

**Review Article****Pulmonary hypertension; aetio-pathogenesis, current treatment and future prospects**

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ABSTRACT

Pulmonary hypertension (PH) is a vascular disorder characterized by pulmonary vascular remodeling and increased pulmonary vascular resistance, ultimately resulting in pressure overload, dysfunction, and failure of the right ventricle. Current medications for PH do not reverse or completely prevent disease progression, and current diagnostic strategies are suboptimal for detecting early-stages of the disease. One way to optimise the management of PH patients is the use of combination therapy. Another approach to the optimisation of PH management is the development of novel treatments and therapeutic strategies that will provide further opportunities to improve outcomes for PH patients. This article discusses the current and recent advancements in the aetio-pathogenesis and treatment of this disorder.

Keywords: Pulmonary, hypertension, endothelin, natrikinase, blood pressure, connective

Introduction

According to the World Health Organization (WHO) the PH has been categorized into five major groups based on clinical associations and histologic appearance [1–3]. The first group comprises a severe form of this disease that has idiopathic, heritable, and comorbid etiologies for e.g., connective tissue disorders, HIV infection, schistosomiasis, and are termed pulmonary arterial hypertension (PH) [1]. PH results from the obliteration of pulmonary arterioles, thereby causing an increase in the pulmonary vascular resistance, subsequent right ventricular hypertrophy, and culminating as right heart failure [4]. Histologically, this panvasculopathy demonstrates intimal hyperplasia, medial hypertrophy, adventitial proliferation, and pathognomonic plexiform lesions in pulmonary arterioles [5]. PH is a rare disease with an estimated prevalence of 15 cases per million patients. The diagnosis is based on pressure measurements by right heart catheterization and defined as mean pulmonary artery pressure of 25 mm of Hg and pulmonary artery wedge pressure of 15 mm of Hg. In patients of idiopathic

pulmonary fibrosis the incidence of PH increases dramatically. Hypoxia plays a role in idiopathic pulmonary fibrosis and reactive oxygen species may contribute to enhancement in the incidence of PH. Endothelin (ET-1) is a key mediator in pulmonary vascular biology and physiology [6]. Abnormal increases in ET-1 production and decreased pulmonary clearance appear to play a major pathogenetic and perpetuating role in the pulmonary hypertensive process, through their vasoconstrictive, smooth muscle cell proliferative and profibrotic effects. The degree of overexpression of ET-1 may correlate with the severity of pulmonary hypertension. Multiple factors contribute in the aetiopathogenesis of PH and the treatment is also multipronged based on the predisposing factors and the mediators involved (refer Fig.1). This article encompasses the recent trends in the aetiopathogenesis of this disorder and the future prospects for treating PH.

Clinical presentation in PH:

PH is generally difficult to diagnose. Infact, the average time from onset of symptoms until diagnosis was initially found to be two years and, despite increased awareness of the mediators and

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pathogenetic factors involved in PH, more recent studies have shown this delay remains unchanged. The initial symptoms are nonspecific and include lethargy, malaise and exercise intolerance, and are often misdiagnosed as reflecting a degree of unfit. Dyspnoea can be possibly mistaken as asthma, but as the disease progresses more ominous signs reflect right heart dysfunction with exertional syncope and angina. This latter symptom is often due to subendocardial hypoperfusion and increased myocardial oxygen demand. Physical examination in the early stages of disease can be normal. The first sign is an increased intensity of the second heart sound, which is subtle and easily missed. A left parasternal heave may be felt as the right chambers hypertrophy, and as the ventricle fails, peripheral oedema, ascites and elevated jugular venous pressure can result. Tricuspid regurgitation can be heard as a pansystolic murmur accentuated on inspiration and this leads to pulsatile hepatomegaly [7-9].

ET-1 and pulmonary fibrosis: ET-1 is a strong vasoconstrictor that has been implicated in both Group I PH and pulmonary fibrosis. ET-1 was found to be produced in the vascular endothelium of patients with both PH and lung fibrosis but not in normal lung or in those patients solely with fibrosis [10]. This increase in ET-1 levels was also seen in the plasma of patients with Group I PH and was correlated with increased mean PAP. ET-1 expression is also elevated in the airway epithelium of patients with IPF [11]. ET-1 acts in several pathways; canonically it binds two ET receptors on vascular smooth muscle cells activating calcium signaling and vasoconstriction; ET-1 can also stimulate proliferation, as well as growth factor and extracellular matrix production [12]. The endothelin receptor antagonists bosentan and macitentan have been shown to reduce both the fibro-proliferative injury and PH in the rat bleomycin model of pulmonary fibrosis with PH. This also correlated with an increased exercise capacity [13]. A potential activator of ET-1, the RhoA pathway, and downstream effectors Rho-kinases I and II (ROCKs) have been associated with the development of PH in several animal models including bleomycin, hypoxia, and monocrotaline [14]. In fact, treatment of the mouse bleomycin model of pulmonary fibrosis and

PH with fasudil, a selective ROCK inhibitor, not only reduced the PH hallmarks of vascular remodeling and right ventricle systolic pressure but also reduced lung fibrosis [15-16]. Numerous studies have confirmed the prominent role of abnormalities in ET-1 in the pulmonary hypertensive process. Patients with primary pulmonary hypertension (PPH) have been shown to have elevated circulating levels of ET-1, with higher arterial than venous levels, suggesting increased pulmonary production. Some investigators have found that levels of ET-1 correlate with the severity of pulmonary hypertension. Ambrisentan (manufactured under the trade names Letairis in the U.S., Volibris in the European Union, and Pulmonext in India) is an FDA-approved oral formulation for treating patients with pulmonary hypertension (PH). Chemically, it is denoted as (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid, and is an endothelin receptor antagonist (ETA), selective for the endothelin type-A (ET_A) receptor. It is recommended for use in patients with WHO classes II and III symptoms of pulmonary arterial hypertension, to improve exercise ability and delay clinical worsening.

Hypoxia inducible factor as a target for treatment of PH: The role of HIF in the pathogenesis of PH is well-documented with its inappropriate induction resulting from a failure of prolyl hydroxylases (PHDs) in facilitating proteasomal degradation of the HIF-1 α /HIF-2 α subunit [17]. Specifically, HIF activation under normoxic or hypoxic conditions is important in the development of WHO Group I PH and Group III hypoxia-induced PH, respectively, with possible contributions to other PH subtypes as well. The role of HIF under conditions of hypoxia and in the pathogenesis of PH has been reviewed [18]. Studies have demonstrated the pathogenic potential of HIF-1 α /HIF-2 α by demonstrating protection from chronic hypoxia and resistance to the development of hypoxia-induced PH in mice heterozygous for either subunit [19]. Other animal models such as the fawn-hooded rat (FHR) demonstrated inappropriate HIF induction under normoxia and a predisposition to develop PH [20]. Additionally, normoxic HIF activation was observed in pulmonary artery smooth muscle cells (PASMCs) from patients with PH. Taken together, the

induction of HIF under normoxia or hypoxia lays the foundation through which subsequent molecular, cellular, and metabolic events occur in idiopathic PH and hypoxia-induced PH, respectively.

Therapies targeting iron deficiency:

There is evidence that iron homeostasis is important in PH, with studies indicating that iron deficiency is common in the patients of PH [21], and is associated with reduced exercise capacity and increased mortality [22]. Worsening of iron deficiency has been shown to correlate with increased disease severity, as assessed by increased mean pulmonary artery pressure, reduced cardiac index and worsening functional class in idiopathic PH patients [23]. Iron deficiency is also a finding in patients with heart failure, and likewise is associated with poor survival and reduced exercise capacity [24-25]. This deficit in exercise capacity can be reversed by iron supplementation. These findings provide a rationale for therapeutic interventions to address iron deficiency in PH patients. To date, the clinical benefit of iron infusions in PH patients has been demonstrated in two small exploratory studies. Although the results of these small studies are promising, it should be noted that low serum iron may offer a protective role in the development of pulmonary hypertension [26]. Thus, randomised controlled trials of iron supplementation in PH patients are warranted to ensure that the impact of addressing iron deficiency in PH can be fully elucidated [27-28].

Nattokinase and combination with other drugs as a novel therapeutic for PH :

Nattokinase is a potent fibrinolytic enzyme that effectively breaks down fibrin strands and thrombi. Nattokinase can both hydrolyze fibrin in blood clots directly and hasten the production of t-PA also known as tissue Plasminogen Activator, which activates plasminogen into active plasmin to hydrolyze fibrin [29]. Decreasing blood viscosity strikes at the root of arteriosclerosis and atherosclerosis as well as hypertension, peripheral vascular disease and congestive heart failure. The fibrinolytic activity of nattokinase resolves the active process of atherosclerosis and lyses the thrombi. The per oral administration along with prolonged half-life of 4-6 hours and extremely safe

profile show favorably upon nattokinase as the key agent for restoration of vasculature health. A combination therapy of nattokinase and endothelin receptor antagonist may be beneficial in the PH and in particularly the cases with IPF or the heart dysfunction [30].

Soluble guanylate cyclase stimulators:

Riociguat is a soluble guanylate cyclase stimulator, and currently the only drug of this class available for the treatment of PH. It directly stimulates guanylate cyclase, and has a synergistic action with endogenous nitric oxide. In the PATENT-1 study, riociguat use increased the distance covered in the six-minute walk test as the primary endpoint, as well as reduced morbidity, improving haemodynamics at right heart catheterisation and reducing NTproBNP levels. Adverse effects include bleeding, dyspepsia/reflux, acute kidney injury, elevation in liver enzymes and hypotension. Riociguat is also the first licensed agent for use in patients with inoperable chronic thromboembolic pulmonary hypertension, including for those who are unfit for pulmonary endarterectomy surgery and those who have persistent elevated pulmonary arterial pressure thereafter [31].

Tyrosine kinase inhibitors

Chemotherapy is commonly used as a front-line therapy for treatment of cancers. Tyrosine kinases inhibitors, including Imatinib and Dasatinib, have been successfully employed in the treatment of chronic myeloid leukemia. In addition to inhibit the BCR-ABL kinase, these inhibitors target other tyrosine kinases including c-KIT and PDGF receptor. Because c-KIT-positive cells infiltrate remodeled vessels and PDGF expression is elevated in lung biopsies of PH patients, studies were undertaken to evaluate the therapeutic benefits of Imatinib and its derivative in preclinical models [32-33]. Imatinib treatment demonstrated remarkable efficacy in several experimental models with established PH, reducing right ventricular systolic pressure and hypertrophy, medial wall thickness, and mortality [34-35]. Similar results were obtained with Dasatinib [36] Despite these remarkable results achieved in pre-clinical PH models, mixed results were obtained in humans. Results from clinical trials indicated that Imatinib is effective in improving exercise capacity, pulmonary hemodynamics, and echocardiographic

measures as add-on therapy in patients with severe PH. Nevertheless, the risk of clinical worsening was enhanced in Imatinib-treated patients likely because of adverse effects. Notably,

cardiotoxicity and occurrence of subdural hematoma in PH-treated patients has tempered the positive reports, discouraging the use of these compounds in PH [37-38]

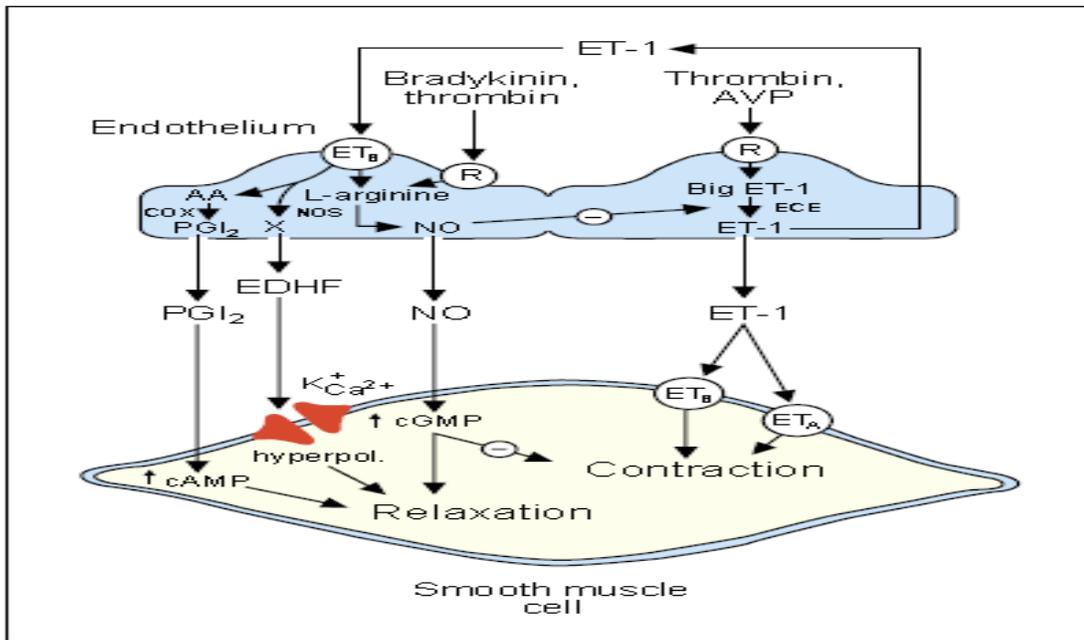


Fig.1: Mediators in pulmonary hypertension

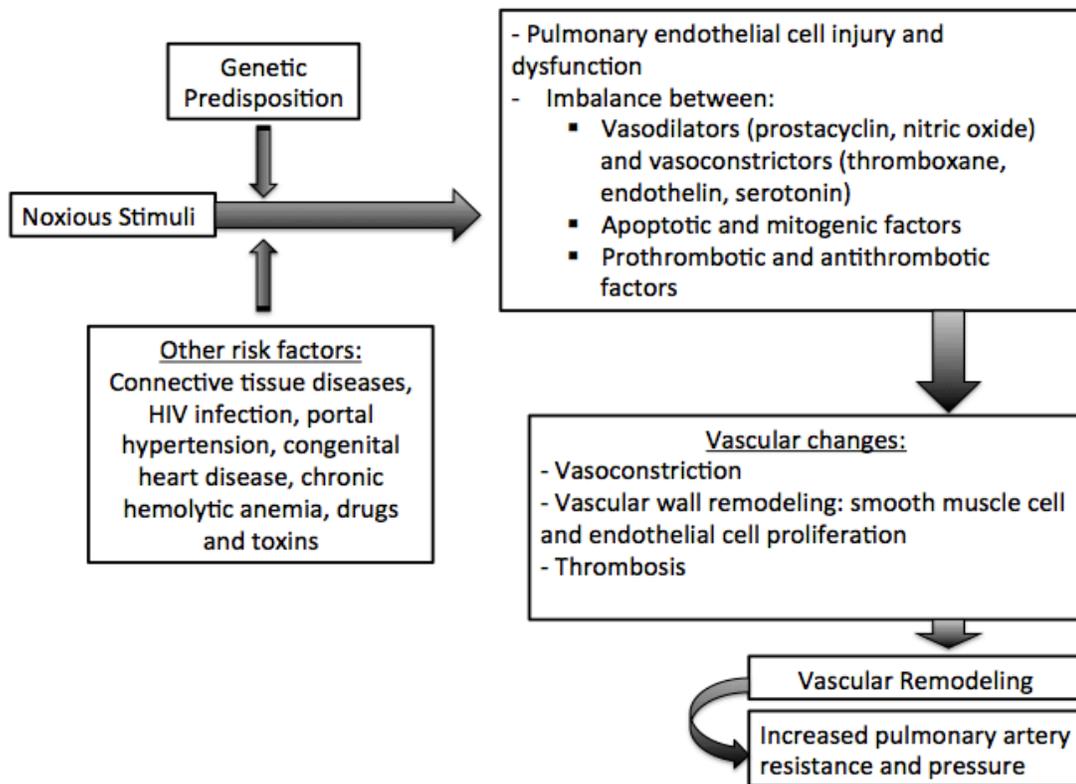


Fig.2: Pulmonary hypertension pathophysiology (Courtesy, Drs. C. Michael Gibson, M.S., M.D., Ralph Matar; Rim Halaby, Wikidoc)

Calcineurin inhibition and PH:

The use of nonspecific calcineurin inhibitors that prevent the dephosphorylation and thereby translocation of NFAT, such as the immunosuppressant drugs like cyclosporin A and tacrolimus, are potential therapeutic candidates. A selective NFAT peptide inhibitor, VIVIT, specifically inhibits the docking of calcineurin onto NFAT instead of broad calcineurin inhibition, thereby limiting the adverse effects of nonspecific inhibitors [39]. One study demonstrated inhibition of NFAT using cyclosporin A or VIVIT in vitro increased Kv1.5 expression, reduced intracellular potassium and calcium levels, decreased mitochondrial membrane potential, and attenuated expression of bcl-2 [40]. The use of cyclosporin A in MCT-induced rat model produced a decrease in pulmonary vascular resistance and pulmonary arterial pressure, while increasing cardiac output [41]. Additionally, administration of low-dose tacrolimus restored signaling through the BMPR2, and reversed severe PH in the MCT-induced model and in the VEGF receptor blockade/chronic hypoxia model, suggesting potential clinical benefit with low-dose therapy [42].

New therapies for PH: The ongoing clinical research studies are aimed at treating PH in a curative and reversible manner. Targeting certain specific enzymes could hold the key to cure hypertension in general [43]. The Potassium sparing diuretic, spironolactone has been evaluated in at least two trials as either as monotherapy or in combination with ambisentan. The current therapies tend to slow down the progression of the disease but cannot completely cure it. Many new drugs form the prospective future therapies which can potentially cure PH. These are aimed at targeting the metabolic or inflammatory approaches and have agents like L-citrulline, a NO dependent stimulator and shows promise in hemodynamics and the quality of life improvement [44]. Another good candidate is the protease inhibitor Ubenimex and oral selective IP receptor agonist ralinepeg and QCC374. There is also recent research into autologous progenitor cell based gene therapy.

Conclusion:

Pulmonary hypertension is a multifactorial anomaly and requires adequate medical care and specific treatment of the causes. Although significant progress has been made in the treatment of PH via the development of drugs that target key patho-physiological pathways, although management remains suboptimal for many patients (refer Fig.2). The complexity surrounding metabolite heterogeneity in PH patient populations can be addressed with novel applications of current technology, such as nuclear magnetic resonance, mass spectrometry, and chromatography. A recently published study utilized high-performance liquid and gas chromatography in combination with mass spectrometry in PH and control populations to examine metabolic fingerprints. It is imperative that research continues into novel treatments in PH to further improve outcomes for patients. Such research should extend to investigating targets beyond the signalling pathways already subject to pharmacological intervention. Furthermore, evolving pre-clinical studies and clinical trial designs hold promise for the continued development of treatment strategies in PH.

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