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RESEARCH ARTICLE

A REVIEW ON PULMONARY HYPERTENSION

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Abstract

Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterised by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. Pulmonary hypertension also characterised by lung endothelial cell dysfunction and vascular remodelling. Five groups of disorders that cause PH was identified During the Fifth World Symposium held in 2013 in Nice, France. Estimates of incidence range from one to two new cases per million per year in the general population and are thought to be similar in children. The prevalence of IPAH in children was estimated to be 2.2 cases per million, and the overall prevalence of PAH was 3.7 cases per million. The precise mechanism(s) of PAH development in adults and children is not thoroughly understood. Nevertheless, endothelial cell dysfunction is thought to play a key role in addition to smooth muscle cell migration, dysfunction and abnormal apoptosis. Smooth muscle cells de-differentiate, achieving a more synthetic than contractile phenotype, grow into the sub-endothelial space, and produce fibrous material responsible for intimal fibrosis. The symptoms of PAH include breathlessness, fatigue, weakness, angina, syncope, and abdominal distension. PAH can also be detected by using Electrocardiogram, Chest radiograph, Echocardiography, Cardiac magnetic resonance imaging etc. Pulmonary vasodilators in general and prostacyclin analogues in particular have improved the outcome of patients with pulmonary arterial hypertension (PAH). Therapy of PAH includes: oxygen, calcium channel-blockers, diuretics, anticoagulants, prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors. But the treatment of this pulmonary disease is still about to develop. There is a huge scope for researcher to look into different molecular mechanisms responsible for the development of this disease.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterised by a progressive increase in pulmonary vascular resistance leading to right heart failure and death [1]. Independent of the aetiology, the pathogenesis of PAH includes a combination of vasoconstriction, inflammation, structural remodelling of pulmonary vessels and in situ thrombosis involving dysfunction of different cellular pathways [2, 3], as well as an imbalance of vasoactive mediators [4,5]. Pulmonary hypertension also characterised by lung endothelial cell dysfunction and vascular remodelling. A number of studies now suggest that endothelial progenitor cells (EPCs) may also induce neovascularisation and could be a promising approach for cell based therapy for PAH [6]. In recent years, the available data on targeted PAH therapies suggest that they are generally well tolerated and effective in children, which is generally the case in adults [33].

Pulmonary hypertension (PH) was previously classified into two categories: 1) primary pulmonary hypertension; or 2) secondary pulmonary hypertension according to the presence of identified causes or risk factors [7]. Since the

second World Symposium on pulmonary hypertension held in Evian, in 1998, a clinical classification was established in order to individualize different categories of PH sharing similar pathological findings, similar hemodynamic characteristics and, similar management. Five groups of disorders that cause PH were identified: pulmonary arterial hypertension (Group 1); pulmonary hypertension due to left heart disease (Group 2); pulmonary hypertension due to chronic lung disease and/or hypoxia (Group 3); chronic thromboembolic pulmonary hypertension (Group 4); and pulmonary hypertension due to unclear multi-factorial mechanisms (Group 5). During the successive world meetings, a series of changes were carried out, reflecting some progresses in the understanding of the disease. However, the general architecture and the philosophy of the clinical classification were unchanged [8]. The current clinical classification of pulmonary hypertension [9] is now well accepted and, widely used in the daily practice of pulmonary hypertension experts. It has been adopted by the Guidelines Committee of the Societies of Cardiology and, Pneumology [10]. Moreover, this classification is currently used by the U.S. Food and Drug Administration and the European Agency for Drug Evaluation for the labelling of new drugs approved for pulmonary hypertension.

During the Fifth World Symposium held in 2013 in Nice, France, the consensus was to maintain the general disposition of previous clinical classification. Some modifications and updates, especially for Group 1, were proposed according to new data published in the last years. It was also decided in agreement with the Task Force on Pediatric PH to add some specific items related to pediatric pulmonary hypertension in order to have a comprehensive classification common for adults and children

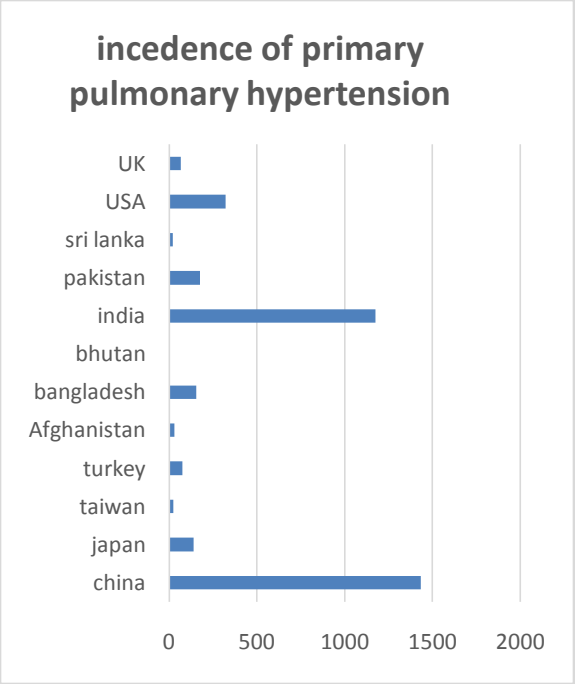
1. Pulmonary arterial hypertension
    1.1 Idiopathic PAH
    1.2 Heritable PAH
    1.3 Drug and toxin induced
2. Pulmonary hypertension due to left heart disease
    2.1 Left ventricular systolic dysfunction
    2.2 Left ventricular diastolic dysfunction
    2.3 Valvular disease
    2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital Cardiomyopathies.
3. Pulmonary hypertension due to lung diseases and/or hypoxia
    3.1 Chronic obstructive pulmonary disease
    3.2 Interstitial lung disease
    3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
    3.4 Sleep-disordered breathing
    3.5 Alveolar hypoventilation disorders
    3.6 Chronic exposure to high altitude
    3.7 Developmental lung disease
4. Chronic thromboembolic pulmonary hypertension (CTEP)
5. Pulmonary hypertension with unclear multi-factorial mechanisms

Others Causes: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH.

OCCURRENCE:

The frequency of IPAH/ PAH in children and adults remains unknown. Estimates of incidence range from one to two new cases per million per year in the general population and are thought to be similar in children. The prevalence of IPAH/ PAH in children was estimated to be 2.2 cases per million, and the overall prevalence of PAH (excluding PPHN and PAH caused by CHD) was 3.7 cases per million. However, the true incidence of APAH-CHD has not been established (US Census Bureau).

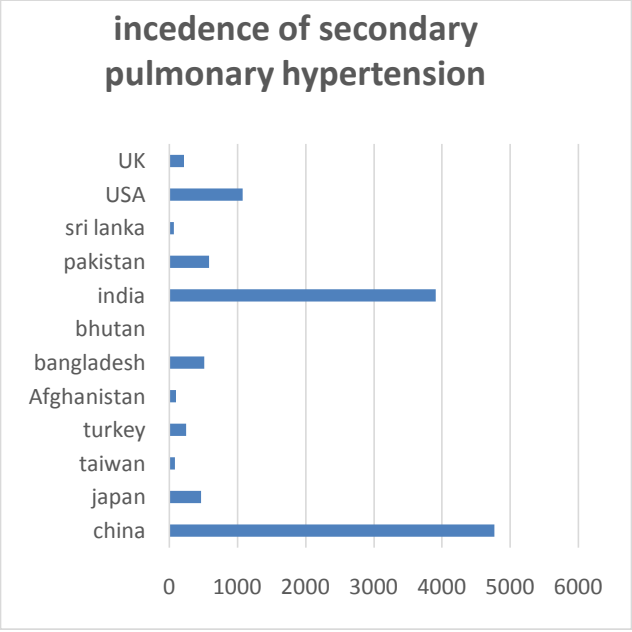
Incidence (annual) of Primary pulmonary hypertension:



Source:

1. US Census Bureau, Population Estimates,2004
2. US Census Bureau, International Data Base, 2004

Prevalence of Secondary pulmonary hypertension:



Source:

1. US Census Bureau, Population Estimates, 2004
2. US Census Bureau, International Data Base, 2004

PATHOGENESIS:

The precise mechanism(s) of PAH development in adults and children is not thoroughly understood. Nevertheless, endothelial cell dysfunction is thought to play a key role in addition to smooth muscle cell migration and

dysfunction, and abnormal apoptosis [2]. Smooth muscle cells de-differentiate, achieving a more synthetic than contractile phenotype, grow into the sub-endothelial space, and appear to produce the fibrous material responsible for intimal fibrosis [3]. Important vasoconstrictive and proliferative mediators implicated to date in paediatric and adult PAH include thromboxane (TXA2) and endothelin-1 (ET-1), opposing vasodilator and anti-proliferative vasoactive mediators, such as prostacyclin and nitric oxide (NO) [4–11]. TXA2 is a potent pulmonary vasoconstrictor and a stimulator for platelet aggregation [12], whereas prostacyclin produces the opposite effects [13, 14], an imbalance between these two vasoactive mediators in favour of TXA2 could contribute to both pulmonary vasoconstriction and local thrombosis in situ. Christman *et al* [15] reported that adult IPAH patients have an elevated ratio of the urinary metabolites of TXA2 to prostacyclin, due to increased release of TXA2 and decreased release of prostacyclin.

NO is a potent endothelium-derived vasorelaxant substance and an inhibitor of smooth muscle cell growth [16, 17]. NO is produced in various cell types by the action of NO synthase (NOS) [18]. Adults with PAH have impaired endothelium dependent relaxation of pulmonary arteries and decreased endothelial NOS (eNOS) gene expression [19, 20].

Von Willebrand factor (vWF), a large multimeric plasma glycoprotein produced by endothelial cells, is involved in platelet adhesion [30]. vWF has been proposed as both a marker of endothelial dysfunction and a prognostic parameter in PAH [31].

In summary, in both adults and children, PAH development involves complex molecular and cellular abnormalities, resulting in vascular remodelling in which fibroblasts, smooth muscle cells, endothelial cells and platelets all appear to play a role. Abnormalities of vascular and endothelial haemostasis, including reduced prostacyclin and NO production, increased TXA2 all been identified in children and adults with PAH. In addition to regulating vasoreactivity and cellular mitogenesis, the endothelium also modulates local haemostasis.

DIAGNOSIS:

The symptoms of PAH are non-specific and include breathlessness, fatigue, weakness, angina, syncope, and abdominal distension [21]. The physical signs of PAH include left parasternal lift, an accentuated pulmonary component of second heart sound, a pan-systolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, and an RV third sound. Jugular vein distension, hepatomegaly, peripheral oedema, ascites, and cool extremities characterize patients in a more advanced state [22]

Electrocardiogram

The ECG may provide suggestive or supportive evidence of PH by demonstrating RV hypertrophy and strain, and right atrial dilatation. RV hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with IPAH [21] The ECG has insufficient sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant PH [22].

Pulmonary function tests and arterial blood gases

Pulmonary function tests and arterial blood gases will identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (typically in the range of 40–80% predicted) and mild to moderate reduction of lung volumes. Peripheral airway obstruction can also be detected. Arterial oxygen tension isnormal or only slightly lower than normal at rest and arterial carbon dioxide tension is decreased because of alveolar hyperventilation [23].

Echocardiography

Transthoracic echocardiography provides several variables which correlate with right heart haemodynamics including PAP, and should always be performed in the case of suspected PH. Transthoracic echocardiography provides several variables which correlate with right heart haemodynamics including PAP, and should always be performed in the case of suspected PH [24].

High-resolution computed tomography, contrast-enhanced computed tomography

High-resolution CT provides detailed views of the lung parenchyma and facilitates the diagnosis of interstitial lung disease and emphysema. High-resolution CT may be very helpful where there is a clinical suspicion of PVOD [25].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging provides a direct evaluation of RV size, morphology, and function, and allows non-invasive assessment of blood flow including stroke volume, CO, distensibility of PA, and RV mass [26].

Circulating endothelial cells

Recently, we have shown that counting circulating endothelial cells (CECs) could be helpful in identifying children who may benefit from closure of a left-to-right shunt responsible for PAH, compared to children with irreversible PAH [27,28]. CEC counts have been shown elevated in adult idiopathic PAH as well [29].

TREATMENT:

Pulmonary vasodilators in general and prostacyclin analogues in particular have improved the outcome of patients with PAH. Endothelial dysfunction is a key feature of PAH and we previously described that circulating endothelial cell (CEC) level could be used as a biomarker of endothelial dysfunction in PAH. We now hypothesized that an efficient PAH-specific vasodilator therapy might decrease CEC level [32]. Idiopathic pulmonary hypertension is a progressive disease with poor prognosis. Therapy of idiopathic pulmonary hypertension includes: oxygen, calcium channel blockers, diuretics, anticoagulants, prostanoids, endothelin receptor antagonists and phosphodiesterase-5 inhibitors. Patients with pulmonary arterial hypertension (PAH) and pulmonary hypertension due to chronic thrombotic or embolic disease should be treated with vasodilatators. The potent vasodilatators are: prostacyclin PGI_2, prostacyclin analogue and endothelin receptor antagonists. For patients with idiopathic PAH classified as NYHA III (New York Heart Association) bosentan is recommended, whereas for patients classified as NYHA IV—epoprostenol [33]. Treatment of patients with PAH associated with CTD appears more complex than that of patients with IPAH. Immunosuppressive therapy combining glucocorticosteroids and cyclophosphamide may result in clinical improvement in patients with PAH associated with systemic lupus erythematosus or mixed CTD [23].

Oral administration has been limited by poor bioavailability, but stable analogues are now available and have been the subject of small clinical studies. One such analogue, beraprost, reduces pulmonary artery pressure [29]. Oral prostacyclin analogues may extend the benefits of prostacyclin treatment to a greater proportion of patients with PH, but there is still considerable room for improvement in quality of life. The view is emerging that PH is caused by an insult to the pulmonary vasculature in a genetically predisposed individual, and that factors such as impaired nitric oxide and prostacyclin production and increased endothelin activity are mediators of disease progression. There will remain a role for drugs that interfere to correct such perturbations for some time to come. Current studies have naturally turned to the effect of prostacyclin analogues, endothelin antagonists, and PDE5 inhibitors on BMPR-II activity and will provide a better rational for their use as well as clues to new therapeutic approaches [34].

CONCLUSION:

Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterised by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. The prevalence of PAH is high in India and china compared to other developing countries as well as other developed countries. This disease causes a serious threat to the society along with the increased pulmonary problems. But the treatment of this pulmonary disease is still about to develop. There is a huge scope for researcher to look into different molecular mechanisms responsible for the development of this disease as well as different drugs to cure PAH and to improve quality of life.

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