulates guanylate cyclase (GC) → catalyzes GTP to cGMP → increase in cGMP inhibits Ca2+ release from sarcoplasmic reticulum leading to pulmonary vasodilation
  - cGMP broken down by phosphodiesterase 5 (PDE5) → decreasing vasodilation
    - PDE5 abundantly expressed in lungs
  - Inhibits platelet activation
  - Inhibits smooth muscle hypertrophy/proliferation

- Prostaglandin I2 (prostacyclin, PGI2)
  - Eicosanoid produced by vascular endothelial cells by prostacyclin synthase
  - Stimulates adenylate cyclase (AC) → enhances conversion of ATP to cAMP → increase in cAMP decreases intracellular Ca2+ stores → pulmonary vasodilation
  - Inhibits platelet aggregation
  - Antiproliferative effects in PA

CELLULAR LEVEL – VASOCONSTRICTORS

- Alveolar hypoxia
  - Reflex hypoxic pulmonary vasoconstriction
    - Normal protective response to target perfusion to better ventilated lung regions → vasoconstriction shunts deoxygenated blood to better ventilated areas
      - Improves V/Q matching
  - Chronic alveolar hypoxia → HIF-1a → persistent pulmonary vasoconstriction (small arteries and arterioles) → increase in PVR → PH
  - Induces PDGF, VEGF, ET-1, serotonin → endothelial call proliferation and vascular remodeling → increased PVR

- Endothelin-1
  - Peptide made by vascular endothelium in response to changes in blood flow, vascular stretch, thrombin concentrations
  - ET-1 binding to endothelin-1 receptor A (ETA):
    - Vasoconstriction (potent)
    - Stimulates growth factors / smooth muscle proliferation
    - Promotes vascular remodeling → smooth muscle proliferation, collagen production
  - Platelet aggregation
  - Pro-inflammatory

CELLULAR LEVEL - VASOCONSTRICTORS

- Thromboxane
  - Derived from prostaglandins
  - Synthesized by and stored in platelets → causes vasoconstriction and platelet activation
  - Imbalance between TXA2 and prostacyclin in idiopathic PH

- Serotonin
  - Produced in GIT by tryptophan → released in circulation and taken up by platelets → released from platelets in response to vascular endothelial damage → local vasoconstriction (potent)
  - Growth factor → vascular remodeling / smooth muscle proliferation
  - Stimulates platelet aggregation

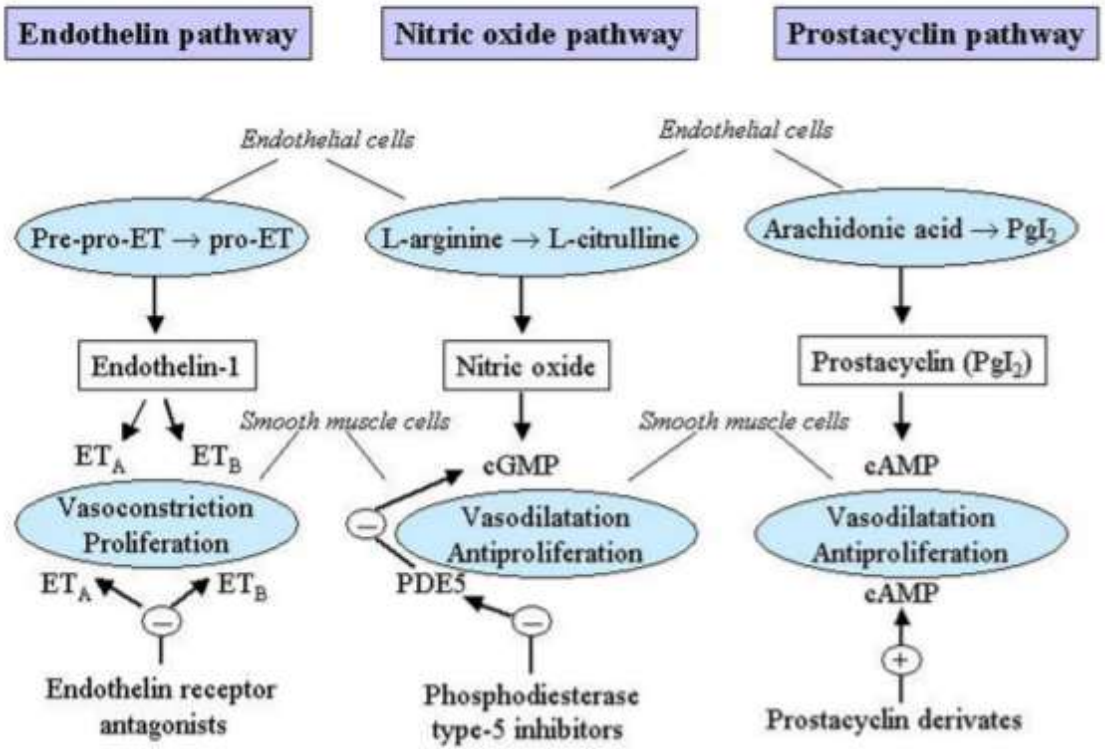


FIGURE 1 | Mechanisms which trigger pulmonary arterial hypertension (PAH) as targets for pharmacological treatments. cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; ET_A, endothelin receptor A; ET_B, endothelin receptor B; PDE5, phosphodiesterase type-5; PgI_2, prostaglandin I_2. Reproduced with permission from Humbert et al. (2004a) and Boutet et al. (2008).

The Physiologic Factors That Affect Pulmonary Arterial Tone and Platelet Function*

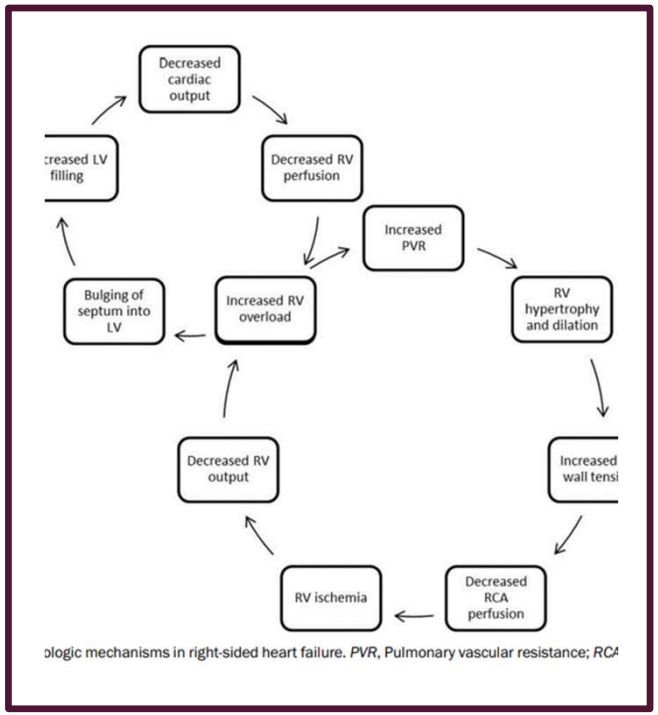
Physiologic Factor	Effect on Pulmonary Arterial Tone		Effect on Platelet Function	
	Vasoconstriction	Vasodilation	Activation	Inhibition
Alveolar hypoxia	X			
Alpha-adrenergic receptor stimulation	X			
Beta-adrenergic receptor stimulation		X		
Prostacyclin		X		X
Prostaglandin E_1		X		X
Prostaglandin $F_{2\alpha}$	X			
Prostaglandin A_2	X			
Thromboxane	X		X	
Nitric oxide		X		X
Endothelin-1	X		X	
Serotonin	X		X	
Angiotensin II	X		X	

*Source: References 1-3 and 8-12.

CONSEQUENCES

- Pulmonary vascular changes / remodeling results as a function of:
  - Chronic vasoconstriction
  - Severe pulmonary parenchymal disease or fibrosis can destroy normal pulmonary vascular structure and stimulate regional hypoxic vasoconstriction
  - Inflammation and increased sheer stress in vessels
  - Abnormal endothelial function → smooth muscle hypertrophy, intimal proliferation and fibrosis, increased extracellular matrix deposition

CONSEQUENCES → RIGHT HEART FAILURE



ologic mechanisms in right-sided heart failure. *PVR*, Pulmonary vascular resistance; *RCA*

- Increased pressures in the pulmonary system will decreased RV stroke volume and increase RVED volume → interventricular septum may bulge into the LV → decreased LV filling and decreased CO
- Elevated pressure and volume in RV may also lead to TR further reducing CO and end-organ perfusion
- Chronic PH – RV has time to progressively compensate up to a certain point → R CHF
- Unlike LV – RV coronary arteries are perfused during diastole AND systole
  - RV perfusion from coronary arteries decreases in proportion to RV pressure → if PAP is higher than systemic pressures the RV wall will not be perfused and will become ischemic = worsening RV contractility, overload, etc
- Patients have little physiologic reserve!
  - Any superimposed illness, hypo/hypervolemia, tachyarrhythmia, changes in oxygenation/ventilation may cause them to tip the scale and precipitate an acute of chronic RV failure
- Low output RV failure seen more commonly in group 1 (PAH) and 4 (chronic PTE) in humans as apposed to group 2 (L CHF) and group 2 (lung disease/hypoxia)

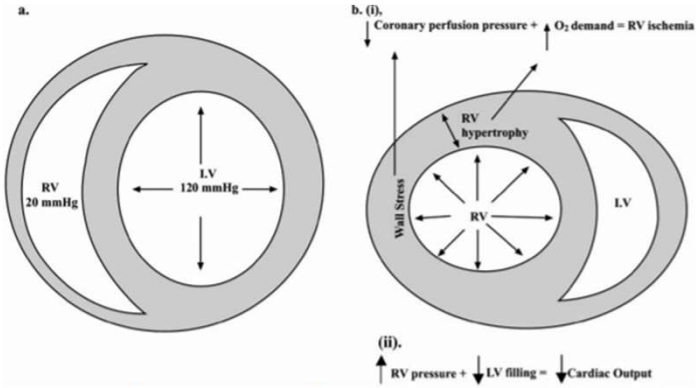


Fig. (1). Short axis view of the right (RV) and left (LV) ventricles in a patient with normal (a) pulmonary pressures and in a patient with pulmonary hypertension (b). In normal individuals, note the crescent shape of the RV and the thin wall. In pulmonary hypertension, elevations in RV pressures increase myocardial wall stress. As the RV hypertrophies, myocardial oxygen demands also increase, culminating into a myocardial supply/demand mismatch (i). With increased RV filling pressure and volume, the septum is displaced towards the LV, reducing cardiac output (ii). Reproduced with permission from Chin *et al.* [4].

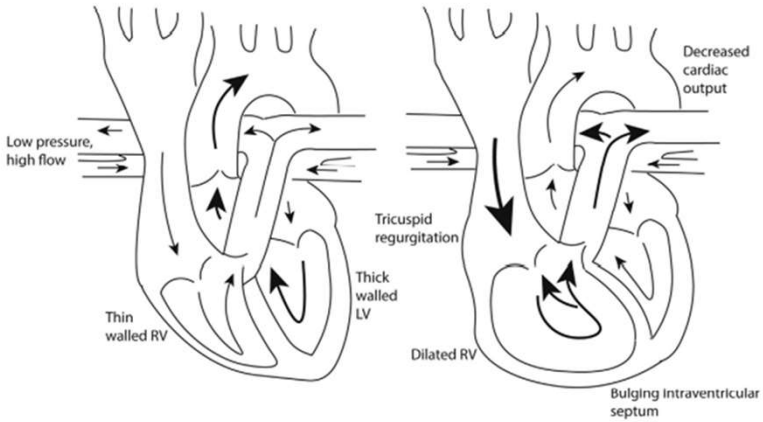


Figure 1. Normal circulation (left) and changes in pulmonary hypertension (right). *RV*, Right ventricular.

CLINICAL CLASSIFICATION SYSTEM

- Vet med: historically most often a secondary condition rather than primary disorder → prevalence unknown, many disorders causing PH may go unrecognized
- Classification - 6 groups as of ACVIM 2020 Consensus Statement (5 prior to this based on Evian classification system)
  - Group 1: pulmonary arterial hypertension (PAH)
  - Group 2: due to left sided heart disease (post capillary)
  - Group 3: respiratory disease/hypoxia
  - Group 4: due to PTE
  - Group 5: parasitic disease (Dirofilaria, Angiostrongylus)
    - Deviation from human classification scheme
  - Group 6: unclear/multifactorial
    - More than 1 cause is possible; if >2 – patient placed in Group 6

GROUP I – PULMONARY ARTERIAL HYPERTENSION

- Rare
- Characterized by proliferative, fibrotic, inflammatory changes in arterial walls
- Common causes in vet med:
  - Congenital shunts (PDA, ASD, VSD)
    - Blood travels from L heart to R side → increased pulmonary blood flow (over circulation) → alterations in vascular wall (hypertrophy/fibrosis)
    - Increased pulmonary vascular resistance is exacerbated by reactive polycythemia
    - Eisenmenger's syndrome = severely increased PVR → reversal of shunt due to increased R sided pressures that exceed L sided pressures
    - Blood now flows R to L through shunt → deoxygenated blood enters systemic circulation → polycythemia, differential cyanosis, CHF

GROUP 1 – PULMONARY ARTERIAL HYPERTENSION

- Other common causes in vet med:
  - Drugs that can cause pulmonary fibrosis may lead to PAH (i.e. Tanovea)
  - Pulmonary veno-occlusive disease (PVOD) – occlusive remodeling of small and medium pulmonary veins → upstream congestion of alveolar capillaries and pulmonary arterial remodeling
  - Pulmonary capillary hemangiomatosis (PCH) – angioproliferative disorder characterized by proliferation of alveolar capillaries that may infiltrate into pulmonary veins, arteries, and bronchioles
    - PVOD, PCH are rare; often diagnosed at necropsy
    - Suspect in acute onset resp distress, enlarged pulmonary arteries, right cardiomegaly, and interstitial or alveolar pattern (often caudal dorsal)
    - Grave prognosis – 66% survived less than 1 day; MST 3 days (Reinero JVIM 2019)

GROUP 2 – POST CAPILLARY / PULMONARY VENOUS HYPERTENSION

- Most common cause of PH
- Secondary to L sided heart disease (MMVD)
  - DCM and HCM less commonly
  - 63% of dogs had PH due to MMVD; other studies 14-31%
- Chronic regurgitation leads to elevated LA volume and LA pressure → increased pulmonary venous pressure and pulmonary hypertension
  - Severe disease – PH can occur just prior to or at time of CHF
- Chronic pulmonary venous hypertension can induce structural changes in pulmonary capillaries and increase the muscularity of resistance arterioles
- Pulmonary edema or congestion →hypoxic vasoconstriction
- Endothelin is also thought to contribute to PH associated with left-sided heart failure

GROUP 3 – PULMONARY DISEASE / HYPOXIA

- Secondary to primary pulmonary disease or chronic hypoxia
  - Less common: infectious pneumonia, pulmonary neoplasia
- Resp disease can be subdivided into phenotype – obstructive vs restrictive

GROUP 3 – PULMONARY DISEASE / HYPOXIA

- Obstructive disorders → decreased airflow
  - Disorders affecting the extra and intrathoracic trachea, bronchi, bronchioles that obstruct airflow
    - Tracheal collapse, bronchomalacia, BOAS, bronchiolar disease, diffuse bronchiectasis
    - BOAS may predispose to pulmonary vascular remodeling due to intermittent hypoxemia, hypercoagulability, systemic inflammation
- Restrictive disorders → decreased lung volume
  - Pleural or parenchymal that restrict lung expansion on inspiration
    - Pulmonary fibrosis, pulmonary neoplasia, pneumocystis pneumonia, aspiration-related respiratory syndrome, uncharacterized parenchymal disease
    - Endothelin-1 implicated in etiopathogenesis of idiopathic pulmonary fibrosis in WHWT
- Obstructive disease more common than restrictive
- Syncope much more common in pulmonary disease causes of PH (64%) as compare to PH secondary to MMVD (7%) – Johnson 2020

GROUP 4 - PTE

- Acute (with or w/o RV dysfunction) or chronic
- Causes: HWD, PLN, PLE, IMHA, HAC, neoplasia, sepsis, trauma
- PH due to:
  - Vascular obstruction results in increased pulmonary pressures + physiologic reaction to the vasoreactive substances released in response to the event
  - Hypoxia induce by the emboli → local vasoconstriction
  - Platelet and thrombin rich clots stimulate the release of vasoactive mediators – serotonin, TXA2, histamine → further increase pulmonary vascular resistance
- Humans: no pre-existing cardiopulmonary disease → 25-30% of pulmonary vasculature must be occluded before pulmonary pressures rise
- RV failure can occur under high afterload conditions 12-48 hours later
- CHEST PAIN!

GROUP 5 – HEARTWORM AND LUNG WORM DISEASE

- Formerly categorized under group 1
- HWD (Dirofilaria immitis); Angiostrongylus vasorum
  - Local damage from worm → inflammation and remodeling
  - Mechanical obstruction of vessels → provokes local hypoxic pulmonary vasoconstriction, reactive changes
  - Small emboli may block many arteries and capillaries (worm or clots)
  - Abnormal pulmonary blood flow and endothelial dysfunction → platelet aggregation, activation of the clotting cascade, and elaboration of vasoconstrictor substances such as endothelin, thromboxane A2, and serotonin
- Pulmonary vascular proliferation, irreversible structural damage, inflammation, vascular dysfunction

GROUP 6 – MULTIFACTORIAL

- Largely unrecognized in vet med
- Humans: chronic hemolytic anemia, myeloproliferative disorders, obstructive tumors in the mediastinum or thoracic cavity, granulomatous disease

FUNCTIONAL CLASSIFICATION

- Groups patients based on severity of clinical signs
- Used in human medicine to determine when and how to institute therapy

Table 2 | Functional classification of pulmonary hypertension according to World Health Organization (WHO).

CLASS I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.
CLASS II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
CLASS III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
CLASS IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

CLINICAL PRESENTATION

- Signalment and history
  - Most commonly secondary to MMVD – middle aged to older small breed dogs
  - Dogs prone to upper airway disease – Yorkies, Poms
  - Dogs prone to lower airway disease – WHWT, Pekingese (pulmonary fibrosis)
  - History of travel from areas endemic with HW

- Any patient with persistent respiratory difficulty, fatigue, cough, or exercise intolerance occurs without apparent cause

CLINICAL PRESENTATION

- Syncope (64%), cough, exercise intolerance, respiratory distress
- Lethargy, anorexia, weight loss, difficulty breathing
- Vomiting or coughing, dehydration, hypothermia, and icterus have been reported in cats
- In humans – 21% of patients with PH had symptoms > 2 years prior to diagnosis only then to be diagnosed late in disease
  - Delayed diagnosis is correlated with poorer survival

TABLE 1 Clinical findings suggestive of pulmonary hypertension (PH) in dogs[a]

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

[a]It should be noted that none of these clinical signs are specific solely for PH and therefore other causes of clinical signs are not excluded. Although these clinical signs may be due to underlying respiratory disease, more pronounced clinical signs reflect more severe disease, with more severe disease likely to result in PH.

PHYSICAL EXAM

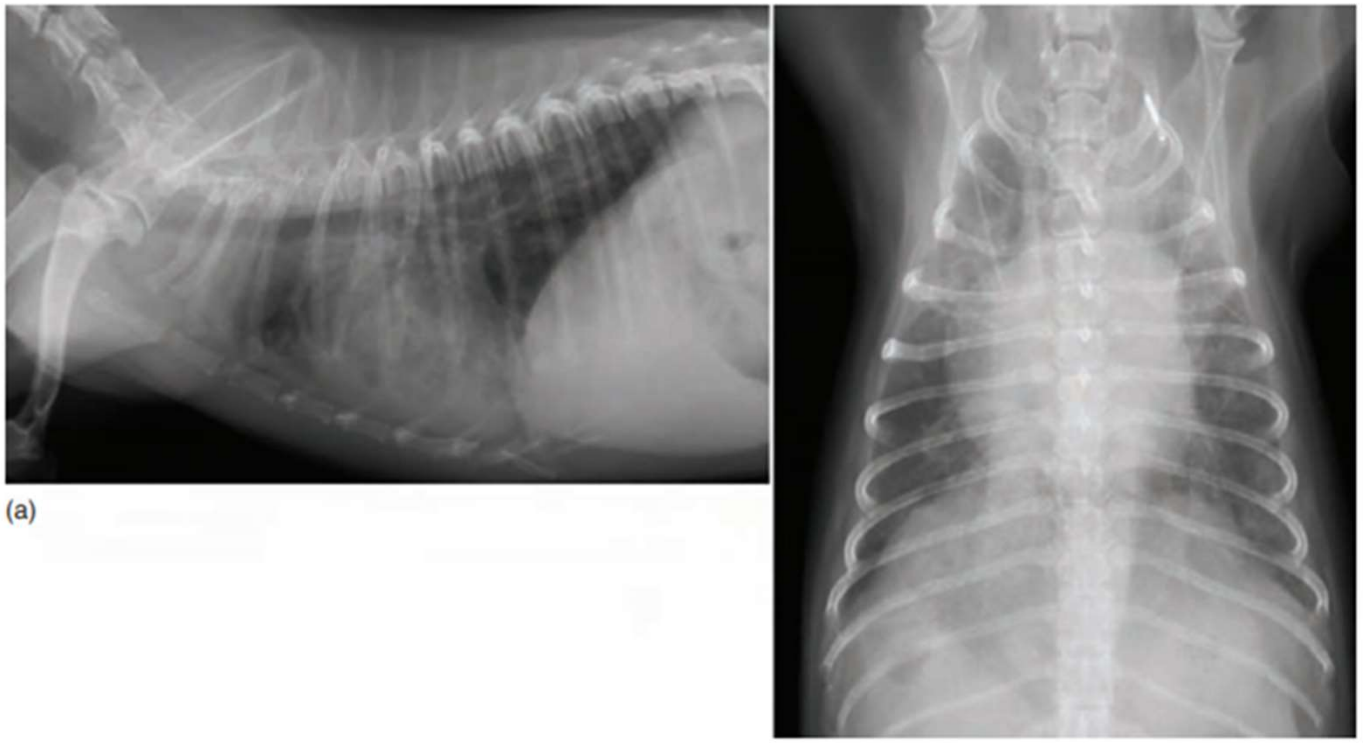
- With severe PH - loud, snapping or split S2 may be heard
- MR and/or TR murmur
- Pulmonary crackles, harsh lung sounds, wheezes with underlying pulmonary disease
- Cyanosis
- Abdominal distension
- Kussmaul sign – jugular distension, pulsation during inspiration

DIAGNOSTIC EVALUATION

- Diagnostic challenge – goals: 1) assess probability of PH using echo and 2) determine underlying cause when possible
- CBC/Chem/4Dx/UA w/ UPC
- TEG/D-dimers
- Endocrine testing
- Biomarkers
  - BNP, cTnI – found to be elevated
- FAST scan
  - R heart – RA and RV dilation, interventricular septal flattening, PA dilation
  - RV >2/3 size of LV on 4-chamber view (humans)

DIAGNOSTIC EVALUATION

- Thoracic radiographs
  - Cardiomegaly (right-sided), MPA dilation, dilation and tortuosity of pulmonary arteries
  - Patchy pulmonary parenchymal infiltrates are common and may also reflect underlying disease (Kellihan 2015)
    - Transient, can improve with sildenafil administration
  - Patchy edema is caused by non-uniform pulmonary capillary perfusion
  - Pulmonary arterial beds can have varying constrictive responses to hypoxia → blood flow is diverted to less constricted vascular bad → high hydrostatic pressure in overcircualted areas → edema formation with high protein and high red blood cell composition
    - Similar to high altitude pulmonary edema



(a) (b)

Figure 59.1 Thoracic radiographs obtained from a dog with chronic pulmonary interstitial disease and class 3 PH. (a) Right lateral thoracic radiograph and (b) ventrodorsal radiograph. The patient has a patchy bronchointerstitial pulmonary pattern consistent with lower airway disease. There is right ventricular hypertrophy and main pulmonary artery dilation. Hepatomegaly and mild pulmonary effusion are present, consistent with cor pulmonale and subsequent hepatic congestion and right-sided congestive heart failure.

DIAGNOSTIC EVALUATION

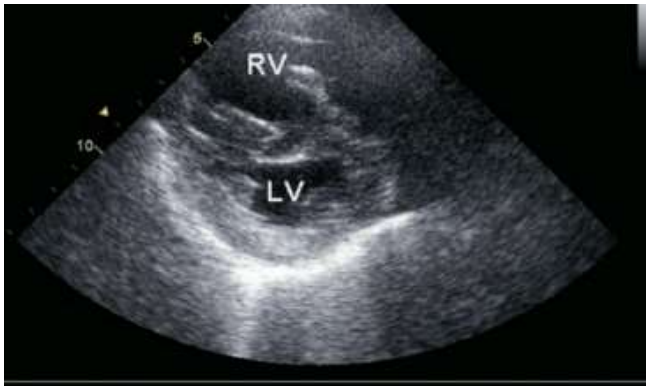
- ECG
  - May show evidence of RA or RV enlargement – inconsistent
  - AF, atrial or ventricular tachyarrhythmias, occasionally bradycardia or slowed AV conduction have been observed
  - R axis deviation; RBBB

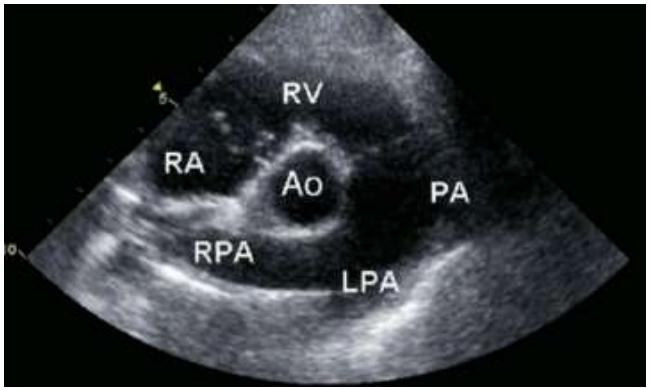
DIAGNOSTIC EVALUATION

- Echocardiography
  - Gold standard NON-invasive tool to identify characteristic changes and estimate PAP – used for diagnosis, classification, management of PH
  - Consider early as part of diagnostic battery when:
    - PE and CXR r/o another specific disorders not associated with PH
    - CXR shows tortuous, blunted, dilated PAs; asymmetric radiolucent lung field on DV/VD views' patchy, diffuse alveolar infiltrates; bulge in PA trunk; R cardiomegaly
    - Clinical signs suggestive of PH and modified transudate ascites; dilated CdVC on FAST; dilated CdVC and hepatic veins on AUS
    - Dogs have spent time in HW endemic areas, history of HW or lung worm positive with clinical signs
    - Dogs with acute or chronic conditions predisposing to PTE/TE – IMHA, HAC, PLN, PLE, sepsis, neoplasia, DIC, HWD

DIAGNOSTIC EVALUATION - ECHO

- Subjective/objective echo findings:
  - RV and RA may be normal or mildly to severely dilated
  - RV wall thickness may be normal or hypertrophied
  - Pulmonary artery dilation
    - PA:Ao > 0.98 (>1.4 on CT) = PA enlargement
  - Flattened or paradoxical septal motion = RV pressure overload
    - Septal flattening seen in moderate to severe PH if RV pressure exceeds LV pressure
  - RV systolic function
  - RA and caudal vena cava size





DIAGNOSTIC EVALUATION - ECHO

- Visser JVIM 2020 – can R heart measurements of size and function be prognostic?
  - RA and RV size, pulmonary artery enlargement – common (>69% of patients)
  - RV systolic dysfunction seen in 33%
  - TAPSE < 3.23mm/kg was significantly less common in dogs with PH secondary to LHD
    - Worse RV function in dogs with PH not secondary to LHD
  - Median survival time 192 days – not significantly different between dogs with or without PH secondary to LHD
  - RA size (RAA), RV function (TAPSE) and R CHF independently associated with decreased survival time

DIAGNOSTIC EVALUATION - ECHO

- Pulmonary thrombus or heartworms are sometimes visualized in the proximal pulmonary artery
- Patent foramen ovale → right-to-left shunting may be evident on echo-bubble study

- Color Doppler assessment of systolic PAP
  - TR regurgitant jet → velocity profile
  - RV and PA pressures are equivalent during systole (assuming no RV outflow tract obstruction)
  - Maximum TR jet velocity estimates the systolic pressure gradient between the RV and the RA using the modified Bernoulli relationship → pressure difference approximates the systolic PAP
    - Pressure gradient = max TR velocity (m/s)^2 x 4
  - PH is associated with peak TR velocities >2.8 m/second
  - If RV failure is present, PH may be underestimated

DIAGNOSTIC EVALUATION - ECHO

- Doppler assessment of diastolic arterial pressure
  - Pulmonic insufficiency occurs in diastole
- Pulmonary insufficiency jet used to obtain pulmonary insufficiency velocity profiles → allows for estimated diastolic PAP
- Velocity of PR jet (m/s) used to calculate gradient between PA and RV– modified Bernoulli
  - Helpful if TR is not present
  - Peak PR velocity > 2.2m/s
  - Normal diastolic PA pressure is < 15mmHg

PH SEVERITY

- PH severity
  - ACVIM does not advocate use – instead severity should be based on clinical signs and outcome data from large prospective longitudinal studies (unavailable)
    - Cut-off value of >46mmHg can be used however
- Mild: ~35–50 mm Hg; TR maximum velocity of 2.9–3.5 m/sec
- Moderate: ~51–75 mm Hg; TR maximum velocity 3.6–4.3 m/sec
- Severe: >75 mm Hg; TR maximum velocity >4.3 m/sec

Table 4
Pulmonary hypertension severity grading system based on peak tricuspid regurgitation velocity and associated TR gradient

	Mild	Moderate	Severe
TR peak systolic velocity (m/s)	≥ 2.8 to < 3.5	3.5–4.3	>4.3
TR systolic gradient (mm Hg)	≥ 31.4 to < 50	50–75	>75

Abbreviation: TR, tricuspid regurgitation.

DIAGNOSTIC EVALUATION

- CT
  - Can provide supportive or definitive evidence of PTE/TE, pulmonary parenchymal disease
  - Evaluate RV size – humans, enlargement of the RV to 9/10 size of LV correlates with increased risk of adverse events
- Lung biopsy – for pulmonary fibrosis
- Bronchoscopy/fluoroscopy/radiograph - tracheobronchomalacia
- 6 minute walk test

DIAGNOSTIC EVALUATION

- Pulmonary artery catheter
  - Gold standard for definitive diagnosis
  - Unacceptably invasive in a compromised patient (or in general)
  - Provides hemodynamic information regarding presence and degree of PH and function of the R heart
    - End diastolic RV pressure; PAP; PCWP

- Swan-Ganz balloon is inflated and advanced into the PA until it (temporarily) obstructs a smaller branch → pressure recorded here reflects pressure in the pulmonary capillaries (pulmonary capillary wedge pressure)
  - PCWP approximates LA pressure (assuming no pulmonary venous obstruction exists)
  - PCWP is elevated in group 2 -- >15mmHg

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	

TREATMENT

- There is no cure and few treatment options for severe PH, although sildenafil is helpful in some cases
- Vascular morphologic changes result in limited capacity for pulmonary vasodilation
- Goals: ameliorate signs, decrease PAP, decrease RV workload, improve survival and QOL
- Treat underlying disease

- PULMONARY VASODILATORS!
  - Endothelin pathway (antagonists), prostanoid pathway (analogs), NO pathway (PDEi), Ca sensitizing agents (PDE3i)
  - Oral vs inhaled – not used in vet med
  - May improve VQ mismatch by directing blood flow to ventilated areas of the lung

TREATMENT

- Supplemental O2
  - Nasal canula; O2 chamber, MV
  - Relieves hypoxia → results in diffuse pulmonary vasodilation in actively constricted vessels, reduces PVR, reduces acidosis and ischemia, and improves right heart function
  - Avoid hypercapnia → causes pulmonary vasoconstriction and increases PVR

TREATMENT

- Sildenafil citrate – selective PDE5i
  - PDE5 highly concentrated in pulmonary vessels → normally breaks down cGMP
  - Inhibition of PDE5 → increase in cGMP concentrations → promotes NO → mediates pulmonary vasodilation, reduction in PVR
  - Can reduce PAP 16-24mmHg (Johnson 2020)
  - Dogs treated with sildenafil had 95% survival at 3mo, 84% 6mo and 74% 1yr – improves QOL and survival time
  - Can consider rectal dosing
  - Tadalafil (SID dosing) is a viable alternative to sildenafil (BID dosing); non inferior to sildenafil
  - In some cases (certain congenital shunts, L CHF) PDE5i may result in worsening pulmonary edema
  - PVOD/PCH – higher pulmonary blood flows are not accommodated by the fixed downstream obstruction in the veins and capillaries → pulmonary edema

TREATMENT

- Other phosphodiesterase inhibitors
  - Pimobendan – PDE3i, Ca sensitizer
    - Can be useful in dogs with PH and RV failure and/or chronic mitral regurgitation with refractory heart failure
    - PDE3 found in large and small resistance PA
    - PDE3 inhibitor promotes PA vasodilation via enhancement of adrenergic relaxation
    - Good for dogs with L heart disease and PVH
  - Theophylline/aminophylline (methylxanthine) – weak, non selective PDEi (3, 4, 5)
    - Mild positive inotropic effects on the heart and can improve diaphragmatic contractility and reduce respiratory muscle fatigue
    - Bronchodilation and improved intrathoracic pressure gradients may reduce the tendency for airway collapse in patients with bronchiectasis or tracheal collapse
    - Little evidence of sustained improvement however

TREATMENT

- NO substrates
  - L-arginine is substrate for NO synthesis → augment endogenous NO production
  - No studies in vet med
- Bronchodilators
  - Theophylline/aminophylline (methylxanthine) – weak, non selective PDEi (3, 4, 5)
  - Terbutaline (beta2-agonist)
    - May also improve pulmonary hemodynamics, but this is not well studied
- Nonselective peripheral vasodilators (CCB, hydralazine, ACEi, nitroprusside)
  - Can have adverse effects (systemic hypotension) – used more as afterload reducer in L CHF
  - Little evidence in humans for CCB in PH

TREATMENT FOR SPECIFIC GROUPS

- Group 1 PAH:
- Congenital cardiac shunts
  - Shunt closure if L to R (or if becomes L to R after pulmonary vasodilators)
  - Polycythemia – phlebotomy and IVF replacement
  - Hydroxyurea to decrease RBC volume
  - Sildenafil – may help attenuate PH and manage erythrocytosis (HCT can be used as objective response measure)
- If PVOD/PCH sildenafil may worsen respiratory distress and cause pulmonary edema – contraindicated in humans, but undetermined in vet med (Reinero JVIM 2019)

TREATMENT FOR SPECIFIC GROUPS

- Groups 2 LHD:
  - Goal to treat cause of L heart disease and decrease postcapillary pressure (via lowering LA pressure)
  - CHF: diuretics, pimobendan, ACEi
    - If PH not due to L CHF - extensive diuresis can further reduce cardiac output in patients with poor RV function (RV output is dependent on preload)
    - If chronic obstructive pulmonary disease underlies PH, diuretics can further impair gas exchange by drying secretions and facilitating mucus plug formation within bronchi
    - PDE5i not recommended as first line treatment but can be considered in patients with high probability of PH and compensated L CHF that develop ascites, syncope
    - Vasodilators can cause worsening pulmonary edema if pulmonary arteries are dilated

TREATMENT FOR SPECIFIC GROUPS

- Groups 3 secondary to respiratory disease, hypoxia:
  - Weight loss – increase thoracic wall compliance, decrease extrathoracic and intrathoracic fat
  - Environmental modifications (reduce stress/anxiety/excitement/barking) to improve air quality and humidity
  - Use harness instead of neck collar
  - Interstitial lung disease: antibiotics, inhaled/oral steroids, bronchodilators
  - Obstructive airway disease: sedation, cough suppressants, supplemental oxygen, antibiotics for secondary tracheitis, corticosteroids; tracheal stent
    - BOAS: surgical correction, management of GI signs
      - Link to PH unclear – possible pneumonia due to regurgitation
  - Sildenafil is recommended and response to treatment can help predict survival

TREATMENT FOR SPECIFIC GROUPS

- Group 4 PTE:
  - Antiplatelet and anticoagulant therapy
  - +/- fibrinolytics if overt RV dilatation, systolic dysfunction, systemic hypotension and collapse
  - Treat underlying hypercoagulable condition
  - Sildenafil can be considered

TREATMENT FOR SPECIFIC GROUPS

- Group 5 heartworm, lung worm:
  - Adulticides, microfilaricides, doxycycline, corticosteroids, bronchodilators
  - AHS does not make recommendations regarding use of sildenafil but has been used to medically manage caval syndrome
  - May be considered in lung worm infection – 15% develop PH and have a worse prognosis that those without PH

- Group 6 multifactorial/unclear:
  - Identify and treat underlying pathology(s)

TREATMENTS – INHALED

- Bridge therapy; short lived effects
- Inhaled/IV prostacyclin (iloprost; treprostinil, epoprostenol)
  - PGI2 endogenously produced by endothelial cells = potent systemic and pulmonary vasodilator (increased cAMP) with anti-proliferative and anti- thrombotic properties
  - Opposes TXA2 (vasoconstriction, platelet aggregation)
  - Improves CO, vasodilation, RV performance
  - Used commonly in humans, no clinical trials in vet med
  - EXPENSIVE
- Inhaled NO
  - Promotes vascular smooth muscle relaxation (increased cGMP), effects are limited to ventilated areas of the lung = improved VQ
  - Inhibits platelet aggregation and proliferation of smooth muscle cells
  - Antianginal effects
  - Not commonly used in vet med due to potential for severe adverse effects

TREATMENT

- Endothelin receptor antagonists (bosentan, sitaxentan, ambrisetan)
  - Blocks vasoconstriction, proliferative, pro-inflammatory effects
  - Cost prohibitive
- Milrinone
  - Inhaled or injectable
  - PDE3i
- Serotonin antagonists
  - Serotonin initiates proliferation of smooth muscle cells; receptors may be increased in PAH

TREATMENT

- Rho-kinase inhibitors
  - Rho-kinase enhances contraction of the vascular smooth muscle cells by inhibiting myosin phosphatase
  - Inhibition can cause vasodilation and increase eNOS expression → suppresses hypercontraction and proliferation of the vascular smooth muscle cells and reducing migration of inflammatory cells in PAH
- Anticoagulation
  - Patient with PH are at increased risk for intrapulmonary thrombosis/TE due to sluggish pulmonary blood flow, dilated RV/RA, venous stasis
  - A small thrombus can produce hemodynamic deterioration in a patient with compromised pulmonary vascular bed → cannot recruit unused vasculature or dilate

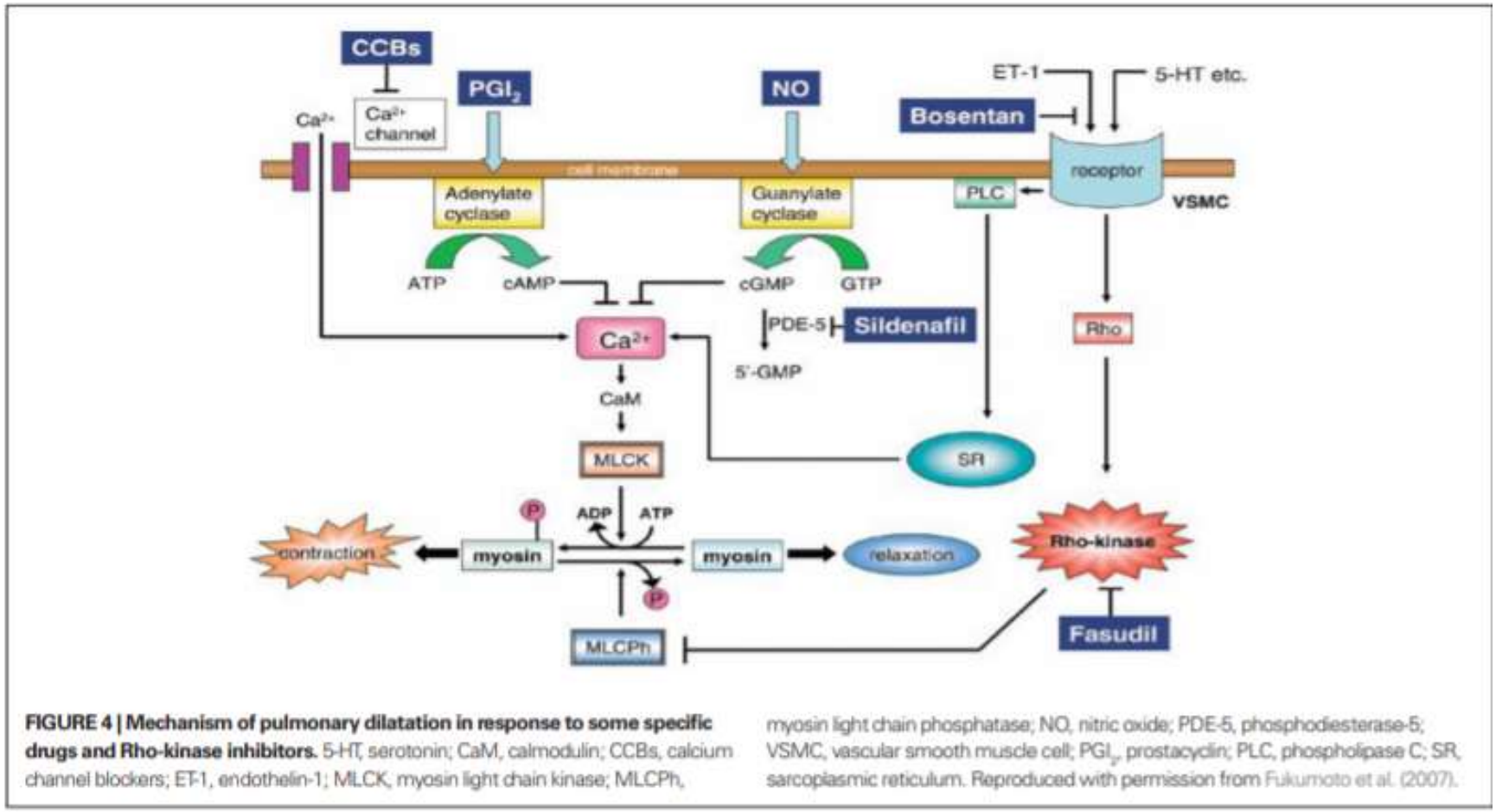


FIGURE 4 | Mechanism of pulmonary dilatation in response to some specific drugs and Rho-kinase inhibitors. 5-HT, serotonin; CaM, calmodulin; CCBs, calcium channel blockers; ET-1, endothelin-1; MLCK, myosin light chain kinase; MLCPh, myosin light chain phosphatase; NO, nitric oxide; PDE-5, phosphodiesterase-5; VSMC, vascular smooth muscle cell; PGI_2, prostacyclin; PLC, phospholipase C; SR, sarcoplasmic reticulum. Reproduced with permission from Fukumoto et al. (2007).

WHAT TO BE CAREFUL ABOUT / AVOID

- Fluid management
  - Hypo and hypervolemia can be detrimental
  - Fluid loading can be helpful and may improve hemodynamics in patients with acute PTE
  - In most cases - patients are already in a volume overloaded state → additional fluids may lead to further increases in RV wall stress/preload → decrease in LV filling due to septal bulge and interventricular dependance
    - Diuretics may help in the volume overloaded patient
  - With clear volume loss – small boluses may be trialed with close monitoring of BP, lactate, UOP
- Diuretics
  - May be used to treat fluid retention due to PH and prevent RV from impeding LV filling
  - ADMINISTER WITH CAUTION
  - Patient who is not overloaded and is diuresed excessively may decrease already low CO (reduced RV/LV preload) → cardiovascular collapse

RV FAILURE

- RV failure with low CO, systemic hypotension
  - Enlarged RV decreasing LV filling (septal wall bulging), reduction in pulmonary blood flow, decreased LA/LV preload
    - CO in patient with advanced PH cannot be augmented because of "fixed" PVR → reduction in SVR will not be followed by a compensatory increase in CO = worsening of hypotension
  - If hypotensive – vasopressors may be indicated
    - Goal is to keep SVR >> PVR to maintain coronary perfusion
    - Norepi – helps maintain coronary perfusion pressure and augments inotropy
      - May also increase SVR/LV afterload which may improve the adverse conformation shape the dilated RV imposes on an underfilled LV
    - Vasopressin – decrease pulmonary vascular resistance through NO-based mechanism; does not cause pulmonary vasoconstriction
    - Dobutamine – can help increase CO but at a cost
      - Increased tachycardia and reduced diastolic filling time
      - Decreased SVR = can worsen systemic hypotension
        - PDE-3i may be preferred

RV FAILURE

- Intubation/MV
  - Risk of sedation, systemic vasodilation, increased intrathoracic pressures (decreased preload, increased RV afterload → worsening CO)
  - Acute, fatal collapse may occur
  - Opt for high flow (humans – CPAP)

PREVENTION

- Strategies to decrease risk of progression / complications of PH
  - Exercise restriction
  - Chemoprophylaxis for HWD, lung worm
  - Avoid pregnancy – exacerbate PH and decrease risk of genetic transmission
  - Avoid high altitude travel
  - Avoid non-essential GA

MONITOR THERAPY

- Recheck 2 weeks after starting therapy and then every 3-6 months or if signs worsen
  - CXR may show improvement in infiltrates
  - Echo may show partial or complete resolution of R sided changes, improved velocity profiles
- QOL scales – functional evaluation of cardiac health

PROGNOSIS

- Guarded
  - Some appear to respond to medical therapy for a time, many die within days to a few months of diagnosis
  - Severity at time of diagnosis plays a role
  - Underlying cause
- Sildenafil found to improve QOL and decrease TV pressure gradient in group 3 PH dogs (Johnson 2020)
- Treatment with sildenafil improves likelihood of survival (Jaffey 2019)
- If respond well initially – may survive for 1–2 years with excellent QOL
  - 32% of dogs did not live to 1 month recheck after starting sildenafil; only 50% alive at 6 months in respiratory cases of PH (Johnson 2020)
  - MST 276 days (Jaffey 2019)
- PAP > 47mmHg is a predictor of non-survival (Jaffey 2019)

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