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Associated PAH

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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This issue of *Advances in Pulmonary Hypertension* highlights several associated conditions causing pulmonary arterial hypertension (PAH) that are of particular relevance globally and deserve to be on our radar: schistosomiasis, Human immunodeficiency virus (HIV), and liver disease. These well-known conditions provide unique challenges to our understanding and treatment of PAH.

Schistosomiasis affects a shocking 200 million or more throughout the world, with 5-10% developing PAH. Yet it can be easy to forget that schistosomiasis is cause of Group I PAH. Brian Graham reviews the background, mechanisms, diagnosis, and treatment schistosomiasis-associated pulmonary arterial hypertension. Graham leaves us with several cutting-edge questions yet to be answered regarding this disease.

Nicholas Kolaitis and Christopher Barnett provide us with an updated review on HIV-associated PAH. They take us through epidemiology, pathogenesis, and the impact of antiretroviral therapy. The approach to treatment includes a critical review of drug-drug interactions between HIV and PAH medications.

Rosechelle Ruggiero and Sonja Bartolome deliver a focused review of portopulmonary hypertension for the treating provider. They take us through current definitions, clinical features, and management with a crucial focus on special considerations for liver transplantation.

We gratefully thank all of our contributing authors for sharing their knowledge and insights. As the world shrinks, and our knowledge of mechanisms of disease and treatment grow, these articles are timely and well worth the read.

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REGULAR ARTICLE

Schistosomiasis-Associated Pulmonary Arterial Hypertension

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Schistosomiasis is a major cause of group 1 pulmonary arterial hypertension (PAH) worldwide. Schistosomiasis results from a parasitic infection present in over 200 million individuals worldwide. Schistosomiasis-associated PAH was initially thought to be obstructive due to egg embolization but has a pulmonary vascular pathology like other forms of group 1 PAH and can be treated using conventional PAH therapies. Mechanisms that underlie the development of schistosomiasis-associated PAH include type 2 inflammation which triggers TGF-β signaling; importantly, TGF-β signaling is a pathway shared with other PAH etiologies. However, many things which are unknown about this disease remain, including if the lung vascular pathology results from egg embolization causing localized inflammation and vessel remodeling, or if this is a form of portopulmonary hypertension resulting from schistosomiasis liver disease.

SCHISTOSOMIASIS BACKGROUND

Schistosomiasis (bilharzia) is one of the etiologies of group 1 pulmonary arterial hypertension (PAH) per the current classification system,[1] although it is perhaps the least understood despite being one of the most common causes. Schistosomiasis is the clinical disease that results from infection with parasitic flatworms (nematodes) of the *Schistosoma* genus. Three *Schistosoma* species cause >95% of disease: *S. mansoni*, *S. haematobium*, and *S. japonicum*. Schistosomiasis is endemic in 51 countries worldwide, with about 90% of the disease burden in sub-Saharan Africa.[2]

Schistosoma have a mandatory 2-host lifecycle, with a snail intermediate host. Snail species are specific for each *Schistosoma* species. Infected snails release the cercariae lifeform of the parasite, which lives about 24 hours in fresh water. Humans are infected by exposure to contaminated water, with cercariae penetrating the skin within about 5 minutes, leaving behind a punctate rash (cercarial dermatitis). The parasite then migrates from the subcutaneous tissue to the systemic veins and then to the lungs, causing a hypersensitivity reaction (Katayama fever) characterized by fevers, cough, chest x-ray infiltrates, and eosinophilia: This syndrome may develop in travelers to endemic settings. After a few weeks, the parasites migrate to the target organ: In the case of *S. mansoni* and *japonicum*, this is the portal venous system; *S. haematobium* migrates to the bladder venous plexus. Here, the mature worms mate and release eggs, from several hundred up to 5000 per day for a *S. japonicum* worm pair. Most of the eggs erode through the intestinal or bladder wall to enter the feces or urine, where after excretion, they infect snails and complete the lifecycle. Eggs retained within the host cause inflammation and immunopathology. The worms have evolved many tactics for evading the host immune system[3] and can live for years or decades in the host while continually laying eggs.

CURRENT STATE OF SCHISTOSOMIASIS

Schistosomiasis is considered a neglected tropical disease. In 2019 (the most recent year worldwide figures are available), it was estimated 237 million individuals (about 3% of the global population) *required treatment*, i.e., were either actively infected or at high risk for infection with the parasite.[2] Of these, 105 million were treated. Praziquantel is the antihelminthic medication most used. It is effective against adult but not juvenile parasites; thus, acutely infected individuals need to receive 2 doses about 6 weeks apart. Praziquantel resistance can be induced in laboratory settings[4] but has not (yet) been reported clinically.

Substantial progress in schistosomiasis control has been made in recent years through public health efforts, including clean water, sanitation, and hygiene preventative measures and mass drug administration particularly of school age children in at-risk settings.[5] Unfortunately, the disease generally has highest prevalence in the regions which are most impoverished, often rural and with limited health care access, leading to concerns about substantial underestimates of the worldwide burden.[6] Environmental change with global warming is shifting the distribution of *Schistosoma* and its snail species, and public infrastructure projects such as dam construction for hydroelectric power or irrigation is changing the endemic territory.[7]

HISTORY OF SCHISTOSOMIASIS-ASSOCIATED PULMONARY HYPERTENSION

Schistosome eggs were initially reported in lung tissue in the 1880s[8] and then associated with pulmonary vascular disease in the 1930s in reports from Egypt.[9] In this era before the development of antihelminthics, autopsy specimens from individuals who died of schistosomal pulmonary hypertension (PH) often

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demonstrated huge numbers (>100/section) of intravascular parasite eggs in addition to remodeled vessels with thickened media and intimal layers.[10] Based on this histopathology, at the time, schistosomal PH was ascribed to potentially be a combination of an embolic or obstructive disease and vascular remodeling. The first PH World Symposium (Geneva, 1973) categorized schistosomiasis-PH as embolic (group 3, at the time).[11] The second World Symposium (Evian, 1998) categorized schistosomiasis-PH as "directly affecting the pulmonary vasculature" (group 5),[12] and the third World Symposium (Venice, 2003) categorized it under embolic obstructive disease (group 4).[13]

At the Dana Point symposium (2008), the classification of schistosomiasis-PH was changed to an etiology of group 1 PAH,[14] and it has remained in group 1 subsequently. The rationale for assigning schistosomiasis to group 1 is multifactorial. Schistosomiasis-PAH (hereafter abbreviated SchPAH) patients often have a similar clinical presentation to idiopathic PAH (IPAH). The characteristic pulmonary vascular lesions found in IPAH are also present in SchPAH, including plexiform lesions.[15] These pulmonary vascular lesions are still present in modern autopsy series after the widespread use of praziquantel, but no significant eggs are present.[16] Evidence of shared underlying pathobiology exists, including altered TGF-β family signaling (see below). SchPAH patients also benefit from treatment with conventional PAH therapies, although these data are from smaller and generally retrospective series (see below).

PREVALENCE

Some of the eggs laid by worms that make their homes in the portal veins (all species other than *S. haematobium*) embolize into the prehepatic sinusoids, causing preportal fibrosis termed hepatointestinal schistosomiasis (HSS). HSS causes portal hypertension, like that seen in portopulmonary hypertension (PPHTN), and it is thought that HSS substantially increases the risk of developing SchPAH potentially as a form of PPHTN. *S. mansoni* is the species most clearly associated with SchPAH, and it has been estimated that approximately 5%–10% of those with chronic *S. mansoni* infection develop HSS.[17–19] On histopathology, it was observed that about 24% of individuals with HSS had evidence of pulmonary vascular disease.[20] By echocardiography, it was estimated that 11% of those with HSS had SchPAH.[21] By right heart catheterization (RHC), one study found that 21% of those with HSS had a mean pulmonary artery pressure (mPAP) > 20 mm Hg (the revised threshold), and 4 (12%) had a mPAP > 25mm Hg (the prior threshold), all with a normal wedge pressure.[22] Another study identified 18% of those with HSS had the suggestion of PH on echocardiography, of whom 5% were ultimately found to have SchPAH on RHC (using the mPAP ≥ 25 mm Hg threshold).[23] Overall, about 5%–10% of those with HSS may develop SchPAH, depending on the specific population, diagnostic test, and threshold. If 5% of those with schistosomiasis develop HSS and 5% of those develop PAH, that is 0.25% prevalence among all those with schistosomiasis, making this an uncommon complication of chronic disease. However, this also equates to a SchPAH prevalence of about 500,000 individuals, or about 64 per million worldwide, making it a relatively common cause of group 1 PAH.

DIAGNOSIS OF SCHPAH

The diagnostic criteria for SchPAH are not well established. Generally, the following 4 criteria are used:

1. PAH, by RHC using standard criteria.
2. At least 1 of the following:
   a. exposure to an endemic region for schistosomiasis,
   b. history of previous treatment for schistosomiasis, or
   c. history of or presence of *Schistosoma* eggs on stool examination or on rectal biopsy.
3. Liver ultrasound consistent with SchHSD, including left lobe enlargement and/or periportal fibrosis.
4. No evidence of other identified PH etiologies.

Practically, however, some major issues with these criteria exist. Foremost, RHC is not widely available in the areas where schistosomiasis is most endemic. The requirement for prior schistosomiasis exposure or infection is subject to recall bias and does not establish a clear causal relationship between prior infection and subsequent PAH development. The requirement for liver disease misses cases from *S. haematobium* or those that may occur in the absence of liver disease. Lastly, often, limited resources are available for a systematic evaluation for other PH etiologies in endemic settings.

In developed settings such as PH clinics in the United States, the diagnosis of SchPAH is sometimes considered among patients being evaluated who have a history of schistosomiasis or who have previously lived in endemic settings. If uncertainty in exposure history exists, serologic testing can be performed, although some serologic tests have species specificity. Serologic testing is less useful if the individual is known to come from a very high prevalence region, as it is almost certain to be positive.

Individuals may have active infection even if they have not been in an endemic area for many years, due to the long-lived nature of the parasite. Suggestive signs and symptoms include eosinophilia and blood in the urine (*S. haematobium*) or stool (other *Schistosoma* species), which can be screened by ova and parasite examination. It should be noted that microscopy has a relatively low sensitivity, particularly for low intensity disease. If there is concern for active infection, praziquantel can be administered: It is relatively safe, and a single dose is usually effective. One concern for side effects is if there are neurologic symptoms which may have resulted from egg embolization to the spine or brain (a condition called neuroschistosomiasis): Individuals with concern for this should be pretreated with steroids to avoid excessive inflammation.[24] If concern for HSS exists, abdominal ultrasound can be used to screen for periportal fibrosis; if periportal fibrosis is not present (and *S. mansoni* or *japonicum* are suspected, based on geography), SchPAH is less likely.

PROGNOSIS AND RESPONSE TO THERAPY

The clinical course of SchPAH may be more benign than IPAH or PH associated with connective tissue diseases,[25] even in the absence of specific PAH treatment.[26] Treatment-naïve SchPAH patients have been reported to have overall survival rates at 1, 2, and 3 years of 95%, 95%, and 86%, respectively,[26] although a more recent series from an endemic setting reported 1-, 3-, and 5-year survival estimates of 92%, 75%, and 51%, respectively,[27] figures closer to the prognosis in IPAH. A recent systematic review that included 18 studies concluded that SchPAH has a better prognosis than IPAH,[28] despite presenting with initially similar hemodynamics, although it should be cautioned that many of these patients were studied in nonendemic settings.

Patients with SchPAH should be treated as those with any other form of group 1 PAH. This conclusion is based on reports from clinicians in endemic settings and published case series and open-label studies, but SchPAH has generally not been included in prospective clinical trials of PAH therapeutics to date. Authors of one study compared survival between historical SchPAH patients (before PAH medications were available) and SchPAH patients receiving provider-selected medications and found that the newer, treated series had significantly better survival.[29] Authors of another study reported that sildenafil improved clinical and cardiac magnetic resonance imaging parameters in 7 SchPAH patients, including an improved 6-minute walk distance from an average of 114 to 335 m ($P < 0.0001$), and an improved right ventricular ejection fraction from an average of 33% to 43% ($P < 0.004$).[30] The same group reported 13 patients with SchPAH treated with sildenafil for 6 months had improved World Health Organization functional class ($P < 0.001$), the 6-minute walk distance improved from 121 to 394 m ($P < 0.0001$), and the average pulmonary artery systolic pressure on echocardiography decreased from 97 to 80 mm Hg, without significant adverse events.[31]

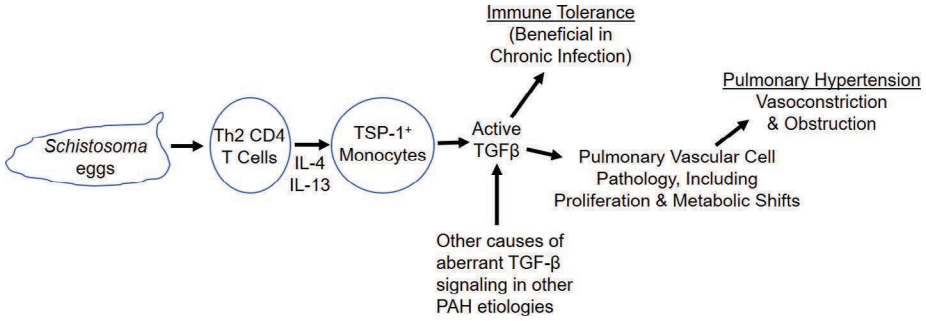

Figure: TGF-β signaling may function as a local immunosuppressant, benefiting the host with chronic schistosomiasis, but TGF-β signaling can also cause pathology in the pulmonary vascular cells resulting in pulmonary hypertension. Embolization of *Schistosoma* eggs to the lungs causes a type 2 immune reaction including the activation of CD4 T cells to a Th2 phenotype, resulting in the secretion of cytokines IL-4 and IL-13. This immune activation causes recruitment of classical monocytes which express the protein thrombospondin-1 (TSP-1), which has the functional ability to activate TGF-β. TGF-β causes a localized immune tolerance, which may be beneficial in the setting of a long-lived infection in which the host cannot effectively eradicate the parasite, through limiting the amount of tissue destruction. TGF-β also causes a pathology among the pulmonary vascular endothelial and smooth muscle cells, including excessive proliferation and changes in cellular metabolism, resulting in vasoconstriction and occlusion of the vasculature, and pulmonary hypertension. TGF-β signaling is a key step shared with other pulmonary arterial hypertension etiologies.

One major limitation in treating SchPAH worldwide is medication availability in endemic settings. In many countries, only PDE5 inhibitors are widely available; in some settings, there is access to endothelin receptor antagonists but only rarely prostacyclin analogues or other medications. Lung transplantation is also generally not available; occasionally atrial septostomy is performed as a rescue procedure. Otherwise, nonvasodilator therapies such as controlling volume status and pulmonary rehabilitation are similarly effective.

SCHISTOSOMIASIS-PH PATHOBIOLOGY: TYPE 2 INFLAMMATION TRIGGERS TGF-B ACTIVATION

Our current concept of schistosomiasis-PH is that the host immune system inadvertently causes the pulmonary vascular disease. *Schistosoma* parasites have evolved mechanisms to evade the host immune system, leading to very long-lived infections. In this setting, the host immune system needs to adapt to the infection without causing excessive tissue destruction in trying to kill the parasite. TGF-β is a classically immunosuppressive cytokine, and the host immune system may use TGF-β signaling as a counterregulatory mechanism to check the immune response to the parasite. Unfortunately, TGF-β also induces pulmonary vascular pathology, which is a shared pathway with many PAH etiologies including familial disease (eg, BMPR2 mutations), IPAH,[32] scleroderma-associated PAH[33] (Figure).

In mice, experimental PH can be induced by administering *Schistosoma* eggs directly to the lung vasculature. Modulating the egg dose to the lungs positively correlates to the PH phenotype, as was observed in $BMPR2^{+/-}$ mice having more liver disease, more egg embolization, and greater PH.[34] After embolization, the eggs induce a strong and localized type 2 immune reaction.[35] It is observed that remodeled vessels occur in proximity to the peri-egg granulomas,[36] suggesting the cytokines and immune cells responding to the eggs also cause the vascular disease.

Blocking type 2 immunity by using $IL\text{-}4^{-/-}IL\text{-}13^{-/-}$ mice suppressed the *Schistosoma*-PH phenotype.[35] More precisely, deleting IL-4 and IL-13 in CD4 T cells also suppresses the PH phenotype.[37] A key role of type 2 inflammation is the recruitment of circulating classical monocytes to the inflamed tissue. These monocytes express thrombospondin-1, which can locally activate TGF-β, and it has been observed that blocking monocyte recruitment or

thrombospondin-1 prevents *Schistosoma*-induced PH.[38]

Activation of TGF-β may benefit the host immune system through promoting regulatory immune mechanisms and acting as an immunosuppressant.[39] However, TGF-β is also toxic to the pulmonary vasculature: Among other effects, TGF-β induces proliferation of endothelial and smooth muscle cells,[40] including a metabolic shift of increased glycolysis which supports pathologic phenotypes.[41]

MAJOR OPEN QUESTIONS IN SCHISTOSOMIASIS-PH

Despite its relatively high prevalence, much is still unknown regarding SchPAH.

What Is the True Prevalence of SchPAH? Does SchPAH Occur in Species Other than S. mansoni?

Most of the literature in this field is from nonendemic settings, and systematic screening in high prevalence regions is lacking. Most clinical data in SchPAH are from Brazil, where only *S. mansoni* is endemic, but less is known about the other species. Case reports have indicated that *S. japoniucm*[42] and *S. haematobium*[43] can cause PH, but it may be substantially less common with these other species. In a recent echo-based study from China (where only *S. japonicum* is endemic), authors found 0.005% of those with schistosomiasis had evidence of PH,[44] a rate ~100-fold lower than is anticipated based on *S. mansoni*-derived data (see calculations above). In a study comparing experimental *S. japonicum*-induced PH to *S. mansoni*-induced PH, authors found that *S. japonicum* could cause PH in mice, but the severity was significantly less than that caused by *S. mansoni*.[45] If these species-specific phenotype differences are real clinically, it is largely unknown why these differences may occur and what the potential phenotype from *S. haematobium* infection is.

What Is the Relationship between SchPAH and PPHTN? Is Schistosomiasis Liver Disease a Necessary Precursor?

It is thought that preportal liver fibrosis in HSS is important in the development of *S. mansoni*-induced SchPAH. HSS could directly cause PPHTN. However, the liver fibrosis and portal hypertension in HSS also causes egg embolism to the lungs through portocaval shunts, and in mice, more severe liver disease increases egg embolization and causes more severe experimental PH.[34] Mice which receive only experimental egg embolism to the lungs develop a PH phenotype without any liver disease.[38] Notably different than viral or alcoholic cirrhosis, SchHSD causes preportal fibrosis without significant hepatocellular injury. Case reports exist of *S. haematobium*-induced SchPAH[43] which causes urinary but not liver disease. Overall, it remains unclear if PPHTN underlies or contributes to clinical SchPAH or if SchPAH largely results from a specific pathobiology induced by egg embolization to the lungs causing localized inflammation and vascular disease.

Does Antihelminthic Therapy (Praziquantel) Benefit SchPAH Patients Who Have Active Infection?

In schistosomal liver disease, eradicating the parasite leads to at least partial reversal of the liver pathology.[46,47] In a mouse model of schistosomiasis coupled with portal hypertension induced by portal vein ligation, the pulmonary disease partially improved after praziquantel administration,[48] and authors of another study of parasite infection alone found more substantial reversal of pulmonary disease with praziquantel treatment.[49] However, SchPAH patients continue to die in the absence of active infection,[16] so it is unclear if praziquantel has clinical benefit in SchPAH. Some favor treating all SchPAH patients with praziquantel due to the severity of the disease and relatively low risk of harm.[50] It may be that the pulmonary disease reaches a point of no return, after which the pathology autonomously progresses even without infection.

Will Targeting the Immune System Be Beneficial to Those with SchPAH? Is There a Way to Block the Inflammation that Causes Pulmonary Vascular Disease without Inhibiting the Global Host Response to the Parasite for Those Susceptible to Reinfection?

In SchPH mouse models, blocking type 2 immunity prevents the schistosomiasis-PH phenotype.[36] However, it is unclear if targeting inflammation later in the disease course can effectively reverse established disease, potentially even after parasite eradication when presumably the type 2 inflammation is reduced. Furthermore, broadly blocking type 2 inflammation in individuals that live in endemic locations may result in more severe reinfection if that occurs. Specific immune responses may be driving the pulmonary vascular disease; if so, precisely targeting host drivers or even vaccinating or inducing immune tolerance against specific parasite factors may prevent or reverse the pulmonary vascular disease without inhibiting the response to the parasitic infection more broadly.

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REGULAR ARTICLE

Human Immunodeficiency Virus–Associated Pulmonary Arterial Hypertension

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Human immunodeficiency virus (HIV) attacks the immune system and can cause acquired immunodeficiency syndrome. Thankfully, antiretroviral therapy is highly effective, and people infected with HIV can live long lives with proper adherence to therapy. One of the important noninfectious complications of HIV is the development of pulmonary arterial hypertension (PAH). This review will cover the epidemiology, pathogenesis, and clinical characteristics of HIV-associated PAH. It will also cover the current knowledge on use of vasodilator therapy in this population.

INTRODUCTION

The human immunodeficiency virus (HIV) is a retrovirus, primarily transmitted via genital fluid or blood, which attacks the immune cells of the human body.[1,2] If left unchecked, HIV can lead to fulminant immune failure and the development of acquired immunodeficiency syndrome (AIDS).[3] The most recent estimates indicate that 38.4 million people are infected with HIV globally, and 1.5 million new infections occurred in 2021.[4] Treatment of HIV with antiretroviral therapy is quite successful and has led to a 32% decline in the annual incidence of new infections over the last decade. Further, regular use of antiretroviral therapy has limited the development of infectious complications and AIDS in those living with HIV, essentially turning a once almost universally fatal disease into a chronic one, the effects of which can be mitigated with good adherence to therapy.[5] As such, patients with HIV are living longer, and the noninfectious complications of HIV require escalating clinical focus.

The development of pulmonary arterial hypertension (PAH) is one of the important potential noninfectious complications of HIV.[6,7] PAH is a disorder of the pulmonary vasculature characterized by a rise in the pulmonary circulatory pressures. The hemodynamic definition of PAH requires an elevation in the mean pulmonary artery pressure to greater than 20 mmHg and an elevation in the pulmonary vascular resistance to greater than or equal to 3 Wood units. Increasingly, evidence of prognostic value exists with even mildly abnormal hemodynamics, and recently published guidelines advocate to diagnose PAH at a pulmonary vascular resistance threshold greater than 2 Wood units.[8,9] Clinically, patients with pulmonary hypertension can be classified into subgroups based on etiology. Patients with HIV-associated PAH (HIV-PAH) fall under the Group 1 classification, with a subgrouping under Group 1.4 (associated PAH).[6] When advanced, PAH can lead to right ventricular failure, respiratory distress, impaired health-related quality of life, and attenuated survival.[10]

EPIDEMIOLOGY OF HIV-PAH

The true prevalence of HIV-PAH is unknown; however, it is estimated to be at least 0.5% among HIV-positive individuals. Preliminary reports of the association between HIV and PAH came from the prospective evaluation of cardiopulmonary limitations in patients who complained of dyspnea within a large cohort of Swiss patients living with HIV.[11] The cohort consisted of 1,200 patients, and of the 74 patients who complained of cardiopulmonary limitations, 6 had echocardiographic evidence of PAH, which accounts for 0.5% of the total cohort. Authors of various other echocardiography-based studies confirmed a higher prevalence of elevations in the pulmonary artery systolic pressure (PASP) in patients living with HIV than the known estimates in the general population.[12-17] While some have postulated that the prevalence of HIV-PAH may be higher in sub-Saharan Africa due to a greater proportion of patients with uncontrolled HIV, a meta-analysis assessing echocardiography estimates of elevations in the pulmonary artery pressures found no regional difference across 25 studies from 17 different countries.[16]

The most comprehensive study, for which authors assessed the prevalence of HIV-PAH with invasive hemodynamics, came in 2008 from a large prospective cohort of 7,648 HIV positive patients living in France.[18] Patients were screened for unexplained dyspnea, and if they met criteria, an echocardiogram was obtained, followed by a right heart catheterization for those with suspicious findings. The study yielded a total of 35 patients with right heart

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catheterization-confirmed PAH or an estimated prevalence of 0.46% (95% CI = 0.32-0.64). Notably, this study was performed after the widespread adoption of antiretroviral therapy, and only 13% of the cohort had a CD4 count <200 cells/μL. As such, even though it is an older study, it is informative on the current state because the HIV control was relatively high in this cohort. Another notable aspect of this study is that it was performed before the 2018 World Symposium on Pulmonary Hypertension hemodynamic change, which lowered the mPAP criteria for diagnosis; thus, a 0.5% estimate may underestimate the current prevalence of HIV-PAH based on the contemporary hemodynamic definition.[6] The prevalence would also rise further based on the recent recommendations from the European Society of Cardiology and European Respiratory Society to reduce the pulmonary vascular resistance threshold for diagnosis of PAH.[8,9] Compiling the evidence together, even using conservative estimates, the prevalence of PAH in HIV-positive individuals is likely many thousand times that of idiopathic PAH in the general population.[19]

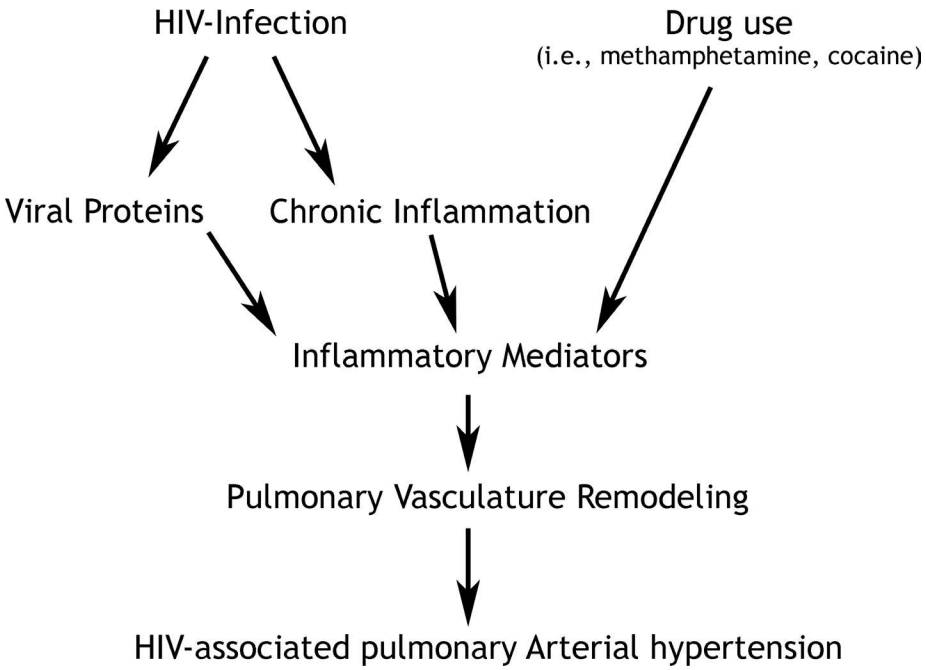

Figure 1: Pathogenesis of the development of human immunodeficiency virus (HIV)-associated pulmonary arterial hypertension (PAH). HIV viral infection of pulmonary vascular endothelial cells has not been seen. However, HIV viral proteins and chronic inflammation are believed to lead to elaboration of inflammatory mediators which cause pulmonary vascular remodeling including plexiform lesions characteristic of Group 1 PAH.

PATHOGENESIS OF HIV-PAH

The pathologic changes found in the pulmonary vasculature of patients with HIV-PAH are the same as those found in other patients with Group 1 PAH. Histopathologic findings in HIV-PAH demonstrate evidence of plexogenic pulmonary arteriopathy, medial hypertrophy, intimal fibrosis, and thrombotic arteriopathy.[20] Indeed, the explants or autopsies of most patients with HIV-PAH are impossible to differentiate from those with idiopathic PAH. Notably, however, some case reports have also demonstrated evidence of pulmonary veno-occlusive disease in HIV-positive individuals.[21,22] It is unclear if these cases represent comorbid conditions or if HIV can drive pulmonary veno-occlusive disease in addition to precapillary PAH.

The pathogenesis of HIV-PAH is believed to be multifactorial (Figure 1). Early investigation into the pathogenesis of precapillary PAH in patients with HIV led to the hypothesis of a direct viral infection of the pulmonary vasculature as the culprit, yet authors of in vitro studies of human lung microvascular endothelial cells have demonstrated a lack of expression of the HIV coreceptors CXCR4 and CCR5.[23] Further, adding HIV to the cell culture of these human lung microvascular endothelial cells demonstrated no active viral infection. Although direct cellular infection does not appear to be involved in the pathogenesis, it does appear that HIV viral proteins may be contributory. A transgenic HIV rat model, which is noninfectious but expresses HIV RNA and HIV proteins, demonstrated increased vascular oxidative stress as well as pathologic changes consistent with PAH.[24] Histology on the transgenic rats showed evidence of pulmonary vascular remodeling with medial thickening and right ventricular hypertrophy.

One potential mechanism by which these proteins lead to PAH is via increased production of vasoconstrictors. HIV envelope glycoprotein gp120, expressed on the surface of the HIV envelope, was shown to induce apoptotic cell death and also increase secretion of the pulmonary vasoconstrictor endothelin-1.[23,25] Circulating monocytes of HIV-infected individuals also demonstrate expression of the endothelin-1 gene, a finding which was not present in healthy controls.[26] Increased endothelin-1 expression is likely a strong driver of HIV-PAH, as higher levels are independently associated with worse hemodynamics assessed by right heart catheterization in HIV-infected patients.[27]

Another potential pathway through which HIV may lead to PAH is via the bone morphogenic protein receptor signaling pathway. Mutations in the gene bone morphogenic protein receptor 2 (BMPR2) account for the most common form of hereditable PAH.[28,29] Loss of BMPR2 signaling leads to increased production of pro-inflammatory cytokines as well as pulmonary vascular remodeling.[30-32] Rebalancing of this pathway is also a potential therapeutic target for the treatment of PAH.[33] Inhibition of BMPR2 expression was found in macaque models infected with a chimeric strain of the simian immunodeficiency virus, which coexpressed the HIV protein Nef.[34] These animals, but not controls exposed to wild type simian immunodeficiency virus, went on

to develop plexiform lesions and cardiac hypertrophy. Further evidence of the Nef protein being involved in HIV-PAH pathogenesis comes from 2 human cohorts, where polymorphisms in Nef were overrepresented in patients with HIV-PAH as compared with HIV-positive controls without PAH.[35]

Chronic inflammation due to immune dysregulation may also play a role. Patients with HIV-PAH had an increased frequency of HLA-DR6 and HLA-DR52 as compared with HIV-positive patients without PAH and noninfected controls, potentially implicating the immune response to HIV as a mechanism.[36] The cardiovascular risks of chronic inflammation persist, even in patients with well-controlled HIV.[37] Markers potentially linking HIV and PAH via inflammation include asymmetric dimethylarginine, an inhibitor of nitric oxide synthase, hypoxemia-inducible factor-1, platelet-derived growth factors, and vascular endothelial growth factor.[24,38,39]

Behavioral factors may also play a role in the development of HIV-PAH. Injection drug use is a known comorbid condition for many infected with HIV.[40] While cocaine is still considered a probable cause of drug and toxin-associated PAH, methamphetamine is now considered a definite cause PAH.[6,41,42] The double hit of HIV viral proteins combined with drug use may potentiate the risk of pulmonary vascular disease.[43] In cell culture, coexposure of HIV viral proteins and cocaine led to a down regulation of the BMPR2 signaling pathway as well as proliferation of smooth muscle cells and increased pulmonary endothelial cell permeability.[44,45] In animal models, early plexiform lesions developed in simian immunodeficiency virus-infected macaques who were also treated with intravenous morphine, whereas lesions were not found in infected macaques not exposed to morphine, or in noninfected macaques exposed to morphine.[46] Evidence for a 2-hit hypothesis between HIV viral proteins and drug use is also found in human cohort studies, as patients with a diagnosis of HIV-PAH reported a higher rate of methamphetamine use than patients with idiopathic PAH.[47]

EFFECT OF ANTIRETROVIRAL THERAPY ON HIV-PAH

Some data exist on the potential beneficial effect of antiretroviral therapy on the pathogenesis of HIV-PAH. Certainly, active viral infection presents greater exposure to the viral proteins implicated in the development of PAH, so many have postulated that HIV-PAH would be associated with poorer control of infection. Authors of various studies assessing the association of HIV-PAH with antiretroviral therapy have demonstrated a benefit of therapy, with a lower rate of HIV-PAH in treated patients.[48,49] Authors of a recent large-scale study of US Veterans demonstrated that noninvasive elevations in the PASP were more likely in HIV-infected veterans who had lower CD4 counts and higher viral loads than uninfected veterans and HIV-infected veterans with good viral control.[50]

One notable exception to the notion of better control leading to less HIV-PAH was a retrospective study in which authors compared the effect of nucleoside reverse transcriptase inhibitors alone versus combination antiretroviral therapy.[51] In this study, increased rate of cardiac complications such as arrhythmias, ischemia, cardiomyopathy, pericarditis, and endocarditis occurred in patients treated with nucleoside reverse transcriptase inhibitors alone. However, an increased rate of PAH occurred in those treated with combination antiretroviral therapy (2.0% versus 0.7%, $P = 0.048$). It does not seem plausible that the driver of PAH was due to better control of the HIV; rather, it likely represents better screening for PAH in providers who chose to use combination antiretroviral therapy instead of nucleoside reverse transcriptase inhibitors alone.

Authors of another important study looked at the effect of antiretroviral therapy on HIV-PAH via invasive hemodynamics.[52] In this study, 77 patients with HIV-PAH were followed longitudinally. Of those patients, 62 were on antiretroviral therapy at diagnosis, and 15 were not. Most patients (65%) were put on PAH-specific therapy and had improvements in functional class, 6-minute walk distance, pulmonary vascular resistance, and cardiac index. Of interest, 8 of the 15 patients who were not on any therapy at the time of PAH diagnosis were treated with initiation of antiretroviral therapy alone and no vasodilators. In those patients, antiretroviral therapy alone improved 6-minute walk distance, with no benefit in functional class, pulmonary vascular resistance, or invasive hemodynamics. Authors of another study that assessed invasive hemodynamics in 62 HIV-infected patients demonstrated that the presence of HIV-PAH was more likely in patients with a detectable viral load and lower CD4 counts than in those with good viral control.[53] Ultimately, without large-scale prospective studies, the true effect of antiretroviral therapy on HIV-PAH is unclear. Based on the evidence, antiretroviral therapy seems to have some utility in controlling the virus, as an association between HIV-PAH and immune dysfunction seems to exist. However, antiretroviral therapy alone does not appear to be enough to control PAH. Regardless, all patients with HIV should be put on antiretroviral therapy based on current guidelines, irrespective of CD4 count, viral load, or presence of PAH.[54]

CLINICAL CHARACTERISTICS AND DIAGNOSIS OF PATIENTS WITH HIV-PAH

Patients with HIV-PAH present in a manner like those with other forms of Group 1 PAH. Literature review of 131 reported HIV-PAH cases demonstrated that the most common clinical features were progressive dyspnea, pedal edema, cough, fatigue, chest pain, and syncope.[20] The interval time between diagnosis of HIV and the diagnosis of HIV-PAH was 33 months. Notably, this was an older study, so it is possible that the time course may be longer in the contemporary era, with more patients being on antiretroviral therapy. Chest radiographs in this review demonstrated that the most common features were cardiomegaly and an enlarged pulmonary arterial prominence. Ventilation or perfusion scans were normal. Electrocardiograms demonstrated features of right ventricular hypertrophy, right axis deviation, and sinus tachycardia. Echocardiograms were notable for the presence of right

ventricular enlargement, tricuspid regurgitation, and paradoxical septal motion. In this group of patients, the PAH was advanced, with a mean pulmonary vascular resistance of 12.2 Wood units. These data highlight the nonspecific nature of symptoms, signs, and routine diagnostic testing so that a high index of suspicion and low threshold to perform an echocardiogram and invasive right heart catheterization is required to detect HIV-PAH.

When PAH is suspected, the most effective noninvasive initial diagnostic test is an echocardiogram.[55] In addition to performing echocardiography in patients living with HIV in patients who have unexplained symptoms, the most recent World Symposium on Pulmonary Hypertension Proceedings propose screening echocardiography in selected asymptomatic patients.[19] In the general population, the echocardiogram has a good sensitivity and specificity for the diagnosis of PAH; however, no substitute for performing a right heart catheterization exists.[6] The necessity of a right heart catheterization in the diagnosis of HIV-PAH is also clear. While the echocardiogram is still a useful test to detect HIV-PAH, it has limitations. Direct comparison of PASP via paired echocardiograms and right heart catheterizations in patients with HIV demonstrated that, while only a mild average bias existed, 1.75 mmHg greater via echocardiogram, 20% of patients had a more than 10 mmHg discrepancy between the 2 modalities so that echo estimated pulmonary artery pressure may miss patients who have HIV-PAH.[56] Patients with HIV are also at an increased risk of left ventricular diastolic dysfunction, which can lead to PASP elevations in the absence of PAH, further confounding echocardiogram results and validating the need for invasive right heart catheterization in the diagnosis of HIV-PAH.[57]

The most contemporary assessment of the clinical characteristics of HIV-PAH comes from the Pulmonary Hypertension Association Registry.[47] While the number of patients assessed with HIV-PAH was small, this study was unique because, in it, authors compared the clinical characteristics between 23 patients with HIV-PAH and 563 patients with idiopathic PAH. As compared with those with idiopathic PAH, patients with HIV-PAH were younger, had a lower body mass index, and had worse renal function. Pulmonary vascular resistance was higher in patients with HIV-PAH than those with idiopathic PAH (12.8 Wood units versus 10.4 Wood units), and a trend for a lower cardiac output, cardiac index, and stroke volume index existed. The authors of the study did not find any difference in generic health-related quality of life as measured by the Short Form-12 instrument or in PAH-specific health-related quality of life as measured by the emPHasis-10 instrument. HIV-PAH patients also had rates of hospitalizations and emergency department visits like those with idiopathic PAH. When assessed by PAH-specific vasodilator class, patients with HIV-PAH were treated in a manner like those with idiopathic PAH.

TREATMENT OF HIV-PAH

HIV-PAH falls in the Group 1 PAH category, and treatment guidelines for Group 1 PAH should be followed in HIV-PAH patients.[8-10] In those patients with low or intermediate risk Group 1 PAH, recommendations include upfront oral combination therapy with an endothelin receptor antagonist and an agent targeting the nitric oxide pathway.[58] If patients do not achieve a low-risk status after 2-drug therapy has been initiated, it is recommended that a prostacyclin pathway agent is started.[10] In those with high-risk disease, parenteral prostacyclin is the standard of care. Because HIV-PAH patients may have multiple comorbidities, it is important these comorbidities be enumerated and well characterized so that decisions about PAH therapies can be tailored to each individual patient.

In the real world, patients with HIV-PAH are generally treated in a manner like those with idiopathic PAH.[47] However, it is important to consider the potential for drug-drug interactions between HIV and PAH medications when choosing therapy for patients with HIV-PAH. Collaboration between the PAH and HIV providers is important to ensure that important drug-drug interactions are identified and appropriately managed (Table 1).[59]

The most notable interaction occurs between antiretroviral therapy and drugs in the nitric oxide pathway. The metabolism of the phosphodiesterase-5 inhibitors tadalafil and sildenafil occurs via the cytochrome P450 enzymes CYP3A4 and CYP2C9. Notably, these enzymes are inhibited by protease inhibitors, and authors of pharmacokinetic studies have demonstrated higher plasma levels of sildenafil when coingested with the HIV drugs ritonavir, indinavir, and saquinavir.[60,61] Despite the known interaction, most patients seem to tolerate coingestion without significant adverse effects.[62,63] Similar findings were seen for tadalafil with protease inhibitors.[64] While trials studying the guanylate cyclase stimulator riociguat excluded patients with HIV-PAH, the interaction is generally considered low risk because riociguat is metabolized via multiple CYP enzymes. Authors of one study assessing the pharmacokinetics between riociguat and 5 different HIV regimens demonstrated tolerability across all the regimens; however, a threefold increase in riociguat exposure occurred when patients coingested riociguat with abacavir, dolutegravir, and lamivudine.[65] Given the potential for higher plasma concentrations of the phosphodiesterase-5 inhibitors and riociguat in patients with HIV-PAH, we recommend starting at lower doses, titrating slowly, and monitoring for adverse effects closely.

The nonselective endothelin receptor antagonist bosentan was assessed for safety and tolerability in a small study of 16 patients with HIV-PAH.[66] The rationale behind this study was that bosentan induces CYP3A, so it could increase metabolism of antiretroviral therapy.[67] In the study, bosentan yielded improvements in PAH-related clinical parameters, and no change in HIV viral control at both the 16-week period and in long-term follow up occurred.[66,68] The newer endothelin receptor antagonists ambrisentan and macitentan have less potential for interaction. Indeed, HIV-PAH patients were included in the various clinical trials of both agents.[58,69,70]

Arguably, the most important pathway in PAH management is the prostacyclin

Table 1. Effects of HIV medication coadministration on PAH medication kinetics and clinical effectsa

PAH medications	HIV medications	Effect on PAH medication	Recommendation
Sildenafil	All PIs	• Darunavir/ritonavir plus sildenafil 25 mg like sildenafil 100 mg alone. • Ritonavir 500 mg twice daily ↑sildenafil AUC 1,000%	• Consider alternative therapy. • Initiate sildenafil at a low dose (i.e., 20 mg every other day), increase slowly with close monitoring for side effects.
	Efavirenz Nevirapine	• ↓ sildenafil possible	• Titrate sildenafil dose based on clinical effect.
	Etravirine	• Sildenafil AUC ↓ 57%	• Titrate sildenafil dose based on clinical effect.
	Elvitegravir/ cobicistat	• ↑ sildenafil expected	• Consider alternative therapy. • Initiate sildenafil at a low dose (i.e., 20 mg every other day), increase slowly with close monitoring for side effects.
Tadalafil	All PIs	• Ritonavir 200 mg twice daily ↑ tadalafil AUC 124%	In patients on a PI > 7 d: • Start tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. In patients on tadalafil who require a PI: • Stop tadalafil ≥24 h before PI initiation. 7 d after PI initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. In patients switching between cobicistat and ritonavir: • Maintain tadalafil dose.
	Efavirenz Etravirine Nevirapine	• ↓ tadalafil possible.	• May need to titrate tadalafil dose based on clinical effect.
	Elvitegravir/ cobicistat	• ↑ tadalafil expected.	In patients on elvitegravir/cobicistat >7 days: • Initiate tadalafil 20 mg once daily. Increase to tadalafil 40 mg once daily based on tolerability. In patients on tadalafil who require elvitegravir/cobicistat: Stop tadalafil ≥24 h before elvitegravir/cobicistat initiation. 7 d after elvitegravir/cobicistat initiation, restart tadalafil at 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability.
Riociguat	Abacavir	• Riociguat ↑ AUC200%.	• Initiate riociguat at 0.5 mg 3 times daily and monitor for adverse effects.
Bosentan	All PIs	With lopinavir/ritonavir: • ↑ bosentan 48-fold (Day 4) and ↑ 5-fold (Day 10). With other PIs: • ↑ bosentan expected.	• Do not coadminister bosentan and unboosted atazanavir. In patients on a PI (other than unboosted atazanavir) > 10 d: • Start bosentan at 62.5 mg once daily or every other day. In patients on bosentan who require a PI (other than unboosted atazanavir): • Stop bosentan ≥36 h before PI initiation and restart bosentan 10 d after PI initiation at 62.5 mg once daily or every other day. When switching between cobicistat and ritonavir: • Maintain same bosentan.
	Efavirenz Etravirine Nevirapine	• ↓ bosentan possible.	If coadministration is necessary, monitor bosentan efficacy.
	Elvitegravir/ cobicistat	• ↑ bosentan possible.	In patients on elvitegravir/cobicistat ≥10 d: • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. In patients on bosentan who require elvitegravir/cobicistat: • Stop bosentan ≥36 h before elvitegravir/cobicistat initiation. At least 10 d after initiation of elvitegravir/cobicistat, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.

Abbreviations: AUC, area under the curve; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PI, protease inhibitor.

[a]Adapted from Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.[59]

pathway. While the initial trials which established the efficacy of the parenteral prostacyclins epoprostenol and treprostinil did not include patients with HIV, these drugs seem to be well tolerated in HIV-PAH without significant drug interactions.[71-75] Prostacyclins can also be administered in oral and inhaled routes, and patients with HIV-PAH were included in the various clinical trials of these agents.[76-78] Additionally, authors of the study investigating the drug selexipag, an oral selective IP prostacyclin-receptor agonist, included patients with HIV-PAH.[79] Given their inclusion in the various clinical trials and the real-world data, the prostacyclin pathway agents are generally considered safe and effective in HIV-PAH.

CONCLUSIONS

HIV-PAH is a unique subset of pulmonary vascular disease. The prevalence of HIV-PAH is at least 0.5% of all people living with HIV. The mechanism by which HIV leads to PAH is felt to be mediated via viral proteins leading to increased endothelin-1-related vasoconstriction, inhibition of BMPR2 signaling, chronic inflammation, and an increased rate of drug and toxin exposure. These patients have clinical characteristics like others with Group 1 PAH. Treatment is also like other types of PAH; however, caution is necessary when starting the nitric oxide pathway agents to avoid potentially dangerous drug-drug interactions.

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REGULAR ARTICLE

Portopulmonary Hypertension: A Review

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Portopulmonary hypertension (POPH) is a rare complication of liver disease occurring when pulmonary arterial hypertension develops in the setting of portal hypertension. It increases the morbidity and mortality compared to patients with cirrhosis alone. POPH is classified in Group 1 pulmonary arterial hypertension, which has important implications on treatment. After aggressive treatment and in carefully selected patients, liver transplantation can be performed; this can be curative of not only their liver disease but also of their POPH. Treatment and patient selection for optimum results continues to evolve. This article provides updates on the definition, clinical course, and treatment of patients with POPH. We will also discuss the evolving data in treatment and liver transplantation in POPH.

DEFINITION AND DIAGNOSIS

Portopulmonary hypertension (POPH) occurs when pulmonary arterial hypertension (PAH) develops in the setting of portal hypertension.[1] The hemodynamic definition of PAH was modified at the 6th World Symposium for Pulmonary Hypertension in 2018 in Nice, now defined as a mean pulmonary arterial pressure (mPAP) > 20 mm Hg (previously > 25 mm Hg), normal left heart filling pressure, and a pulmonary vascular resistance (PVR) of > 3 Wood units.[2] The subclassifications of Group I PAH all fall under this new definition. However, specific data regarding the implications of the changed diagnostic criteria and response to treatment for many of these subgroups are lacking (Table 1).[3] POPH is included in the Group 1 classification of PAH, which has important implications for treatment (see the section on "Management," below).[3] Since many patients with cirrhosis also have volume overload and the wedge pressure can be > 15 mm Hg while still having concomitant small vessel arteriopathy, some experts suggest using a transpulmonary gradient (mPAP – wedge pressure) > 12 mm Hg in the diagnosis of POPH to adjust for the confounder of intravascular volume expansion.[4]

In the United States and other developed countries, POPH occurs most often in the setting of chronic liver disease leading to cirrhosis.[5] Interestingly, the development of POPH may not correlate with the severity of the patient's liver disease. It is estimated that 4% to 8% of patients with liver disease have POPH, but this number may be an underestimate.[6-8] In some studies, up to 15% of patients with portal hypertension have pulmonary hypertension (PH).[9] Data regarding the incidence of POPH are taken chiefly from liver transplant centers that employ routine screening via echocardiography.[10]

In the developing world, noncirrhotic POPH is more common and is often caused by infection with *Schistosoma mansomi* leading to extrahepatic portal hypertension. This infection is suspected to be the most common form of POPH in the world. Schistosoma first enters the skin, then travels to the lungs, where it produces an immune complex hypersensitivity reaction. Portal hypertension results from the mechanical obstruction of the presinusoidal vessels by ova; when this occurs, the ova can bypass the liver and travel to the lungs, causing a granulomatous inflammatory reaction. Pulmonary vascular remodeling is suspected to result from both mechanisms: direct inflammation and portal hypertension.[11]

PATHOLOGY

The specific pathology of POPH is unknown. Patients with POPH have been found to have higher levels of endothelin-1. The liver is a major site of the synthesis, clearance, and action of endothelin-1, and one theory is that in portal hypertension, more endothelin-1reaches the pulmonary circulation, resulting in vasoconstriction by binding with the endothelin A receptor.[12] There may also be an autoimmune component to the disease since the female sex and the presence of autoimmune hepatitis seem to be particular risk factors.[13] Recent research has suggested that estrogen signaling may play a role as well. A case-control study showed that a single-nucleotide polymorphism in aromatase rs7175922 was associated with higher levels of estradiol and increased odds of developing POPH (odds ratio: 2.38).[14]

PRESENTATION AND CLINICAL FEATURES

The initial presentation of POPH is similar to other etiologies of PAH with fatigue and dyspnea. This eventually progresses to the more apparent signs of right ventricular failure with edema (both lower extremity and abdominal), elevated jugular venous pressure, lightheadedness, and syncope.[15] While the insidious development of PAH is difficult to diagnose in all comers, it is particularly difficult in patients with liver disease as many of the early nonspecific, and even late symptoms can be

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Table 1. Classification of Pulmonary Hypertensiona

Group 1, PAH
Idiopathic
Heritable
Drug and toxin induced
PAH associated with • Connective tissue disease • Human immunodeficiency virus • Portal hypertension • Congenital heart disease
Schistosomiasis
Long-term responders to calcium channel blockers
Pulmonary veno-occlusive disease
Persistent PH of the newborn
Group 2, PH due to left heart disease
Due to heart failure with preserved LVEF
Due to heart failure with reduced LVEF
Valvular heart disease
Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3, PH due to lung diseases and/or hypoxemia
Obstructive lung disease
Restrictive lung disease
Other or mixed obstructive or restrictive lung diseases
Hypoxia without lung disease
Developmental lung disorders
Group 4, PH due to pulmonary artery obstructions
Chronic thromboembolic PH
Other pulmonary artery obstructions
Group 5, PH due to unclear and/or multifactorial mechanisms
Hematologic disorders
Systemic and metabolic disorders
Other
Complex congenital heart disease

Abbreviations: PAH indicates pulmonary arterial hypertension; PH, pulmonary hypertension; LVEF, left ventricular ejection fraction.

[a]Table was adapted with permission from Galie et al.[2]

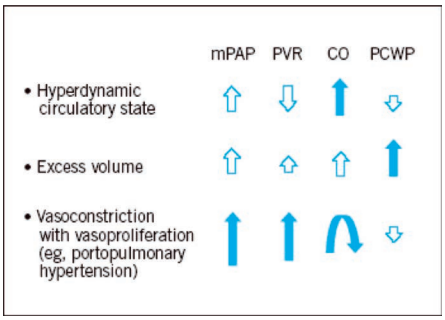

Figure 1: Illustration of the various hemodynamic parameters that occur in patient with cirrhosis. mPAP indicates mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CO, cardiac output; and PCWP, pulmonary capillary wedge pressure.

attributed to their underlying liver disease. Screening tests for POPH mirror screening in other patient populations and includes a transthoracic echocardiogram.[16] Signs of right heart dysfunction or elevated estimated PA systolic pressures >38 mm in one registry were used as positive screening tools, followed by a right heart catheterization (RHC). In other institutions, a right ventricular systolic pressure of 50 mm Hg is used due to the other confounding hemodynamic abnormalities common in the cirrhotic patient.[17] The hemodynamic derangements in cirrhotic patients are complex and may present with a few different patterns, emphasizing the need for a careful hemodynamic evaluation. In cirrhotic patients without POPH, the most common hemodynamic pattern is a high cardiac output, high flow state with low systemic vascular resistance, low PVR, and low pulmonary capillary wedge pressure. This occurs in 30% to 50% of patients with cirrhosis. In patients with more advanced liver disease and volume overload, the hemodynamics change but are still characterized by high cardiac output, high circulating pulmonary pressures, and a high pulmonary capillary wedge pressure. However, the calculated PVR is still in the range of normal due to the increased cardiac output.[18]

In POPH, the hemodynamics are characterized by high pulmonary pressures with a normal pulmonary capillary wedge pressure and high, normal, or even low cardiac output; the cardiac output will vary due to the degree of hemodynamic derangement due to underlying liver disease and the degree of right heart failure. This results in a high PVR (Figure 1). Notably, a low cardiac output in patients with POPH portends a very poor prognosis since cirrhosis is typically associated with a high-output state.[12,19]

Patients with cirrhosis can also have other risk factors for PAH. Some risk factors for developing cirrhosis overlap with risk factors for developing PAH. For example, intravenous drug abuse increases the risk of acquiring both hepatitis C and human immunodeficiency virus; methamphetamine use, in particular, is associated with the development of Group 1 PAH as well.[2] Therefore, to firmly establish the diagnosis of POPH, there needs to be objective evidence of elevated portal pressures. Often, this is clinically evident by history, laboratory evaluation, and physical exam (ascites, presence of varices, etc.). If the diagnosis is in question, it can be confirmed with hemodynamic measurements. Portal hypertension can be diagnosed by measuring the difference between the hepatic vein wedge and free pressure; wedged hepatic venous pressure is an

estimate of pressure within the portal venous system, whereas free hepatic venous pressure reflects systemic venous pressure. A difference of > 5 mm Hg is consistent with portal hypertension.[20] This pressure gradient can be measured during RHC and is easier to do when the femoral vein is accessed.

Table 2. POPH Survival Statistics

Treatment	5-year survival
No treatment	14%
Liver transplant alone	25%
Pulmonary hypertension treatment alone	45%
Pretreatment for POPH then liver transplant	67%

Abbreviation: POPH indicates portopulmonary hypertension.

CLINICAL COURSE

Compared with other forms of Group 1 PAH, patients with POPH have a worse prognosis. Decreased survival and increased hospitalization rates were seen compared to patients with idiopathic PAH in the REVEAL registry, which is the largest data set available for POPH. Patients with POPH were 3 times more likely to die despite having "better" hemodynamic parameters.[6] In a paper out of the French registry, outcomes were reported in 154 POPH patients, both treated and untreated. There was a 68% 5-year survival. Child B and C cirrhosis and lower cardiac index were associated with worse outcomes.[19]

Similarly, in the chronic liver disease population, outcomes for patients with POPH in the moderate to severe range (mPAP > 45 mm Hg) are worse compared with matched controls with the same model for end-stage liver disease (MELD) score.[4]

A retrospective screening RHC analysis of 74 patients with POPH seen at the Mayo Clinic demonstrated a 14% 5-year survival in patients that received no PH-directed treatment, a 45% survival in those who received vasodilator therapy, and a 67% survival if they received pretreatment for PH followed by orthotopic liver transplantation.[4] This has led to the paradigm that POPH survival improves with treatment and should be treated with PH-directed therapy. Also, and of equal importance, if the hemodynamic parameters become favorable enough, liver transplantation significantly increases long-term survival.[4]

MANAGEMENT

General management of patients with both right ventricular failure and cirrhosis includes diuretics, a low-sodium diet, and lifestyle modifications.[16,21,22] It is also worth addressing nutritional status as patients with liver disease are typically in a catabolic state, and sarcopenia is common.[23]

Beta-blockers are typically used in cirrhotic patients with a history of varices. However, in a small series of 10 patients with POPH on beta blockers, baseline RHC and walk distance was measured. After this initial assessment, their beta blockers were stopped. Nine of the 10 patients improved their walk distance, and their cardiac output improved by 28%, with a 19% increase in PVR. Since moderate to severe PH patients may be stroke-volume limited and highly dependent on heart rate for cardiac output, beta blockers are not recommended in patients with POPH, and banding of their varices may be a better option than medical therapy.[24]

Additionally, although they are commonly used to control severe sequelae of portal hypertension in cirrhotic patients, it is also recommended to avoid transjugular intrahepatic portosystemic shunts in patients with POPH. This procedure will increase flow through the pulmonary circulation, increase right-sided pressures, and may precipitate worsening right ventricular failure.[25] Screening echocardiograms are often done before elective transjugular intrahepatic portosystemic shunt procedures to rule out subclinical PAH.

As delineated above in Table 1, POPH is classified into Group 1 PAH, and there are several US Food and Drug Administration (FDA)-approved medications for this group.[16] The pivotal trials for these medications typically excluded patients with cirrhosis, so it is unclear how generalizable the results of these randomized double-blinded controlled trials are for patients with POPH. Thus, we often rely on case series, single-center studies, and expert opinions to guide therapeutic choices for POPH. The classes of medications with Group 1 PAH indications are phosphodiesterase (PDE)-5 inhibitors and cyclic guanosine monophosphate (GMP) inhibitors (both targeting the nitric oxide pathway), endothelin antagonists, and prostacyclins.

Nitric Oxide Pathway

The 2 FDA-approved PDE-5 inhibitors for Group 1 PAH are sildenafil and tadalafil. The data available are from small trials but do show that the 6-minute walk distance is increased and the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are improved when these medications are used in patients with POPH.[26]

Riociguat, a soluble guanylate cyclase stimulator, was approved by the FDA based on the PATENT clinical trial, which showed improvement in walk distance, PVR, biomarkers, functional class, and time to clinical worsening in patients with World Health Organization Group I PAH. Patients with POPH were included in this trial (a rarity) but only comprised 3% of the trial participants.[27]

Of note, since both PDE-5 inhibitors and cGMP stimulators increase nitric oxide, they cannot be used in combination with each other as the combination can lead to severe hypotension.[28]

Endothelin Pathway

Bosentan, ambrisentan, and macitentan are the FDA-approved endothelin receptor antagonists for Group 1 PAH. Trials of endothelin receptor antagonists have demonstrated improvements in hemodynamics and walk distances.[29] The data for POPH patients are less robust.

Bosentan has some limited data in POPH patients showing improvements in exercise capacity and survival[30,31]; still, its use has largely fallen by the wayside given its risk for hepatotoxicity due to

interference with a bile salt transporter and the resultant need for liver function monitoring.[32] This side effect would be hazardous in patients with chronic liver disease, and it is not recommended for use in patients with POPH. Ambrisentan does not cause hepatotoxicity and is a much more attractive agent for patients with POPH. A large open-label trial looked at ambrisentan and POPH; it showed improvement in hemodynamics but no change in exercise capacity.[33] Macitentan, in a recent multicenter randomized controlled trial specifically in POPH patients, showed significant (35%) improvement in PVR but no significant improvement in 6-minute walk distance.[34] Macitentan, like ambrisentan, has no significant hepatotoxicity. The incidence of anemia is 13.2%[35]; this should be monitored and is an important consideration in patients with chronic liver disease.

Prostacyclin Pathway

Prostacyclins have been the mainstay of PAH treatment for decades, and clinicians rely on them to improve the hemodynamics of patients with poor functional status and concerning hemodynamic parameters.[36] The intravenous formulations include epoprostenol and treprostinil. The latter is also available in subcutaneous, intravenous, and oral forms. Iloprost is another prostacyclin available in the intravenous (Europe only) and inhaled formulation.

The oral prostacyclin (treprostinil) and selexipag, an oral prostacyclin receptor agonist, have data in Group 1 PAH, but no data exist in the POPH population.

Prostacyclin infusions have been used to improve the hemodynamics in patients in anticipation of undergoing liver transplantation with overall success. In small single-center trials, mPAP, cardiac output, and PVR all improve on prostacyclin infusions in patients with POPH.[37-39] Specifically, in liver transplant candidates, studies have demonstrated improvement in hemodynamics followed by liver transplantation.[37,40,41]

LIVER TRANSPLANTATION

Liver transplantation has a long and storied history in patients with POPH. Historically, due to either lack of diagnosis or lack of treatment of POPH in patients with cirrhosis, patients with POPH who underwent liver transplantation had significantly worse outcomes than matched controls without POPH.[5] If the preoperative systolic pressure was estimated at > 60 mm Hg, the 9-month mortality after liver transplantation was 42%.[42] Given that, for many years, many centers had not offered transplantation for patients with moderate or severe POPH. However, with the advances in medical therapy in POPH, the data now show that if the hemodynamics can be improved with intravenous and/or oral PAH-directed medications, liver transplantation can be pursued with success.[37,40,41,43] Retrospective data suggest that if the mPAP is < 35 mm Hg and there is normal right ventricular function, the perioperative mortality is not increased beyond that of a patient without POPH undergoing transplantation in carefully selected patients. Conversely, if the mPAP is > 50 mm Hg, the perioperative mortality approaches 100%.[44-46] Therefore, if pursuing liver transplantation, the treatment goal is to maximize medical therapy to obtain an mPAP of < 35 mm Hg.[47]

The United Network for Organ Sharing (UNOS) allows for exception points to be given to transplant candidates with mortality risks not calculated by the MELD score. Given the increased mortality risk in patients with POPH compared to their MELD-matched controls, UNOS suggests adding exception points for patients with a confirmed diagnosis of POPH that have reached the goal mPAP of < 35 mm Hg and PVR < 5 Wood units.[48] Of note, this documentation needs to be updated every 3 months with a repeat RHC to remain current. In a retrospective cohort study of patients in the Organ Procurement Transplant Network database who were listed for liver transplantation with MELD exception points, 11.1% of patients were reported as removed from the transplant list for clinical deterioration or as a 1-year waitlist mortality. Age, initial MELD score, and initial PVR were predictors of waitlist mortality.[49,50]

Of note, most of the data on which the current guidelines and exception-points rules were based were collected before the advent of current medical therapies, or patients were not on any PH-directed therapy. Often, these data were obtained in the operating room at the time of transplant; therefore, mPAP was recorded, but not the full hemodynamic profile. Because of this, mPAP is the hemodynamic criteria emphasized in MELD exception guidelines. Recently investigators queried whether a strict cut-off of 35 mm Hg was necessary to ensure successful transplantation. The investigators noted that modern PH therapy may drive up the patient's cardiac output, thereby increasing pulmonary pressures above this threshold while having a low PVR and good right ventricular function, likely better markers of transplant candidacy than mPAP alone. Sixteen patients with a diagnosis of POPH on PH-directed medications were included. The hemodynamics prior to transplant showed an mPAP > 35 mm Hg but with a PVR < 250 dynes s cm^{-5}. One-year survival was 69%; this survival is similar to other cohorts of patients with POPH undergoing transplant. More than half of the survivors were able to discontinue PH medications posttransplantation.[51] This suggests that a full hemodynamic profile, including right ventricular function, may be more important than the strict mPAP number cutoff in the modern era of PH therapy.

Despite the evidence that the survival of patients with POPH is improved with liver transplantation,[4] the perioperative course can be complicated, and a team of PH experts to manage the hemodynamics in the intra- and perioperative periods is recommended. An intraoperative event known as *reperfusion syndrome* may be poorly tolerated in patients with compromised right ventricular function. Cardiac output increases acutely at the time of liver allograft reperfusion and rises to triple its baseline in as little as 15 minutes.[52] This can cause acute elevations in right ventricular pressures, bradycardia, and acute right ventricular failure. Prompt and adept use of inhaled or intravenous prostacyclins and nitric oxide has been used to mitigate this injury with mixed results.[43,53] It is also suspected that sur-

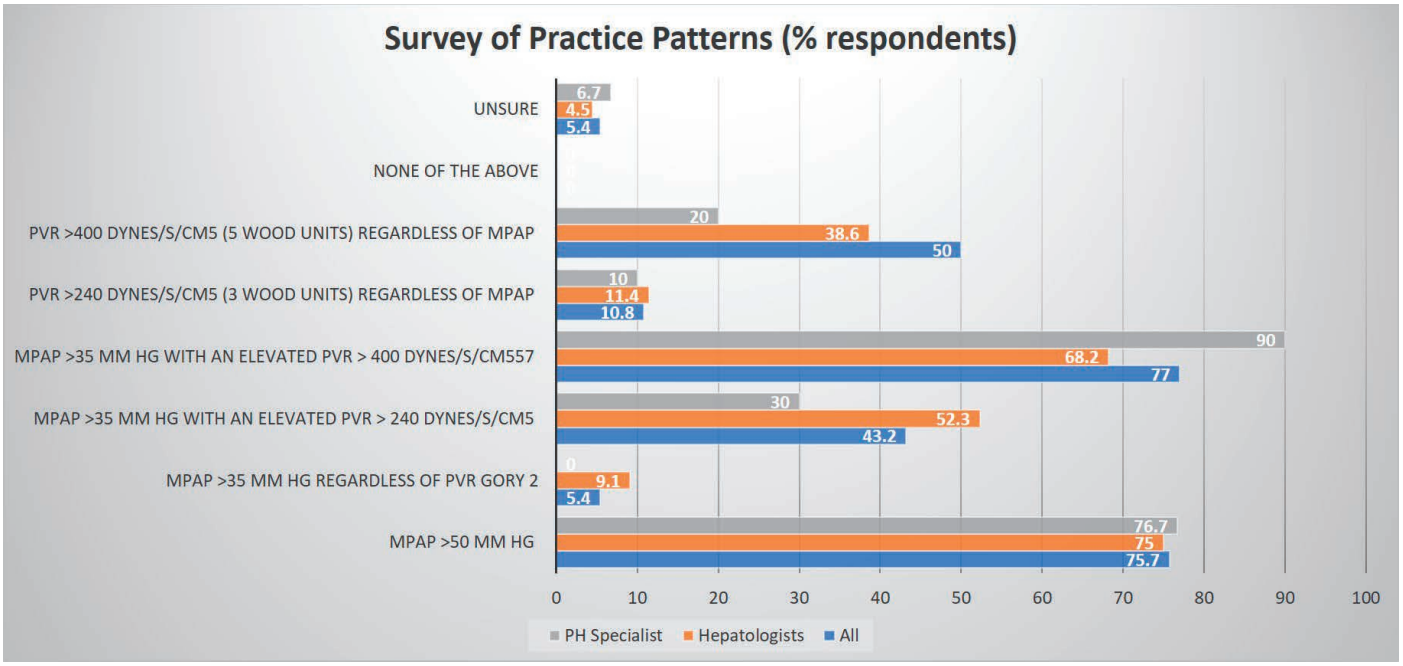

Figure 2: Graph depicting the vast range of provider attitudes and beliefs at high-volume liver transplant centers surrounding liver transplantation criteria for patients with portopulmonary hypertension. The graph represents the percentage of respondents of pulmonary hypertension specialists (grey bar), hepatologists (orange bar), and combined (blue bar) who responded "yes" when asked: "Which of the following were considered absolute contraindications to liver transplantation?" PVR indicates pulmonary vascular resistance; mPAP, mean pulmonary artery pressure. Figure adapted with permission from DuBrock et al.[57]

gical factors play a role; less blood loss, less time under anesthesia, and fewer fluid shifts are likely associated with a smoother intraoperative course.

The 5-year survival posttransplantation in patients with POPH has been reported as 54% to 87%; worse than non-POPH patients posttransplant.[54,55] Most patients' hemodynamics will improve posttransplant as the portal hypertension is improved; however, this is not entirely consistent, and it takes time for the pulmonary vasculature to reverse remodel; 3 to 6 months is typical, and patients should stay on their PH-directed medications until they are followed up as an outpatient. Forty percent to 50% of patients will eventually discontinue their medication, but a substantial portion may need some long-term pulmonary vasodilators.[37,40,41,56]

Because of inconsistent postoperative results, provider beliefs and attitudes on liver transplant in patients with POPH is far from unanimous, even among the experts in the field. A recent article by DuBrock et al[57] highlighted provider attitudes regarding POPH and liver transplantation at centers that performed > 50 transplants/year. The responses varied widely even among this select group (Figure 2). This survey highlighted the variability of management strategies and attitudes among POPH specialists. For example, 15% of providers believed that POPH rarely or never improves after transplantation, while 42% responded that the PH always or often improves. Fifty percent agreed that treated POPH should be an indication for liver transplantation. This, of note, does not line up with current guidelines. Again, nearly half thought that the MELD exception criteria should be modified. This survey highlights the need for multicenter prospective studies, updated practice guidelines, and adherence thereof to improve the standardization of care.[57]

CONCLUSIONS

POPH is a rare complication of portal hypertension. It is characterized by progressive pulmonary arteriopathy and vasoconstriction similar to other forms of PAH, progressing to right ventricular failure over time. Its presence increases the mortality rate compared with both similarly matched patients with PH or cirrhosis alone. The past 2 decades have demonstrated the efficacy of PH-directed therapy in this patient population, showing improvements in hemodynamics and other clinical outcomes. The role of liver transplantation in POPH continues to evolve; however, it is evident that in a select group of patients who have controlled hemodynamics, liver transplantation can be curative of not only their liver disease but also of their POPH. Additional prospective multicenter studies are necessary to help determine posttransplant outcomes and hemodynamic responsiveness in the era of updated PH therapeutics.

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The Role of the Advanced Practice Nurse With Patients Undergoing Pulmonary Thromboendarterectomy and Balloon Pulmonary Angioplasty for CTEPH

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Advanced practice nurses play an integral role in the management of chronic thromboembolic pulmonary hypertension patients undergoing pulmonary thromboendarterectomy and balloon pulmonary angioplasty. As integral members of the multidisciplinary team, advance practice nurses assist chronic thromboembolic pulmonary hypertension patients in the presurgical, postsurgical, and procedural settings by ensuring appropriate referral, workup, evaluation, and education.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disorder characterized by the deposition of chronic thrombotic material in the pulmonary arterial vasculature leading to obstruction of flow and ultimately remodeling of the vasculature and subsequent right heart failure if left untreated. Estimates vary, however the overall incidence of CTEPH following acute pulmonary embolism (PE) is approximately 3% (1% to 5%).[1-3] Notably, a substantial number of patients report no prior history of PE.[1] The management and treatment of CTEPH differs from other forms of pulmonary hypertension (PH) in that it is potentially reversible with pulmonary thromboendarterectomy (PTE) surgery.[4] In addition, for patients who are not surgical candidates or those with persistent PH following PTE, medical therapies and interventional therapies, specifically balloon pulmonary angioplasty (BPA), may play a crucial role in achieving improvement.

At our center, patients with PH and CTEPH are initially seen and managed by the Pulmonary Vascular Disease service, comprised of critical care pulmonologists and advanced practice nurses (APNs). Once diagnosed with CTEPH, patients are evaluated to determine candidacy for PTE or BPA by the CTEPH multidisciplinary team. This multidisciplinary team is comprised of additional disciplines including cardiothoracic surgery, interventional radiology (IR), and APNs in each of these specialties. The multidisciplinary team approach to assess candidacy for surgical PTE or BPA includes comprehensive review of the patient's medical history, presence of comorbid conditions, and right heart catheterization data, as well as imaging modalities including ventilation-perfusion scans, echocardiograms, chest imaging, and pulmonary angiography.[1,5-7] This process is critical in achieving positive surgical and procedural outcomes.

APNs play an integral role in the evaluation, management, and education of CTEPH patients, guiding them through an often complicated, and at times overwhelming, process from diagnosis to treatment. At our center, APNs provide patient education and management including evaluation for potential surgical and/or medical therapies, perform preprocedural evaluations, provide inpatient postoperative and postprocedure management, and provide continuity with outpatient follow-up after a given treatment strategy. Using a patient-centered approach in which the patient and family are involved, the APN is tasked to ensure patients and their families understand the diagnosis and treatment options and assist them in setting realistic expectations in terms of procedural outcomes and possible improvements in functional ability.[1,7-9] The APNs are available to answer any questions that often arise and are a valu-

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able component to a successful CTEPH program.[6,7] In this article we will review the role of the APN, specifically the nurse practitioner, as part of the interdisciplinary team caring for CTEPH patients.

APN ROLE: PTE

PTE is a potentially curative treatment option for CTEPH. The surgery is relatively young and has improved throughout the years. The first pulmonary endarterectomy was performed in 1957, approximately 30 years after the disease was first noted.[10] That patient lived for just a few hours.[10] The introduction of cardiopulmonary bypass during PTE allowed for greater success, and by 1989, 250 surgeries had been performed. At that time, the mortality rate was around 20%.[10] Today the mortality rate is less than 5%.[10] Techniques devised at the University of California San Diego, including the use of circulatory arrest during PTE and the creation of specific surgical instruments that allow for more distal retrieval of fibrous clots, have resulted in lower mortality rates.[10] Perhaps most important in the success of PTE is using a multidisciplinary approach at dedicated CTEPH centers that include the cardiothoracic surgeon, pulmonologist, interventional radiologist, and APNs. This section will highlight some of the roles of the APN in the care of PTE patients.

First and foremost, any patient with a history of PE and chronic dyspnea should be referred to a CTEPH center. Early referral can prevent the development of secondary small vessel vasculopathy that will result in suboptimal outcomes post-PTE (ie, residual PH) and reduce the increased risk of morbidity and mortality.[11] At our institution, patients are referred directly from our pulmonary colleagues. The APN in the cardiothoracic setting ensures each patient has undergone a thorough workup and orders appropriate testing that has not yet been completed. These tests include a transthoracic echocardiogram to evaluate right ventricular function and systolic pressure, a computed tomography of the chest to evaluate for presence and extent of thrombotic disease, a ventilation-perfusion scan to confirm and determine the amount of perfusion and ventilation mismatch, and a pulmonary angiogram to delineate disease location and provide baseline left and right pulmonary artery pressures. Other important preprocedural considerations the APN includes are evaluating anticoagulation, obtaining a complete history and physical, and determining if the patient has a history of recurrent deep vein thrombosis or PE. To minimize complications, the APN refers any patient with recurrent deep vein thrombosis, PE, or suspected coagulopathy to hematology prior to surgery. A patient with concurrent deep vein thrombosis and evidence of anticoagulation failure is referred for inferior vena cava filter placement prior to surgery.[12] IR places the inferior vena cava filter, and given documented low rates of retrieval, follow-up by the APN is necessary to prevent potential complications such as filter migration, thrombosis, or inferior vena cava fracture and embolization.[13]

Surgery for PTE is approximately 8 hours in duration. The patient recovers in the intensive care unit and is followed closely by the pulmonary and cardiothoracic teams. Careful monitoring for reperfusion injury or pulmonary edema is imperative in the immediate postoperative period. The APN will order nitric oxide, allowing for decreased pulmonary vascular resistance and improved oxygenation.[14] PTE is performed with deep hypothermic circulatory arrest, a cooling of the body to less than 20 degrees to reduce harm to the central nervous system. A neuro exam is performed by the APN to evaluate for possible neurological sequela. Transient neurological dysfunction, such as confusion, motor weakness, seizure, agitation, and/or delirium can occur after PTE and is typically seen in patients with longer deep hypothermic circulatory arrest time and in individuals greater than 64 years of age.[15] Additional management considerations include right ventricular support with inotropes and early mobilization and ambulation to improve patient functionality and reduce the risk of postoperative deep vein thrombosis, lung infection, and pleural effusion.[16] The length of stay for a PTE patient at our institution is approximately 5 days. Patients are discharged on warfarin anticoagulation with a goal international normalized ratio (INR) between 2 to 3. The APN must emphasize adherence to lifelong anticoagulation as it remains integral to the treatment of the CTEPH patient.[17] Before discharge, it is common practice at our institution to obtain an echocardiogram. Approximately 25% of PTE patients develop a pericardial effusion postsurgery, and 5% require surgical drainage.[18] Zhang and colleagues reviewed 502 patients that underwent PTE between 2018 and 2020 and determined that younger, taller males were more likely to experience postoperative pericardial effusion as well as patient patients with re-entry sternotomies.[18] Once a pericardial effusion is found, the patient is serially monitored with echocardiogram to ensure stability or improvement. The APN will need to monitor and maintain tight control of the patient's INR to prevent supratherapeutic levels that may result in potential worsening effusion or tamponade physiology.

Following discharge, the PTE patient will have a return follow-up visit in the cardiothoracic outpatient clinic. The surgical APN provides recovery expectations and continues to closely monitor for complications through an in-person follow-up in addition to telehealth monitoring. At our institution, it is common for the APN to manage the patient's INR in the outpatient setting until the INR reaches a therapeutic level. The pulmonary team will schedule a visit and perform baseline testing postsurgery that allows for an objective assessment of pulmonary artery pressure, right ventricular function, exercise capacity, and quality of life.[11]

Early referral of patients with unexplained dyspnea following PE with appropriate anticoagulation to a CTEPH center remains a critical first step in successful treatment. PTE is an option for some patients with CTEPH and can be curative. The APN assists the CTEPH patient in the presurgical and postsurgical settings by ensuring appropriate referral, surgical workup, postoperative monitoring, and medication management.

APN ROLE: BPA

BPA is a safe and effective catheter-based therapy for select CTEPH patients. BPA is an option available to CTEPH patients who are not eligible for surgical intervention with PTE for a variety of reasons including certain comorbidities, persistent symptoms despite optimized surgical or medical therapy, patient request for a less invasive procedure, or for residual PH post-PTE.[1,2,4,16,19-21] The survival rate for nonsurgical PTE candidates has significantly improved since the availability of BPA as well as newer medical therapies.[22] Taniguchi and collegues looked at the survival rates of nonoperative CTEPH patients that underwent BPA and found 1-year and 3-year survival rates of 98.8% and 92.9%, respectively.[23]

BPA was first attempted in 1988 to treat acute PE in patients that did not respond to treatment with anticoagulation or thrombolytic therapy. The first reported case of BPA for CTEPH occurred in the same year and resulted in improved cardiac function, pulmonary pressures, and exercise tolerance, however, it was not widely adopted because of high complication rates. Work continued refining the procedure and once BPA was performed in a staged manner, the risk of complications was significantly reduced.[21,24]

At our institution, BPA is performed by vascular interventional radiologists. As the CTEPH patient volume and case complexity grew, IR reevaluated their resources which lead to the addition of an APN to their multidisciplinary team to assist with preprocedural evaluations and postprocedure follow up.[25,26] Preprocedure, the APN reviews the patient's medical history, pertinent laboratory work, and evaluates for any possible contrast allergies which would indicate a need for premedication orders. Coagulopathies may be identified which require the APN to involve hematology in the case.[1,2,17] A transthoracic echocardiogram is reviewed to evaluate pulmonary artery pressure and RV function.[1,7] In addition to echo data, the severity of PH is evaluated by review of the patient's right heart catheterization data and the patient's functional status including current symptoms and limitations. A thorough medication reconciliation as well as documentation of baseline activity tolerance and oxygen requirements are also evaluated prior to BPA. Imaging review with the IR and multidisciplinary team is an integral step to identify the location and nature of thromboembolic lesions. Distal lesions in the segmental and subsegmental vasculature, down to small pulmonary arteries of 2 to 5 mm in diameter, that are considered inaccessible to PTE may be amenable to BPA.[5,7]

As an educator, the APN has an important role within the multidisciplinary team providing patient and family education to enhance understanding of the disease state, explaining the BPA procedure, and assisting with care coordination to help the patient navigate successfully through the process.[7,28] Quality preprocedural education empowers the patient to make decisions that will meet their needs and goals of care. The APN provides this education through the creation of patient-specific education materials and helps to educate hospital staff in the care of these complex patients to optimize outcomes.[29]

BPA is performed in a staged, stepwise manner to reduce radiation exposure and to decrease the risk of complications such as reperfusion pulmonary edema and renal impairment due to contrast medium over 1 or multiple sessions.[1,19,21] Multiple vessel locations may be addressed during a single BPA session and are generally limited to 1 lung. At our institution, 2 separate sessions are usually performed during 1 hospitalization, allowing for at least 24 hours in between sessions. Postprocedural monitoring takes place in the medical intensive care unit and involves cardiac monitoring and ongoing evaluation of oxygenation with close attention to increased oxygen requirements that may indicate lung injury. The IR APN also monitors the patient for potential procedural complications, all of which require prompt intervention, including reperfusion pulmonary edema that may manifest immediately or several days postprocedure, hemoptysis, contrast associated renal dysfunction, and access site issues.[21] Postprocedural labs including CBC and BMP are monitored closely. Serial chest x-rays are reviewed to survey for reperfusion pulmonary edema and/or pulmonary hemorrhage that may occur as a result of vascular injury during BPA.[21] At our institution, resumption of oral anticoagulation is multifactorial, taking into consideration the patient's overall stability, and is usually resumed the evening after the procedure if there are no bleeding complications or subsequent procedures scheduled. Close monitoring for signs and symptoms of bleeding after restarting anticoagulation is imperative. The APN ensures that patients understand the importance of taking oral anticoagulation as directed with a discussion of warning signs to contact their provider post-BPA. The CTEPH multidisciplinary team collaborates to determine if a second session is appropriate during a given hospitalization based on the patient's response to the initial BPA including change in PA pressures post-BPA, and overall stability without complications or increases in oxygen requirements. Similar criteria are used to determine timing of discharge with most patients being discharged as early as 24 to 48 hours post-BPA. In the event future procedures are warranted, the risks and benefits of additional interventions will be reviewed by the multidisciplinary CTEPH team as an outpatient.

APN ROLE: FOLLOW UP POST-BPA

Post-BPA follow up with Pulmonary Vascular Disease clinic is essential and should be arranged during the hospital admission to ensure a seamless discharge and continuity of care in the outpatient setting. At our institution, like other expert BPA centers, 4-week follow-up includes repeat perfusion imaging, echocardiography, functional class assessment, 6-minute walk testing, and evaluation of brain natriuretic peptide levels.[30,31] At this first posthospital visit, discussion about timing of the next staged BPA procedure, if indicated, occurs. The quantity of procedures performed will vary from patient to patient and is determined by severity of disease, target lesion morphology and accessibility, as well as the expertise of the BPA center.[30,32] If additional targeted areas

are identified, a repeat BPA session is scheduled within 4 to 6 weeks.[30] On average, anywhere from 2 to 10 sessions are required.[30,32]

Medical therapy to treat inoperable CTEPH, both pre-BPA and post-BPA, is also discussed in the outpatient setting. Riociguat is a soluble guanylate-cyclase stimulator that works to promote vasodilation and decrease pulmonary vascular remodeling and inflammation, and is the only drug approved for treatment of CTEPH.[31,33] Current research is investigating the use of riociguat and BPA in combination therapy to improve patient outcomes. These data suggest that patients treated with medical therapy prior to BPA decrease the risk of complications in the postprocedure setting, indicating the benefit of sequential treatment methods to improve functional capacity and hemodynamics, and reduce potential complications associated with BPA.[30-34]

Anticoagulation in this patient population is lifelong, usually with use of either vitamin K antagonists or direct oral anticoagulants, however there is limited data to make formal recommendations in regards to direct oral anticoagulants therapy specifically.[31,32,35] Current guidelines recommend vitamin K antagonists for CTEPH patients, with a target INR range of 2 to 3, though there is clearly a need to evaluate the safety of direct oral anticoagulants therapy compared to standard of care in this population with further prospective data review.[31]

Ultimately, further research is needed to define the standards of practice across institutions and provide data on long-term outcomes in BPA.

SUMMARY

Research has consistently demonstrated that APNs provide high-quality care with excellent outcomes that are safe, patient-centered, and cost effective. Involvement of an APN on the multidisciplinary team for patients with complex illnesses such as CTEPH has been shown to lead to improved outcomes and greater patient satisfaction.[8,22,36-43] At our center, the addition of APNs from the pulmonology, cardiothoracic surgery, and IR specialties enhances multidisciplinary collaboration among the CTEPH team and is aimed at improving care and outcomes in this patient population.[29]

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