Pulmonary Arterial Hypertension
(part one)

H.Mortezaeian M.D.

Department of Pediatric Cardiology: *Shahid Rajaee Heart Center*

Introduction

Pulmonary hypertension is usually classified as primary (idiopathic) or secondary.1 It is now clear, however, that there are conditions within the category of secondary pulmonary hypertension that resemble primary pulmonary hypertension in their histopathological features and their response to treatment. For this reason, the World Health Organization (WHO) classified pulmonary hypertension into five groups on the basis of mechanisms, rather than associated conditions.

In 2003, the World Health Organization revised the classification of PAH into 5 categories based in part on etiology: pulmonaryarterial hypertension, pulmonary venous hypertension, pulmonary hypertension associated with hypoxemia, pulmonary hypertension resulting from chronic thrombotic or embolic disease, and miscellaneous. 2 Group I of the WHO classification, designated pulmonary arterial hypertension, is the principal focus of this review.

Pulmonary arterial hypertension is defined as a sustained elevation of pulmonary arterial pressure to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mm Hg.3Diagnosis of PPH one must excludes all secondary cause of PHT and demonstrate normal pulmonary wedge pressure. 2,3

Pathophysiology:

The histopathology of pulmonary vascular disease has been classified in two phases, early description in the 1950s (the Heath-Edwards classification) and an extension of this by Rabinovitch et al. 2.3

Although pulmonary vascular resistance(PVR = mPAP _ mPCWP/Q p) may be as high as 8-10 Wood units immediately after birth, it normally falls rapidly through the first week of life. By 6-8 weeks, pulmonary vascular resistance usually has reached a normal adult level of 1-3 Wood units. In an infant, although the pulmonary pressure is at systemic levels, the pulmonary vascular resistance is low and there is pulmonary over circulation. 2.3,23,26,28

Frequency data are difficult to confirm, as there are no international registries tracking the incidence and prevalence of pulmonary hypertension. Elevated pulmonary artery pressure in congenital heart disease is caused by pulmonary over circulation, pulmonary vasoconstriction, and pulmonary vascular disease, either alone or in combination.

Table1.

The Revised Word Health Organization Classification of Pulmonary Hypertension

Group1. Pulmonary arterial hypertension

Idiopathic(primary)

Familial

Related conditions:collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs

And toxins (e.g, anorexigens, rapeseed oil, l-tryptophan, methamphetamine, and

Cocaine); other conditions: thyroid disorders, glycogen storage disease, Gaucher`s

disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy.

Associateg with significant venous or capillary involvement

Pulmonary veno-occlusive disease

Pulmonary-capillary hemangiomatosis

Persistent pulmonary hypertension of the newborn

GroupII. Pulmonary venous hypertension

Left-sided atrial or ventricular heart disease

Left-sided valvular heart disease

Group III. Pulmonary hypertension associated with hypoxemia Chronic obstru ctive pulmonary disease Interstitial lung disease
Sleep – disordered breathing
Alveolar hypoventilation disorders
Chronice exposure to high altitude
Developmental abnormalities

Group IV. Pulmonary hypertension due to chronic thrombotic disease , embol – ic disease , or both
Thromboembolice obstruction of proximal pulmonary arteries
Thromboembolice obstruction of distal pulmonary arteries

Group V. Miscellaneous
Sarcoidosis , pulmonary Langerhans – cell histiocytosis , lymphangio - matosis , compression of pulmonary vessels (a denopathy , tumor , fibrosing mediastinitis)

**The table has been adapted from Simonneau et al . 2*

Pulmonary HypertensiHypertension in Congenital Heart Disease:

Congenital heart defects are cardiac abnormalities present at birth. Approximately 8 out of every 1,000 infants are born with congenital heart disease. Some defects are mild and may not even be apparent during infancy or childhood. Others are life threatening and require surgery during infancy. The care of infants and children with congenital heart disease has been a monumental success. The incidence of SPAH is dependent on its etiology. 13

Secondary pulmonary hypertension (SPHT) in CHD is caused by pulmonary over circulation , pulmonary vasoconstriction, and pulmonary vascular disease. On the basis of the pathophysiology as described above, the most common causes include (1) Hypoxic vasoconstriction (2) pulmonary vasculature obliteration (PE), and (3) pressure/ volume overload (CHF). 2,16,24,25

Pulmonary vascular disease with morphologic alterations of the pulmonary vasculature is one of the most serious complications of congenital heart disease. Once established, it is progressive and leads to premature death. Pulmonary vascular disease can occur in patients with unrepaired (Eisenmenger's syndrome) or partially repaired congenital heart disease, as well as patients with appropriately corrected heart disease. Late secondary pulmonary hypertension has been reported in patients who have had appropriately repaired congenital heart surgery, such as patients with transposition of the great vessels who underwent an arterial switch procedure as newborns. Why these patients develop this condition is unclear and may represent a primary mechanism similar to that which triggers idiopathic PAH.

The lesions causing pulmonary vascular disease can be divided into several physiologic groups, including patients with a left-to-right shunt leading to excessive pulmonary blood flow, patients with cyanotic heart disease with or without excessive pulmonary blood flow, and patients with elevated pulmonary venous pressure. The risk of developing irreversible pulmonary vascular disease depends on the specific physiology of each lesion, including the degree of pulmonary over circulation, the pressure that the pulmonary arteries are exposed to, and the degree of hypoxia. One important factor is the degree of pulmonary over circulation. Only 3% of patients with small to moderate VSD develop pulmonary vascular disease, whereas 50% of patients with a large VSD (> 1.5 cm diameter) will be affected. The exposure of the pulmonary circulation to elevated pressure and/or hypoxia also influences the risk of developing pulmonary vascular disease. Only 10% of patients with unrepaired atrial septal defect (ASD) develop Eisenmenger's syndrome compared with 50% of patients with unrepaired VSD and almost all patients with unrepaired truncus arteriosus.25,27 The presence of extracardiac disease also contributes to the risk of pulmonary vascular disease. Children with Down's syndrome and other chromosomal abnormalities have an increased risk for pulmonary hypertension, as do children with congenital heart disease and chronic lung disease.

The age at which specific lesions cause irreversible pulmonary vascular disease varies along with variances in the specific physiology. For example, children with large VSDs who have increased pulmonary blood flow and elevated pressures generally do not develop irreversible pulmonary vascular changes before 1 to 2 years of age, while children with truncus arteriosus can develop pulmonary vascular lesions in infancy. Other defects, such as ASD, do not produce irreversible pulmonary vascular disease until adulthood. 21

Congenital heart disease with increased pulmonary blood flow commonly leads to the development of pulmonary hypertension and increased vascular reactivity. These serious sequelae are associated with the following two major categories of congenital heart defects: those resulting in increased pulmonary blood flow and increased pulmonary arterial pressure and those resulting in increased pulmonary venous pressure. Recent evidence

that the pulmonary vascular endothelium is an important determinant of vascular tone has led to the hypothesis that endothelial injury, secondary to congenital heart disease with increased pulmonary blood flow, disrupts these regulatory mechanisms and thereby plays a role in the development of pulmonary hypertension and its associated increased vascular reactivity.

PATHOGENESIS:

Although the pathogenesis of most forms of pulmonary arterial hypertension is unknown, there have been many recent developments, especially pertaining to the molecular genetics and cell biology of idiopathic pulmonary arterial hypertension. In this review, we discuss these developments and relate them to other forms of pulmonary arterial hypertension, when appropriate. Treatment is discussed briefly as it relates to the disease mechanism; more information on treatment can be found in recent reviews of this topic.5,6

The main vascular changes in pulmonary arterial hypertension are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. These findings suggest the presence of perturbations in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants. These homeostatic imbalances are probably consequences of pulmonary endothelial-cell dysfunction or injury.4, 5,6 ,31

Prostacyclin and thromboxane A2 are major arachidonic acid metabolites of vascular cells. Prostacyclin, a potent vasodilator, inhibits platelet activation and has antiproliferative properties; in contrast, thromboxane A2 is a potent vasoconstrictor and platelet agonist.7 In pulmonary arterial hypertension, the imbalance between these two molecules is shifted toward thromboxane A27,8:

Endothelin-1, a potent vasoconstrictor, stimulates the proliferation of pulmonary-artery smooth-muscle cells.10,11,12 The synthesis of nitric oxide, a potent vasodilator and inhibitor of platelet activation and vascular smooth-muscle cell proliferation, is catalyzed by the family of nitric oxide synthase enzymes. Decreased levels of the endothelial isoform of nitric oxide synthase have been observed in the pulmonary vascular tissue of patients with pulmonary hypertension, particularly those with idiopathic pulmonary arterial hypertension.13,14 Serotonin (5-hydroxytryptamine) is a vasoconstrictor that promotes smooth-muscle cell hypertrophy and hyperplasia.17,18,22 Vasoactive intestinal peptide, a potent systemic vasodilator, decreases pulmonary-artery pressure and pulmonary vascular resistance in rabbits with monocrotaline-induced pulmonary hypertension and in healthy human subjects; it also inhibits platelet activation and vascular smooth-muscle cell proliferation. In acute and chronic hypoxia, the production of vascular endothelial growth factor (VEGF) is increased. In pulmonary arterial hypertension, disordered angiogenic responses appear to underlie the formation of plexiform lesions and the clonal expansion of endothelial cells within the lesions. 9

Vasoconstriction	Call Proliferation	Thrombosis
Increased TxA2	Increased VEGF	Increased TxA2
Decreased PGI2	Decreased PGI2	Decreased PGI2
Decreased NO	Decreased NO	Decreased NO
Increased ET-1	Increased ET-1	
Increased 5-HT	Increased 5-HT	Increased 5-HT
Decreased VIP	Decreased VIP	Decreased VIP

Figure 1. *Mediators of Pulmonary Vascular Responses in Pulmonary Arterial Hypertension.*

Clinical presentation:

Dyspnea, the most frequently present complication in patients with PHT, is due to impaired oxygen delivery during physical activity as the result of an inability to increase cardiac output in the presence of increased oxygen demands. Chest pain results from RV ischemia as coronary blood flow is impaired in the setting of increased RV mass and elevated systolic and diastolic pressures .Syncope, often exertional or post exertional ,implies a severely restricted cardiac output leading to diminished cerebral blood flow. The two most frequent mechanisms of death are progressive RV failure and sudden cardiac death suggesting an increased incidence of arrhythmias or acute PHT crises.

Symptoms of right-sided heart failure in PAH include progressive dyspnea, sometimes accompanied by fatigue, syncope, or chest pain. The interval between the onsets of symptoms of PHT and diagnosis is about 2 years. The most common presenting symptoms are the following: Exertional dyspnea, Fatigue and lethargy, Angina, Syncope, Raynaud phenomenon and Edema .Less common symptoms include cough, hemoptysis, and hoarseness. 2,20

Physical Examination

Physical examination centers on detecting signs of right ventricular hypertrophy and right ventricular failure secondary to pulmonary hypertension. Physical examination in a patient with PHT is RV lift ,palpable P2 ,increased intensity of P2 with a single loud P2 ,pulmonic ejection sound associated with a dilated pulmonary trunk and a diastolic murmur of PI. Useful findings on physical examination include paradoxical splitting of the second heart sound, murmur of pulmonic regurgitation and tricuspid regurgitation, right ventriclular heave, increased jugular venous pressure, hepatomegaly, and lower extremity edema. If there is CHF ,edema, ascites and hepatosplenomegaly may occur. Central cyanosis and clubbing of digits are presentations of Eisenmenger syndrome. Eisenmenger syndrome is characterized by peripheral oligemia, indicating the reversal of a left-to-right shunt due to increased vascular resistance. The peripheral vasculature is diminished, and the cardiac morphology is consistent with cor pulmonale.

(End of part one.)

Acknowledgment:

I would like to appreciate Dr Yasaman Khalili for her role as an editor of the article.

References:

1.Barst RJ. Medical therapy of pulmonary hypertension: an overview of treatment and goals. Clin Chest Med 2001; 22:509-515

2.Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:Suppl S:5S-12S.

3.Aschner JL: New therapies for pulmonary hypertension in neonates and children. Pediatr Pulmonol 2004 Feb; 37 Suppl 26: 132-5

4.Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997;336:111-117. Galie N, Manes A, Branzi A. Prostanoids for pulmonary arterial hypertension. Am J Respir Med 2003;2:123-37.

5.Mehta S. Drug therapy for pulmonary arterial hypertension: what's on the menu today? Chest 2003;124:2045-2049.

6.Pistolesi M, Milne ENC: Radiology of cardiopulmonary hemodynamic disturbances. In: Radiology: Diagnosis, Imaging, and Intervention . Philadelphia: Lippincott; 2001.

7.Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992;327:70-75.

8.Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999;159:1925-1932

9. Mason NA, Springall DR, Burke M, et al. High expression of endothelial nitric oxide synthase in plexiform lesions of pulmonary hypertension. J Pathol 1998;185:313-318

10. Stelzner TJ, O'Brien RF, Yanagisawa M, et al. Increased lung endothelin-1 production in rats with idiopathic pulmonary hypertension. Am J Physiol 1992;262:L614-L620.

11.Allen SW, Chatfield BA, Koppenhafer SA, Schaffer MS, Wolfe RR, Abman SH. Circulating immunoreactive endothelin-1 in children with pulmonary hypertension: association with acute hypoxic pulmonary vasoreactivity. Am Rev Respir Dis 1993;148:519-522.

12.Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328:1732-1739.

13. Vincent JA, Ross RD, Kassab J, Hsu JM, Pinsky WW. Relation of elevated plasma endothelin in congenital heart disease to increased pulmonary blood flow. Am J Cardiol 1993;71:1204-1207

14.Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995;333:214-221.

15.Miller SW, Waltman AC: The pulmonary circulation. In: Radiology: Diagnosis, Imaging, Intervention . Philadelphia: Lippincott; 2001.

16.Lilienfeld DE, Rubin LJ: Mortality from primary pulmonary hypertension in the United States, 1979-1996. Chest 2000 Mar; 117(3): 796-800

17.Rich S, Kaufmann E, Levy PS: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992 Jul 9; 327(2): 76-81.

18.Herve P, Launay JM, Scrobohaci ML, et al. Increased plasma serotonin in primary pulmonary hypertension. Am J Med 1995;99:249-254.

19.Frank H, Mlczoch J, Huber K, et al: The effect of anticoagulant therapy in primary and anorectic drug- induced pulmonary hypertension. Chest 1997 Sep; 112(3): 714-21

20.Fraser RG, Pare JA, Pare PD: Pulmonary hypertension and edema. In: Diagnosis of Diseases of the Chest. Vol 3. 4th ed. Philadelphia: WB Saunders; 1999.

21.Grossman W, Braunwald E: Pulmonary hypertension. In: Heart Disease: A Textbook of Cardiovascular Medicine. 4th . Philadelphia: WB Saunders; 1997.

22. Marcos E, Adnot S, Pham MH, et al. Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. Am J Respir Crit Care Med 2003;168:487-493.

23.Abman SH: Neonatal pulmonary hypertension: A physiologic approach to treatment. Pediatr Pulmonol 2004 Feb; 37 Suppl 26: 127-8.

24. Dumas JP, Bardou M, Goirand F, Dumas M. Hypoxic pulmonary vasoconstriction. Gen Pharmacol 1999;33:289-297.

25.shigeo Y.,Ai Abe,Koichi T.Ann Inoperable pulmonary vascular disease in infants with congenital heart disease Thorac Surg 1998;66:1565-1570.

26. Nigel J. Wilson, J. A. Gordon Culham, George G. S. Sandor, Glenn P. Taylor. (1993) Pulmonary wedge angiography for prediction of pulmonary vascular disease in down syndrome. Catheterization and Cardiovascular Diagnosis 28:1, 22.

27.Cigarroa RG, Lange RA, Hillis LD. Oximetric quantitation of intracardiac left-to-right shunting: limitations of the Qp/Qs ratio. Am J Cardiol. 1989; 64: 246–247.

28. Huhta JC .Calculating pulmonary vascular resistance in children with congenital heart disease.J Am Coll Cardiol. . 1984 Nov;4(5):1071.

29.Berger RM. Possibilities and impossibilities in the evaluation of pulmonary vascular disease in congenital heart defects. Eur Heart J. 2000; 21: 17–27.

30.Chemla D, Castelain V, Herve P, et al. Haemodynamic evaluation of pulmonary hypertension. Eur Respir J. 2002; 20: 1314–1331.

31.Atz AM, Adatia I, Lock JE, et al. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. J Am Coll Cardiol. 1999; 33: 813–819.