Paediatric pulmonary hypertension: aetiology, pathophysiology and treatment

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Abstract

Paediatric pulmonary hypertension (PH) is associated with great morbidity and mortality. Various classifications have been formulated according to the aetiology or pathophysiology. The aetiology of pulmonary hypertension is very diverse and trying to pinpoint a cause can help us in optimizing the treatment as much as possible. Nonetheless, in a large number of children, the aetiology remains unclear. There is a large spectrum of the disease presentation and the diagnosis is still mainly based on echocardiographic and cardiac catheter findings with many supportive investigations. Once a diagnosis of PH has been established a thorough diagnostic workup is helpful as the treatment options depend critically upon the underlying cause which may be treatable. This article describes the known causes in children, the important diagnostic tests required and the currently available treatment options.

Keywords aetiology; paediatric pulmonary hypertension; pathophysiology; treatment

Definition

Pulmonary arterial hypertension is defined as mean pulmonary artery pressure more than 25 mmHg at rest, in the absence of left atrial hypertension (less than 15 mmHg) and where the pulmonary vascular resistance is more than 3 wU m^2 (Woods Units).

Normal fetal circulation and neonatal transition

During fetal life the pulmonary resistance is very high. The lungs at this stage are dense organs and not aerated. The blood supply to the lungs is needed mainly for growth of the organs and not for oxygenation and so the high pulmonary resistance helps to divert the blood from the pulmonary into the systemic circulation, the lungs only receiving 10% of the cardiac output in fetal life. The foramen ovale directs oxygenated blood from the placenta into the left atrium. The duct is another structure that helps to divert 90% of the blood from the pulmonary artery into the aorta without having to go through the lungs.

When a child is born and takes its first breath, the lungs inflate and became aerated. There is a fall in the pulmonary resistance and hence a reduction in the pulmonary pressures. The pulmonary pressures continue to fall and usually by 2–3 months reach normal values.

Any process that disrupts this transition can lead to pulmonary hypertension. This may be due to increased pulmonary blood flow from congenital heart defects that cause large left to right shunts. There may be problems more downstream in the pulmonary capillary bed, the vaso-reactivity of the small vessels, or even back-pressure from the left side of the heart.

Congenital heart disease as a cause for PAH

Large left to right shunt can be at the levels of the atria, ventricles or great arteries. These may be most commonly in the form of ventricular septal defect (VSD), atrio-ventricular septal defect (AVSD), persistent arterial duct (PDA) or common arterial trunk. Also, more complex diseases can lead to high pulmonary blood flow, without being recognized as left to right shunt, such as transposition of the great arteries with ventricular septal defect.

When large amount of blood flows into the lungs, there is stretch on the smooth muscles of the pulmonary artery wall. There are multiple mechanisms which are involved in the response to this process. There is initially proliferation of smooth muscle cells in the media of the arterioles. Once high pulmonary blood flow is prolonged this proliferation can increase to involve the distal vessels. There is action on multiple levels with the pulmonary endothelium being affected, hypertrophy of the smooth muscle cells and proliferation of the endothelium. This all leads to increased pulmonary vaso-reactivity, pulmonary vasoconstriction and pulmonary vascular remodelling, generally recognized to occur in a serial fashion as demonstrated by the Rabinovitch classification (Figure 1).

The pulmonary vascular endothelium has been implicated as a major contributing factor to pulmonary vasoconstriction in part due to the abnormal endothelial function. It is believed that endogenous pulmonary vasodilators are reduced and the pulmonary vasoconstrictors are increased. The vasodilator factors that are derived from the endothelium are nitric oxide and prostacyclin, whereas endothelin-1 and serotonin have vasoconstrictor activity. These serve as one of the major targets in the treatment of pulmonary hypertension.

Pulmonary hypertension due to left heart disease

When there is involvement of the left heart downstream from the lungs, this in turn leads to back pressure (pulmonary venous hypertension). The problem may be at the level of the pulmonary veins (pulmonary vein stenosis), left atrium (e.g. supravalvar mitral membrane), mitral valve or aortic valves (stenosis/regurgitation), or the left ventricle itself. There may be dysfunction of the LV (e.g. cardiomyopathies), which can be due to its systolic (impaired contractility) or diastolic function (impaired relaxation). All these in turn lead to a back-pressure with raising of pulmonary venous pressure, pulmonary arteriolar pressure and eventually to hypertension in the pulmonary arteries.

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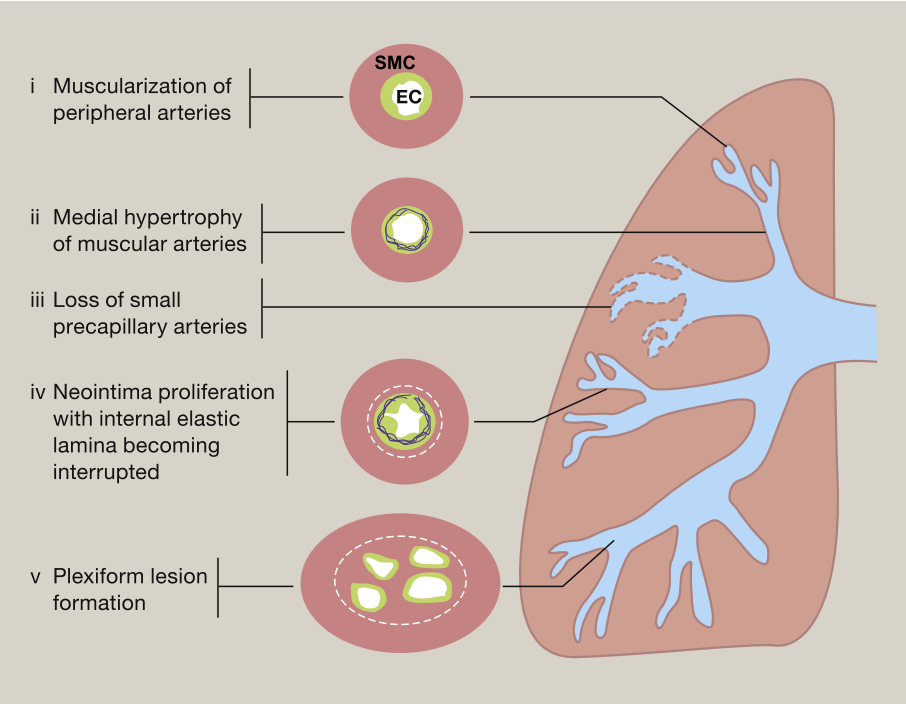

Figure 1 Rabinovitch histopathological classification of pulmonary arterial hypertension. SMC – smooth muscle cells, EC – endothelial cells. (Adapted from Molecular pathogenesis of pulmonary arterial hypertension. *J Clin Invest* 2008; 118(7): 2372–2379).

Pulmonary hypertension due to lung disease and/or hypoxia

Oxygen is one of the most potent pulmonary vasodilators and hence hypoxia leads to pulmonary vasoconstriction. This is a protective mechanism by which part or all of a lung that is not well-ventilated will have a reduced blood supply, and this blood is then diverted to the better ventilated part of the lungs. If the hypoxia is chronic, vasoconstriction continues and will in turn lead to increased pulmonary vascular resistance. Lung disease leads to hypoxia, stimulation of erythropoietin, erythrocytosis and endothelial damage. Endothelial damage leads to an imbalance between the vasoconstrictors and vasodilators. Prolonged hypoxia causes hypoxic injury to the LV itself and subsequently may contribute to PH by increasing pulmonary venous pressure. Upper airway obstruction contributes to PH by causing chronic hypoxia. Hypoxia induces remodelling in the pulmonary vasculature. This is thought to be dependent on the site and also has a temporal relationship. The cellular and molecular mechanisms have different effects at different levels resulting in altered proliferation, growth factor expression, matrix protein, cytokines and receptors.

Obstructive sleep apnoea is increasingly being recognized as a potential trigger for pulmonary hypertension. Frequent nocturnal

WHO classification proposed at Dana Point 2008

The classification of pulmonary arterial hypertension according to aetiology:

1.1 Idiopathic PAH
1.2 Heritable PAH e.g. *BMPR2*; *ALK-1*, *ENG*, *SMAD9*, *CAV1*, *KCNK3*; or unknown
1.3 Drug and toxin induced
1.4 Associated with: Connective tissue disease; HIV infection; Portal hypertension; Congenital heart diseases; Schistosomiasis; Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis; Persistent pulmonary hypertension of the new-born (PPHN)
2. Pulmonary hypertension due to left heart disease e.g. Ventricular systolic/diastolic dysfunction; Valvar disease; Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia e.g. COPD; Interstitial lung disease; Other pulmonary diseases with mixed restrictive and obstructive pattern; Sleep-disordered breathing; Alveolar hypoventilation disorders; Chronic exposure to high altitude; Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms e.g. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy; Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangio-leiomyomatosis; Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders; Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Table 1