

The pathophysiology of pulmonary hypertension in the dog and the cat

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INTRODUCTION

Pulmonary hypertension (PH) is a well-recognised condition in human patients seen with primary or secondary pulmonary vasculature disease. In veterinary medicine, the condition remains underdiagnosed. Primary pulmonary hypertension is extremely rare, but the secondary form has been described with a variety of congenital and acquired cardiorespiratory conditions (Table 1).

DEFINITION

Pulmonary hypertension is critically defined in human medicine by systolic and mean pulmonary artery pressures exceeding 30 and 20 mm Hg at cardiac catheterisation in the absence of pulmonic stenosis.

NORMAL PULMONARY CIRCULATION

Foetal and neonatal circulation

Foetal cardiac output differs from the adult. Left and right ventricles pump in parallel instead of in series (essentially because the aorta and pulmonary trunk are united by the massive ductus arteriosus), and the cardiac output in the foetus is considered to be the sum of right ventricular and left ventricular outputs (=combined ventricular output).

In the foetus the right ventricle pumps nearly twice as much blood per unit time as the left. Hence in the foetus the right ventricle is doing more work than the left, the opposite to what happens in the adult.

The distribution of blood throughout the body of the normal foetus and newborn mammal is governed by two main resistances (Fig. 1). The placenta is a low-resistance pathway and since the umbilical artery is a branch of the aorta, systemic arterial circulation as a whole is a low resistance pathway. The pulmonary circulation is a high-resistance pathway resulting in the diversion of a very large volume of blood away from the lungs to the placenta. The high vascular resistance of the pulmonary circulation is maintained chiefly by a combination of mechanical factors and vasomotor factors operated by the blood gases. The collapsed state of the foetal lungs, which is maintained until

the first breath after birth, compresses the alveolar vasculature. The low pO_2 of the blood passing through the alveolar vascular bed maintains arteriolar vasoconstriction.

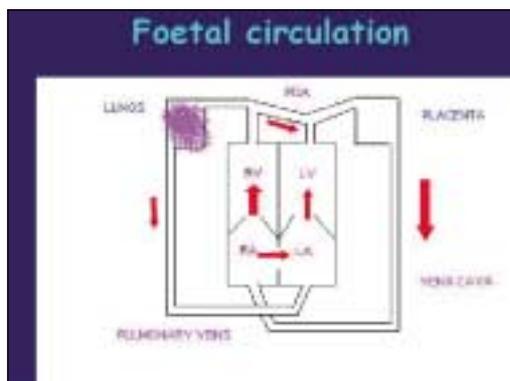


Fig. 1: The neonatal circulation.

At birth, taking of the first breath and the loss of the placenta cause these two resistances to be reversed (Fig. 2) with an immediate and radical redistribution of blood in the neonate. With the loss of the placenta, resistance in the systemic arterial circulation increases, whilst following expansion of the lungs, pulmonary resistance decreases.

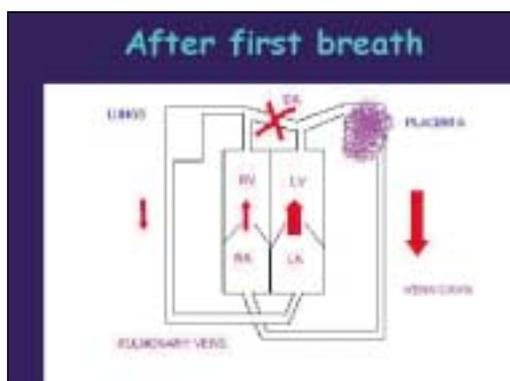


Fig. 2: Transition at birth.

The principal change is the sudden great increase in blood flow through the pulmonary veins, and hence venous return to the left atrium. A left-to-right pressure gradient develops across the foramen ovale, closing its flap. A pressure gradient from the aorta to the lungs is also created. Consequently, at the point where the aorta is joined by the ductus arteriosus (DA), the aortic flow divides with most

TABLE 1: Veterinary classification of pulmonary hypertension (modified from Kittleson 1998)

1. INCREASED PULMONARY BLOOD FLOW

Congenital left-to-right shunts

- Patent Ductus Arteriosus
- Ventricular Septal Defect
- Atrial Septal Defect
- Multiple congenital defects
- AV pulmonary shunts
- AV fistula
- Aorticopulmonary window

Post lobectomy: in dogs right-sided pneumonectomy can be fatal because the right lung takes 60 % of total lung volume.

Increased cardiac output

- Anaemia
- Fever
- Exercise

2. INCREASED BLOOD VISCOSITY

Polycythaemia vera

Secondary polycythaemia

3. INCREASED PULMONARY VASCULAR RESISTANCE

Increased resistance to pulmonary venous drainage

Prolonged left atrial hypertension

- Mitral valve disease
- Mitral stenosis
- Dilated Cardiomyopathy

Prolonged elevation of the left ventricular end-diastolic pressures

- Hypertrophic/ restrictive cardiomyopathy
- Severe aortic stenosis
- Constrictive pericarditis

Pulmonary venous obstruction

- Cor triatriatum sinister

Congenital anomalies of pulmonary veins and/or left atrium

Loss of pulmonary vessels

Pulmonary thrombo-embolism

Severe parenchymal disease

Luminal narrowing

Anatomic

- Eisenmenger's syndrome: decreased cross-sectional area of the pulmonary vascular bed (and also right-to-left shunts)
- Heartworm disease
- Primary PH (rare)

Pulmonary vasoconstriction

- High altitude disease
- Acidosis
- Severe parenchymal disease
 - Chronic bronchitis/ pneumonia*
 - Interstitial fibrosis*

- *Idiopathic (WHWT and other Terriers)*
- *Drug-induced: paraquat, bleomycin, amiodarone*

Hypoventilation: work in dog models indicate that the hypoxic stimulus is not limited to the alveolar and mixed venous oxygen tensions, but also is dependant on a third source of oxygen, coming from the vasa vasorum supplying the walls of the pulmonary arteries.

Upper airway obstruction

- *Brachycephalic upper airway syndrome*
- *Laryngeal paralysis*
- *Severe tracheal collapse*

Neuromuscular disease (ex. Myasthenia Gravis)

Obesity (Pickwickian syndrome)

Chest wall deformities

of it continuing down the aorta, but one third enters the DA. Blood continues to flow through the DA until it closes by contraction of the smooth muscles in its wall. This occurs within minutes to days after birth in the dog and the cat, and is secondary to a combination of haemodynamic and neurologic effects and changed oxygen tension.

Adult circulation

There are two circulatory systems in the lung: **pulmonary** and **bronchial** circulation.

The pulmonary circulation is a large volume system, with a low-pressure input from the pulmonary trunk, carrying venous blood to the lungs. The bronchial circulation is a low volume system, with a high pressure input from the aorta, conveying arterial blood to the lungs. The pulmonary arteries are true end-arteries, and the bronchial arteries supply a wide network of anastomoses along the bronchus, thus the very opposite of end-arteries.

The function of the pulmonary circulation is to carry mixed venous blood to the lung for gas exchange, and then to return it to the left side of the heart as arterialised blood. The role of the bronchial arteries is to carry arterialised blood from the systemic arterial system to the tissues of the bronchial tree in order to supply their metabolic needs. The resulting deoxygenated bronchial blood supply should ideally be returned to the right side of the heart as venous supply, but by an apparent quirk of evolution it is returned to the wrong side of the heart, i.e. to the left side, thus creating a small but recognisable right to left (R-L) shunt.

Although the bronchial arteries are rather insignificant in the normal animal, they are exceptionally responsive to pathological changes and contribute to the defence of the lung if the pulmonary arteries are occluded or if oedema arises in the lungs or pleural cavities.

The pulmonary circulation is unique among other organs as the entire cardiac output is pumped through it and the lungs therefore receive a blood supply vastly in excess of their metabolic requirements.

The design requirements of the pulmonary vasculature are as follows:

1. low resistance, to economise on the energetic cost of pumping large volumes of blood
2. large capacitance for accommodating high rates of blood flow, especially during exercise
3. sufficient smooth muscle in the arterial and arteriolar walls to control regional flow within the lung.

The vessels of the pulmonary circulation are short and

wide for low resistance, thin-walled for capacitance, but equipped with minimal smooth muscle for control.

The thin walls of the pulmonary arteries and arterioles possess very little smooth muscle. Nevertheless, pulmonary arterial pressure (PAP) is so low that even small amounts of smooth muscle can decrease the vascular diameter. This allows vasoconstriction to shunt from poorly ventilated alveoli to well ventilated alveoli, thus correcting a mismatch of ventilation and perfusion. Conversely, inhibition of vasoconstrictor tone permits the opening during exercise of many capillaries that are closed when the body is at rest. Pulmonary blood flow describes the amount of blood per unit time that passes from the pulmonary arteries, through the pulmonary capillaries to the pulmonary veins. Normal awake dogs at sea level have a peak systolic PAP between 15-25 mm Hg, end-diastolic between 5 and 10 mm Hg and mean values ranging from 10-15 mm Hg.

The pressure within the PA is directly related to the pulmonary venous pressure, right ventricular cardiac output, and pulmonary vascular impedance. Pulmonary vascular resistance (PVR) is the dominant factor in impedance and reflects several factors that include cross-sectional area of small muscular arteries and arterioles. The main determinants of PVR are the activity of the vascular smooth muscle in these small arteries and arterioles, the intravascular pressure, and the extravascular pressure. Other determinants include blood viscosity, total lung mass, and the presence or absence of proximal vascular obstruction.

$$\text{POISEUILLE'S LAW: } R = \Delta P / Q = 8\eta l / \pi r^4$$

Q: flow; η : viscosity of fluid, l and r: length and radius of the vessel

Ageing changes

Pulmonary artery pressure and pulmonary vascular resistance increase with advanced age, similar to increases in systemic vascular resistance. Reduced compliance of the pulmonary vascular bed secondary to intimal fibrosis or increased wall thickness in the muscular pulmonary arteries is a possible cause. It is also possible that some of the changes in the pulmonary arteries relate to reduced compliance of left ventricular filling, which is passively reflected back on the pulmonary vascular bed.

AETIOLOGY AND PATHOPHYSIOLOGY

The aetiology of secondary PH is multifactorial, and often multiple abnormalities lead to the development of PH.

Vasoreactivity of the pulmonary arterioles

The endothelium is a very active organ. It appears to serve

as a mechanoreceptor within the vasculature that senses flow or pressure and modulates vascular tone accordingly. Several molecules and factors will induce vasoconstriction or vasodilation (Figs. 3 and 4). In physiological circumstances the normal vascular endothelial cell maintains the vascular smooth muscle in a state of relaxation.

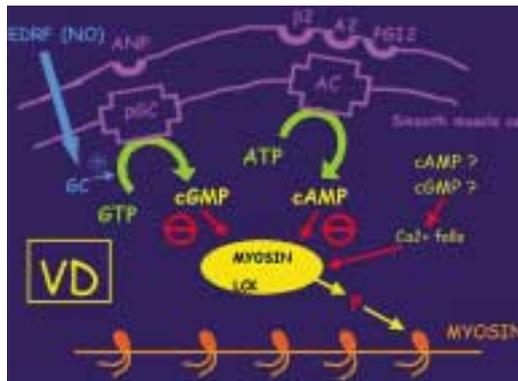


Fig. 3: Vasodilators of the pulmonary circulation (modified from Opie 1997). Most act by the formation of cyclic nucleotides, c-GMP, and c-AMP. These are both vasodilatory (VD), possibly by the inhibition of myosin light chain kinase (MLCK). C-GMP is the messenger for guanylate cyclase, which in turn is stimulated by atrial natriuretic peptide (ANP) or by endothelium derived relaxation factor (EDRF/NO). Vasodilatory c-AMP is formed by stimulation of adenylate cyclase (AC) in response to β_2 adrenoreceptor stimulation, or by adenosine stimulation via A2 receptors, or by the prostacyclin receptor (PC).

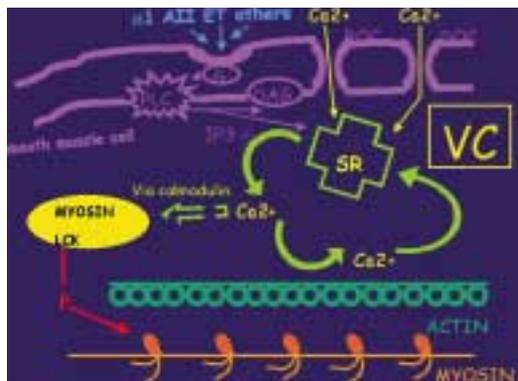


Fig. 4: Vasoconstrictors of the pulmonary circulation (modified from Opie 1997). Several act by releasing calcium of the sarcoplasmic reticulum. Stimulation of the vascular receptors by endothelin (ET), angiotensin II (AII), or noradrenaline leads to increased activity of phospholipase C (PLC), which splits phosphatidylinositol into two messengers: IP3 (inositol triphosphate) and 1, 2 DAG (1, 2 diacylglycerol). IP3 promotes release of calcium from the sarcoplasmic reticulum (SR). Cytosolic calcium will activate myosin light chain kinase (LCK) (via calmodulin) and the latter will favorise actin-myosin cross-linking by phosphorylation. Membrane-bound DAG activates protein kinase C (PKC). The latter may act by a breakdown product on the contractile apparatus to promote a sustained contractile response. Vasoconstriction (VC) also occurs in response to enhanced activity of the calcium channels which are either receptor operator channels (ROC) or depolarisation operated channels (DOC).

Intima thickening (Fig. 5)

Several growth factors (endothelial fibroblast growth factor, platelet derived growth factor, transforming growth

factor β) have been implicated in the development of pathological intima thickening. Enhanced growth factor release, activation and intracellular signalling may lead to smooth muscle cell proliferation and migration as well as extracellular matrix synthesis (elastin, collagen, fibronectin).

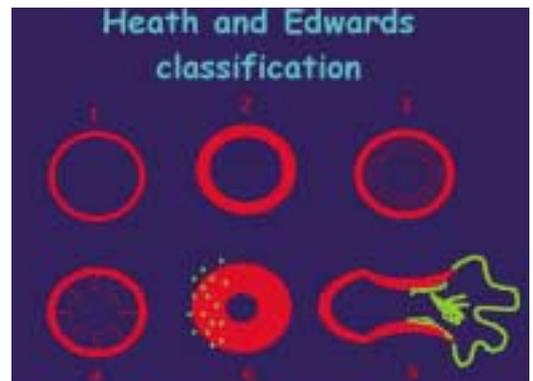


Fig. 5: Heath and Edwards histopathological classification. Grade 1: Hypertrophy of the media of small muscular pulmonary arteries and arterioles. Grade 2: Intimal proliferation is added to the medial hypertrophy. Grade 3: Advanced medial thickening with hypertrophy and hyperplasia, together with progressive intimal proliferation and concentric fibrosis that results in obliteration of many arterioles and small arteries. Grade 4: Dilatation and so-called 'plexiform lesions' of the muscular pulmonary arteries and arterioles. Grade 5: Complex plexiform, angiomatous, and cavernous lesions and hyalinisation of intimal fibrosis. Grade 6: Necrotising arteritis.

Thrombosis and endothelial denudation (Fig. 5)

An equally important factor is the widespread development of thrombosis in small pulmonary arteries. Various defects in coagulation, including abnormal platelet function and defective fibrinolysis have been demonstrated in primary PH. Increased production of biologically active von Willebrand factor could predispose to platelet fibrin microthrombi, and exposure of subendothelial cell surface structures due to injury may provide the substrate for ongoing vascular thrombosis. Alteration of the normal



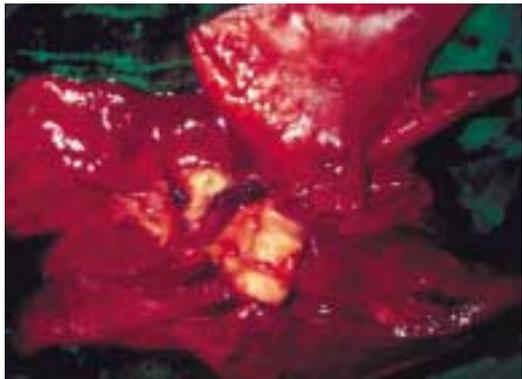
Fig. 6: Cyanotic mucous membranes in a dog with pulmonary hypertension secondary to interstitial pulmonary fibrosis.

physiological function of endothelial cells has been shown to create a local procoagulant environment. Endothelial denudation results in platelet adherence to exposed tissue collagen, with release of platelet derived smooth muscle mitogens, which also have vasoconstrictor properties. This process leads to an inflammatory response and thrombosis and intense vasoconstriction may lead to fibrinoid necrosis of the arteriolar wall.

- whether obstruction occurs early or late in life
- the acuteness and rapidity of progression
- the severity of the vascular obstruction
- the activity status of the animal
- very species specific

The ability of the right ventricle (RV) to increase its wall thickness in response to a pressure overload is greater in the foetus and in early life. This is probably because the myocardium can thicken through both hypertrophy (increased cell size) and hyperplasia (increased cell number). As a result, patients that develop PH *in utero* demonstrate striking degrees of concentric hypertrophy. In many cases, the hypertrophy can compensate for even marked elevations of RV systolic pressure, and RV myocardial failure occurs only late in life.

Conversely, acute increases in PAP in adult animals, such as seen with thrombo-embolism or high altitude disease are poorly tolerated by the RV because of its inability to develop and sustain high wall tension and stress imposed by the increased afterload. In this situation, the RV acutely dilates, further increasing wall tension, and acute RV failure characterised by a decrease in cardiac output and elevated end-diastolic pressure may occur. Between the two extremes of hypertrophy and dilation is a spectrum of pathophysiological changes that relate to the rate of development and progression and the magnitude of vascular obstruction. Prominent right atrial enlargement occurs as a consequence of tricuspid incompetence secondary to pressure/volume overload. This might lead to right-sided heart failure.



Figs. 7a and 7b: Post-mortem specimen showing massive pulmonary thrombo-embolism.



Fig. 7b.

Increased blood viscosity

Increased blood viscosity from hypoxia-induced increases in red blood cell mass can contribute to PH by increasing the resistance.

Right ventricular response: Cor Pulmonale

Chronically elevated PA pressure leads to increased impedance to right ventricular emptying. Right ventricular pressure overload results, and if severe, it can ultimately lead to right-sided heart failure. The actual physiological abnormalities that result in right-sided heart failure remain unclear, but probably relate to either tricuspid valve incompetence resulting from right ventricular remodelling or failure of the right ventricular myocardium.

The right ventricular response to PH varies depending on several variables including:

- congenital versus acquired obstruction

REFERENCES AND FURTHER READING

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These multiple choice questions are based on the above text. Readers are invited to answer the questions as part of the RCVS CPD remote learning program. Answers appear on page 99. In the editorial panel's view, the percentage scored, should reflect the appropriate proportion of the total time spent reading the article, which can then be recorded on the RCVS CPD recording form.

- 1. Which statement is false? Primary pulmonary hypertension is:**
 - a. Very common in the dog and cat.
 - b. A primary disease of the pulmonary vasculature.
 - c. Well recognised in human medicine.
 - d. Defined in human medicine by mean pulmonary artery pressure exceeding 20 mm Hg at cardiac catheterisation
 - e. Can induce cor pulmonale.

- 2. Which statement is false? The foetal circulation differs from the adult circulation in that:**
 - a. The Ductus Arteriosus is open in the foetal circulation
 - b. Left and right ventricles pump in series instead of parallel in the foetal circulation
 - c. The pulmonary circulation is a high resistance pathway in the foetal circulation
 - d. The placenta is a low resistance pathway in the foetal circulation
 - e. In the foetus the right ventricle pumps nearly twice as much blood per unit time as the left

- 3. Which is not a main determinant of pulmonary vascular resistance?**
 - a. The activity of the vascular smooth muscle (vasodilation or vasoconstriction)
 - b. Intravascular and extravascular pressure
 - c. Cross-sectional area of small arteries and arterioles
 - d. Blood viscosity
 - e. Presence of pulmonary stenosis

- 4. Secondary pulmonary hypertension is due to:**
 - a. The vasoreactivity of the pulmonary arterioles
 - b. Intima thickening
 - c. Thrombosis and endothelial denudation
 - d. Increased blood viscosity
 - e. Multiple factors including all of the above

- 5. Which statement is false? The right ventricular response to pulmonary hypertension varies and is depending on several variables including:**
 - a. Congenital versus acquired obstruction
 - b. Occurrence early or late in life
 - c. Left ventricular output
 - d. Acuteness of onset
 - e. Species specific

