Pulmonary arterial hypertension in human immunodeficiency virus infections

Tushi Singh MD, Arunee Motes MD, Myrian Vinan-Vega MD, Kenneth Nugent MD

ABSTRACT

Pulmonary arterial hypertension (PAH) is an important health issue in the twenty-first century. The introduction of highly active retroviral therapy has prolonged survival in patients infected with the human immunodeficiency virus (HIV), and this has led to the emergence of new health issues, including PAH, in those patients. This review considers the advances in understanding the pathophysiology of PAH in HIV infections and the approaches to the treatment of these patients.

Keywords: Pulmonary arterial hypertension, HIV, pathophysiology, treatment

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening condition characterized by an elevated mean pulmonary artery pressure of at least 20 mm Hg on supine right heart catheterization at rest and pulmonary vascular resistance of 2 Wood units or greater with a pulmonary artery wedge pressure of 15 mm of Hg or less.[1] The estimated prevalence of PAH is 10.6 per 1 million adults in United States of America.[2] The current classification of pulmonary hypertension is outlined in the Table.[3]

EPIDEMIOLOGY

Human immunodeficiency virus-associated PAH is subclassified under Group 1.4.2 (see Table 1). Studies from before the highly active anti-retroviral therapy (HAART) era, notably by Opravil and colleagues in 1991, reported a prevalence of PAH in HIV patients at 0.5%.[4] Studies in the post-HAART era have reported a prevalence of PAH in HIV at 0.46% compared to the 10 per 1 million in the non-HIV general population.[5,6] This contrasts with the prevalence of HIV-associated PAH in Africa, which varies from 5% to 13%.[7] This is important since Africa has a high prevalence of HIV-infected individuals.[8] However, these studies were all completed prior to the revised definition of PAH in 2019. The current prevalence of HIV-PAH could be higher, and with improved survival in HIV patients could increase in the future. Patients with HIV-associated PAH have a median survival of 1.3 years compared to 2.6-year survival in other patients with PAH.[9,10] All the studies report a male preponderance and higher frequency in intravenous drug abusers.[4,5,11–14] However, the role of intravenous drug use as an independent risk factor for PAH in HIV has been ruled out.[14,15] This complication occurs at all stages of HIV infection and does not seem to be related to the degree of immunosuppression.[13,15,16] This suggests that HIV-associated PAH could become a bigger public health issue in the future, if more HIV infections occur and survival improves.

PATHOPHYSIOLOGY

The pathogenesis of HIV-associated PAH is multifactorial. Human immunodeficiency virus infections affect small and medium-sized pulmonary arteries, and

Corresponding author: **Tushi Singh**
Contact Information: Tushi.Singh@ttuhsc.edu
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Table 1. Pulmonary Hypertension Classification

Group I	Group II	Group III	Group IV	Group V
Pulmonary arterial hypertension (PAH)	PH due to left heart disease	PH due to lung disease and/or hypoxia	PH due to pulmonary artery obstruction	PH with unclear and/or multifactorial mechanisms
1.1 Idiopathic	2.1 Heart failure with preserved LVEF	3.1 Obstructive lung disease	4.1 Chronic thromboembolic PH	5.1 Hematologic disorder
1.2 Heritable	2.2 Heart failure with reduced LVEF	3.2 Restrictive lung disease	4.2 Other pulmonary artery obstruction	5.2 Systemic disorders and metabolic disorders
1.3 Drug and toxin induced	2.3 Valvular heart disease	3.3 Other lung disease with restrictive and obstructive pattern		5.3 Others, e.g., fibrosing mediastinitis
1.4 Associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis	2.4 Congenital or acquired cardiovascular conditions leading to post capillary PH	3.4 Hypoxia without lung disease		5.4 Complex congenital heart disease
1.5 Long term responders to calcium channel blockers		3.5 Developmental lung disease		
1.6 With overt features of venous/capillary involvement				
1.7 Persistent PH of the newborn				

the majority of the cases have plexogenic arteriopathy. Histological studies have not found the virus in pulmonary vessels.[17] This led to studies on HIV-associated proteins and other factors which might contribute to the pathogenesis of this complication. Palakeel et al. listed six possible pathogenic pathways:[18] 1) HIV proteins; 2) Inflammatory cytokines; 3) NADPH oxidase enzymes (NOX) and reactive oxygen species (ROS); 4) Other viruses; 5) Genetic factors; 6) Illicit drug use.

HIV PROTEINS

The HIV-1 transmembrane glycol protein 120 (GP 120) is required for viral entry into CD4 T lymphocytes. After GP 120 is bound, it triggers the activation of chemokines CXCR4 and CCR5 which stimulate the release of inflammatory cytokines and causes apoptosis. Studies show that CCR5 promotes apoptosis, and CCXR4 results in resistance to apoptosis.[19]

The HIV-Nef protein helps the virus evade the host immunity, and Nef causes endothelial cell death by apoptosis.[20,21] This releases inflammatory cytokines and vascular endothelial growth factor (VEGF), which causes impairment of endothelium-mediated vasodilation.[22] The initial endothelial cell death is followed by formation of complex plexiform and obliterated angio-proliferative lesions linked to a severe form of PAH.[23–26] HIV transactivator of transcription (Tat) is necessary for viral replication. This protein attaches to VEGF-A, a tyrosine kinase receptor, and this activates angiogenesis leading to endothelial cell proliferation.[25,26] These viral proteins persist despite an undetectable viral count with the use of anti-retroviral therapy.[27]

Inflammatory cytokines, NOX and ROS

Human immunodeficiency virus infections trigger an inflammatory cascade, and the major cytokines are IL-6, IL-1-beta, TNF-alfa, and macrophage inflammatory protein-1(MIP-1) (26,28). These cytokines act on the endothelium and stimulate p38 mitogen-activated protein kinases and NF-KB pathway, thus inducing ROS production. Growth factors, like VEGF, PDGF and FGF, are responsible for the migration, proliferation, and angiogenesis of endothelial cells and smooth muscle cells.[28]

Oxidative stress is a major cause of vascular dysfunction in PAH pathogenesis.[25,29] NADPH oxidase (NOX) generates reactive oxygen species in the pulmonary vasculature and alveolar epithelium. Chronic exposure to HIV protein, Tat in particular, causes the transition from autophagy dependance to an apoptosis resistant hyperproliferative state.[29] Studies by Agarwal et al. showed that ROS formation is high at the early stage and declines with chronic exposure resulting in decreased cell death.[26,29] Estrogen inhibits ROS generation in human umbilical endothelial cells, and studies in transgenic mice have reported low NADPH oxidase activity in female mice and a lower incidence of experimental PAH in them.[29,30] Ehrenreich and colleagues found that GP 120 stimulates the secretion of endothelin-1 (ET-1) and other cytokines. They found a distinct expression of the ET-1 gene in HIV-infected individuals, suggesting a possible role in the pathogenesis of HIV- associated PAH.[31]

Reactive oxygen species (ROS) generated by the NADPH oxidase system have a significant role in pulmonary vascular remodeling. This oxidative process disrupts the cellular architecture thus decreasing endothelial resistance, eventually causing disintegration of the pulmonary vessels.[32] During periods of oxidative stress, viral replication increases, and this increases vascular injury. Another factor is the formation of peroxynitrite from NOX enzymes, which regulates VEGF and thus stimulates angiogenesis.[33]

Viruses

Several viral infections accelerate the progression of HIV-PAH. Hepatitis C virus (HCV) is responsible for dysregulation of micro-RNAs to advance the disease. Micro-RNAs are non-coding RNA molecules and are increased in HIV, HIV-PAH, and HCV coinfected patients compared to the uninfected patients. These mi-RNA activate pro-inflammatory mediators and upregulate the inflammatory cascade, resulting in extracellular matrix modelling, cellular proliferation, and PAH.[34,35] Human herpervirus-8 is also implicated in HIV-PAH. The virus affects angiogenesis, inflammation, and apoptosis pathways by downregulation of BMPR-2 pathway.[36] Hepatitis B, cytomegalovirus, and *Pneumocystis jirovecii* have also been studied for a potential role in HIV-PAH.[37]

Genetics and illicit drugs

Cocaine and morphine have been shown to affect pulmonary vascular endothelial dysfunction and smooth muscle proliferation. This is mediated by cytokines and platelet derived growth factors.[38,39] Genetic factors may also have a role since HLADR5 and HDL-DR6 alleles have a high prevalence among HIV, and it has been postulated that individuals with these alleles may have an autoimmune basis for PAH.[40,41]

In summary, HIV-associated proteins have a critical role in development of PAH. Studies have demonstrated the causal relationship between HIV and PAH

and the increased risk of pulmonary hypertension in patients with high viral loads and low CD4 counts. This suggests that anti-retroviral therapy should reduce the risk of PAH. Co-infection with other pathogens and illicit drug use also contribute to the development of PAH in HIV infections.

Clinical presentation

Patients often present with vague and nonspecific symptoms, and this can lead to a delay in diagnosis. A study by Mehta et al. in 2000 reported that progressive dyspnea was the most common symptom. This was followed by pedal edema, cough, fatigue, syncope; the least frequent symptom was chest pain.[42]

Management

Diagnosis

The clinical investigation of patients with possible HIV-PAH should include an electrocardiogram, which may reveal right axis deviation, right ventricular hypertrophy, and/or right bundle branch block.[42] A chest x-ray often shows enlarged pulmonary arteries and helps exclude other causes of pulmonary hypertension, such as chronic obstructive pulmonary disease and interstitial lung disease. The 2018 World Symposium of Pulmonary Hypertension recommended that any patient with HIV and one of the following risk factors should have echocardiographic screening. These include female sex, intravenous drug use/cocaine use, hepatitis C infection, origin from a high prevalence country, known Nef or Tat HIV proteins, and African American patients independent of symptoms.[43]

Right heart catheterization is the gold standard for confirmation of the diagnosis and also mandatory prior to initiation of PAH specific therapy.[1] During the catheterization, the pulmonary artery pressures, the right atrial pressure, pulmonary artery wedge pressure, and cardiac output should be measured. This information allows the calculation of cardiac index and pulmonary vascular resistance. This helps confirm the diagnosis and assess the prognosis as well.

Treatment

Antiretroviral treatment

Anti-retroviral therapy (ART) is the essential step in HIV management and has resulted in increased longevity of these patients. A large French cohort study suggested that ART therapy did not change the prevalence of HIV-PAH.[5] However, another prospective study showed that initiation of ART improved PA pressures if done in early stages (WHO Classes I and II).[44] However, this same effect was not present in advanced stages. Quezada et al. reported that the presence of HIV RNA leads to increased risk of development of HIV-PAH.[45] The recent Veterans Aging Cohort Study (VACS) reported that low CD4 counts and high viral loads contribute to the increased risk of pulmonary hypertension in HIV, thus making a case for HIV suppression.[46] Antiretroviral therapy can cause insulin resistance and dyslipidemia, and these adverse effects could affect pulmonary vessels.[46] This possibility needs more investigation.

Data for the effect of ART on HIV-PAH may be controversial, but current guidelines recommend ART irrespective of the CD4 counts.[47] It remains to be seen if one regimen of HAART is superior to others in management of HIV-associated PAH. The CCR5 pathway has been explored as a therapeutic target for HIV-associated PAH.[48]

General measures should include diuretics for hypervolemia and supplemental oxygen for hypoxemia. If vasoreactivity testing is positive during right heart catheterization, then calcium channel blockers should be used.

PAH therapy

Phosphodiesterase inhibitors

These drugs inhibit the degradation of cyclic guanosine monophosphate, which results in vasodilation. Several studies have reported benefits with sildenafil in HIV-PAH.[49] Sildenafil and tadalafil are metabolized by cytochrome P(CYP) enzymes, but initial concerns about detrimental drug interactions with protease inhibitors were reduced in later studies.[50]

There are now guidelines on modulating the doses of PDE inhibitors when a protease inhibitor is started.[51]

Endothelin receptor antagonists

Sitbon et al. demonstrated improvement in exercise capacity, quality of life, hemodynamics, and echocardiography variables with 16 weeks of bosentan.[52] Ambrisentan and macitentan have replaced bosentan due to a lower frequency of liver function abnormalities and fewer drug interactions with ART.[53]

Prostanoids

Aguilar et al. reported beneficial effects with epoprostenol in HIV-PAH; this drug causes significant long-term decreases in pulmonary artery pressures. There were concerns about the risk of infectious complications with an indwelling central venous catheter.[54] With the development of subcutaneously administered and inhaled prostacyclin analogues, these risks have been overcome to some extent. Ghofrani et al. reported improved 6-minute walk distance tests and pulmonary vascular function with inhaled ilioprost.[55]

Prognosis

The development of PAH is an independent predictor of death and poor outcomes in patients with HIV infection.[11] Poor HIV control (low CD4 counts), NYHA class IV, and reduced cardiac index are associated with decreased survival. The REVEAL registry showed that survival in HIV-PAH may be better than that of other forms of PAH.[1] Some reports have suggested that PAH therapy even cured HIV-PAH in a few individuals.[56]

Conclusion

Pulmonary arterial hypertension is an important complication in patients with HIV and creates a significant disease burden. Its pathogenesis is multifactorial, and some of the factors are still not fully understood. Biomarkers of the disease are an important area of research and might reveal specific markers that can be tested for diagnosis and risk stratification. Pulmonary arterial hypertension therapy in HIV has been important in improving patients' quality of life and longevity. With the approval of the activin inhibitor, sotatercept, there is optimism that newer therapies will result in better outcomes for HIV-PAH.

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From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas
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