ISSN 1933-088X

Advances in Pulmonary Hypertension

Vol 22, No 4; 2023

Official Journal of the Pulmonary Hypertension Association

Diseases Related to PH Without Effective Therapies

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.

Advances in
Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

PUBLISHER
Pulmonary Hypertension Association
Matt Granato, LL.M., MBA, President and CEO

PHA OFFICE
Pulmonary Hypertension Association
8401 Colesville Road, Suite 200
Silver Spring, MD 20910
301-565-3004; 301-565-3994 (fax)
Advances@PHAssociation.org

PUBLISHING OPERATIONS
Tori Cortez,
Managing Editor

Advances in Pulmonary Hypertension is available online at www.AdvancesinPH.org.

Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

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.

Advances in Pulmonary Hypertension's Web Platform

Advances in Pulmonary Hypertension is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

This issue of *Advances in Pulmonary Hypertension* focuses on forms of pulmonary hypertension (PH) for which Food and Drug Administration–approved specific therapies are limited or nonexistent. While these diseases share some similarities in clinical presentation and hemodynamics with pulmonary arterial hypertension (PAH), there are differences in pathogenesis and, often, the coexistence of lung or left-sided heart disease which make clinical management more challenging. We are thankful to our authors and roundtable participants for their outstanding contributions to this issue. A review of these articles will demonstrate that these diseases, while similarly affecting the pulmonary vasculature, are quite different from each other. In reading through this issue, we are impressed with how clinically useful these papers will be for all clinicians involved in the care of people living with PH.

Mazen O. Al-Qadi and H. James (Jimmy) Ford start off the issue by providing an updated review of the complexity of sarcoidosis-associated PH. We understand that, in individual patients, the contributions of pulmonary arteriopathy, left-sided cardiac dysfunction, interstitial lung disease, and chronic thromboembolism to sarcoidosis-associated PH is variable, and this has impact on the therapeutic approach. Their review is a helpful, focused overview for clinicians at all levels of clinical experience, and they discuss how to approach off-label use of PAH therapy in segments of this population.

We really enjoyed the overview of the rare and extremely challenging pulmonary veno-occlusive disease (PVOD) written by Marc Humbert and David Montani. This is one of the most comprehensive overviews of the biology, diagnostic approach, and management of PVOD we have read. It is a must for all involved in the care of patients with PH, as PVOD is a critical diagnosis not to be missed, especially as many of our therapies are not well tolerated in these patients. This paper is coupled with the report by Martin Rofael et al. on the use of lung transplantation in patients with PVOD prior to the development of PH, which represents an interesting and provocative approach to treating these patients.

The round table discussion on off-label use of PAH therapy in patients with non-Group 1 PAH brought together experts in the management of PH related to left-sided heart disease, end-stage renal disease, sarcoidosis, sickle cell disease and other chronic hemolytic anemias, and chronic thromboembolic disease for a lively overview of how clinicians approach these challenging cases in their own practices. We were impressed by the often-overlapping approaches across centers, although clearly there were some differences in opinions.

This issue concludes with the 2023 PH Professional Network (PHPN) Symposium abstracts which allow all of us to review the science presented last fall at the conference. It is exciting to see the great work going on in PH clinical care.

We want to thank our contributing authors for their hard work in putting this issue together and for sharing their knowledge and experience with all of us. To our readers, we hope you enjoy this issue and learn things you can take back to your patients.

Elizabeth S. Klings, MD
Professor of Medicine
Director, Center for Excellence in Sickle Cell Disease
Boston University School of Medicine

Murali Chakinala, MD
Professor of Medicine
Division of Pulmonary and Critical Care
Washington University in St. Louis School of Medicine

REGULAR ARTICLE

Sarcoidosis-Associated Pulmonary Hypertension

Mazen O. Al-Qadi, MD
Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, University of Pittsburgh, Pittsburgh, PA

H. James Ford, MD
Division of Pulmonary Diseases and Critical Care Medicine, University of North Carolina-Chapel Hill, Chapel Hill, NC

Sarcoidosis is characterized by non-necrotizing granulomatous aggregations affecting a range of organs, with thoracic structures involved in 90% to 95% of cases. This granulomatous disease can impact the pulmonary vasculature via different mechanisms resulting in sarcoidosis-associated pulmonary hypertension (SAPH). These include postcapillary disease (left heart disease), immune-mediated granulomatous vasculopathy, hypoxemia, thromboembolism, pulmonary vascular compression and/or stenosis by mediastinal lymph nodes/fibrosis, or sarcoidosis-related portal hypertension. SAPH is a serious complication, especially in those with end-stage lung disease. A thorough evaluation is crucial to delineate the predominant mechanism of PH in the affected individual. The management of SAPH is complex and necessitates a personalized, multifaceted approach, targeting the specific mechanisms and underlying pathologies. Such patients are best served at specialized Pulmonary Hypertension and Sarcoidosis Centers. A notable phenotype within SAPH is the "pulmonary arteriopathy" group, characterized by milder parenchymal disease and a favorable response to PAH-targeted therapy, whereas patients with active granulomatous inflammation are likely to respond to immunosuppression. Several PAH therapies have been used to treat SAPH, however, clear direction on the use of PAH therapies in SAPH is still lacking. Patients receiving pulmonary vasodilators should be carefully monitored for potential deterioration in gas exchange or development of pulmonary edema, which could suggest underlying left heart disease or pulmonary veno-occlusive disease. Timely referral for lung transplant evaluation is crucial for those with SAPH and severe parenchymal lung disease, ensuring a comprehensive and patient-centered care approach. Much work remains to be done to understand the exact pathogenesis of SAPH, as well as to develop therapies that clearly improve outcomes for these patients.

INTRODUCTION

Sarcoidosis is a multisystem disease characterized by the aggregation of nonnecrotizing granulomas in various organs. Thoracic involvement is the most common, found in 90% to 95% of the cases.[1] The disease can affect all chest compartments, including the lung parenchyma, airways, lymph nodes and lymphatic vessels, pleural space, and pulmonary vasculature. While many patients experience spontaneous resolution of the disease, even without treatment, a subset will progress to develop severe fibrocystic disease. Approximately 5% of patients with advanced sarcoidosis succumb to the disease, primarily due to respiratory failure. Pulmonary hypertension (PH) frequently complicates sarcoidosis, especially in patients with end-stage lung disease. Epidemiologic studies have shown that the prevalence of sarcoidosis-associated PH (SAPH) depends on the stage of pulmonary disease and the diagnostic methods used to measure or estimate pulmonary vascular pressures. In a study by Iwai et al,[2] evidence of pulmonary vascular disease was found on autopsy in 5% of cases with significant parenchymal involvement. This prevalence aligns closely with the findings from a study in the Netherlands where SAPH was found in approximately 9% of patients using transthoracic echocardiography (TTE) and 3.5% by right heart catheterization (RHC).[3] However, other studies revealed a higher prevalence of SAPH. For example, a study of 162 sarcoidosis patients by Bourbonnais et al[4] revealed a SAPH prevalence of 21% by TTE and 15% by RHC. Importantly, SAPH occurs in up to 74% of patients with advanced parenchymal involvement listed for lung transplant.[5]

A recent meta-analysis by Zhang et al,[6] which included a pooled sample of 632 368 patients with sarcoidosis found a prevalence of SAPH in general sarcoidosis population to be 16.4% when estimated by TTE and 6.4% by RHC. In patients with advanced sarcoidosis; however, the prevalence of SAPH diagnosed by RHC was 62.3%.

It is important to note that PH can occur in sarcoidosis in the absence of significant parenchymal lung disease in 11% to 32% of patients.[7,8] These patients may behave clinically much like a patient with group 1 pulmonary arterial hypertension (PAH). The histopathology of the pulmonary vessels in such patients is described in Figure 2.

In addition, patients with sarcoidosis also develop left heart disease and may present with PH related to elevated left ventricular filling pressures, much like

Key Words—Sarcoidosis; pulmonary hypertension; pulmonary arteriopathy; SAPH
Correspondence: hubert_ford@med.unc.edu

 DOI:10.21693/1933-088X-22.4.152

group 2 PH. These varying contributors and potential multifactorial influences on hemodynamics can create a challenge for the clinician attempting to parse out the relative contributions to PH of each, and further determine the best management approach. This heterogeneity adds to the complexity of these patients and is one of the reasons SAPH is categorized under group 5 PH.

PATHOGENESIS

PH is defined as an elevated mean pulmonary artery pressure (mPAP) >20 mm Hg according to the 6th World Symposium on Pulmonary Hypertension. It is categorized into 5 groups based on the underlying mechanism, as shown in Table 1. SAPH is classified under group 5 due to its often multifactorial etiology and overlapping mechanisms, as illustrated in Figure 1.[9]

Mechanisms of Pulmonary Arteriopathy

Immune-Mediated Vasculopathy: Pulmonary arteriopathy is the hallmark of PAH. It is characterized by progressive proliferative and occlusive vascular pathology that results from endothelial dysfunction, pulmonary vascular smooth muscle hyperplasia, and the proliferation of myofibroblasts. Vascular remodeling leads to excessive pulmonary vasoconstriction, intimal fibrosis, and angiogenesis. These structural changes develop under the influence of several inflammatory mediators and growth factors. A similar proliferative arteriopathy has been well recognized in SAPH and resembles PAH. T lymphocytes have been shown to play important roles in the pathogenesis of PAH. Helper T cells (Th1 and Th17 cells) produce several cytokines (interleukin[IL]-2, IL-6, tumor necrosis factor [TNF]-α,

Table 1. Classification of Pulmonary Hypertension Based on the 6th World Symposium on Pulmonary Hypertension

Group 1 PAH	1.1 Idiopathic PAH 1.2 Heritable PAH 1.3 Drug- and toxin-induced PAH 1.4 PAH associated with: 1.4.1 CTD 1.4.2 HIV 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH long-term responders to calcium channel blockers 1.6 PAH with overt features of venous/capillaries involvement (PVOD/PCH)
Group 2 PH due to left heart disease	2.1 PH due to heart failure preserved LVEF 2.2 PH due to heart failure reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular disease leading to post-capillary PH
Group 3 PH due to lungs and/or hypoxia	3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed obstructive/restrictive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders
Group 4 PH due to pulmonary artery obstruction	4.1 Chronic thromboembolic PH 4.2 Other. Pulmonary artery obstructions
Group 5 PH with unclear and/or multifactorial mechanisms	5.1 Hematologic disorders Hemolytic anemias Myeloproliferative disorders 5.2 Systemic and metabolic disorders Pulmonary Langerhans cell histocytosis Glycogen storage disease Neurofibromatosis Sarcoidosis 5.3 Others Chronic renal failure with or without hemodialysis Fibrosing mediastinitis 5.4 Complex congenital heart disease Segmental PH - Isolated pulmonary artery of ductal origin - Absent pulmonary artery - Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries - Hemitruncus - Other Single ventricle - Unoperated - Operated Scimitar syndrome

Abbreviations: CTD indicates connective tissue disease; HIV, human immunodeficiency virus; LVEF, left ventricle ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; - PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

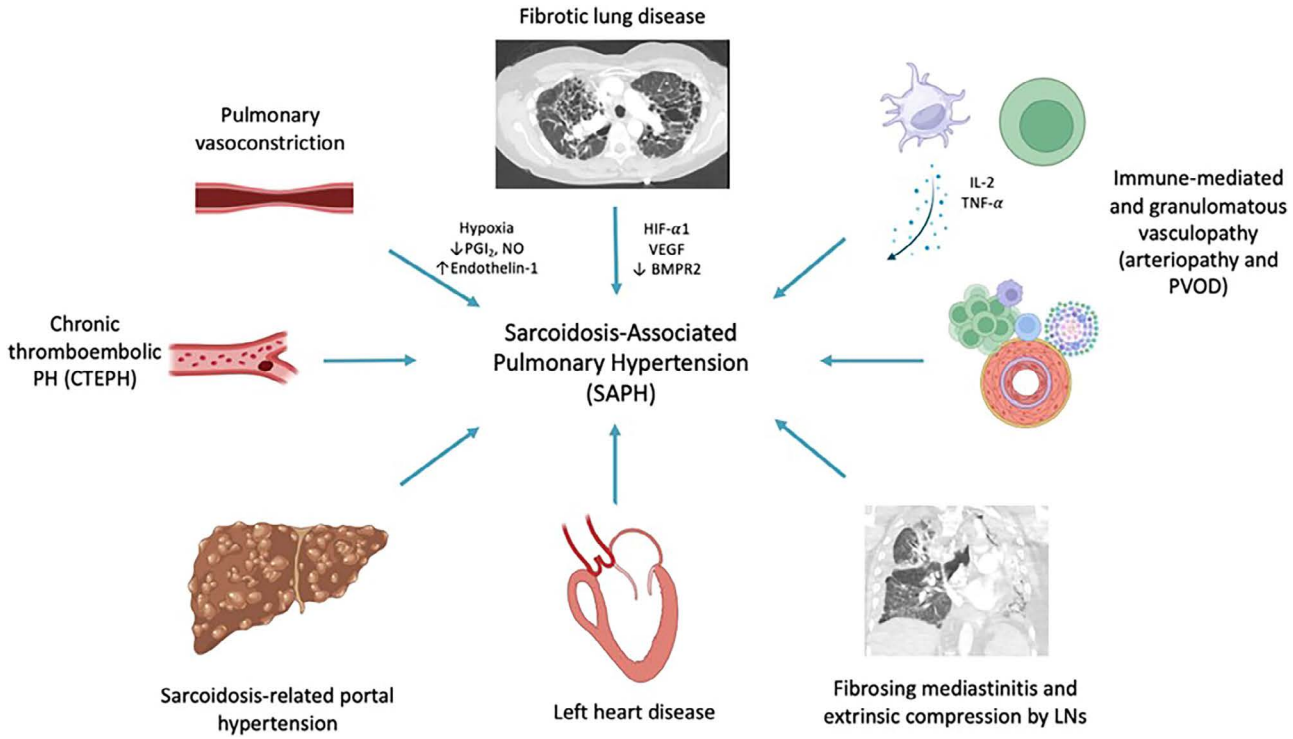


Figure 1: Multiple potential mechanisms contributing to the development of sarcoidosis-associated pulmonary hypertension (SAPH). BMPR2 indicates bone morphogenetic protein 2; CTEPH, chronic thromboembolic pulmonary hypertension; HIF, hypoxia-inducible factor; LN, lymph nodes; NO, nitric oxide; PGI_2, prostacyclin; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; VEGF, vascular endothelial growth factor. Image created with BioRender.com.

interferon-γ) that propagate the inflammatory response seen in PAH.[10,11]

In sarcoidosis, T lymphocytes, mainly CD4 cells, are known to be the primary drivers of inflammation, eventually progressing to granuloma formation. The cytokine profile in the granulomatous inflammation of sarcoidosis overlaps with that seen in PAH. IL-2 is an important growth factor released by activated immune cells, resulting in differentiation and proliferation of T lymphocytes. IL-2 levels are often elevated in patients with active and extensive granulomas due to sarcoidosis. The absence of IL-2 promotes apoptosis of activated T lymphocytes. Binding of IL-2 to its receptor on the surface of lymphocytes results in the cleavage and release of the receptor into the circulation. Therefore, soluble IL-2 receptor levels serve as a marker of T lymphocyte activation in sarcoidosis and can be used to monitor disease activity.[12,13]

In animal models of guinea pigs, IL-2 has been shown to cause pulmonary vasoconstriction and increase pulmonary capillary permeability, leading to pulmonary edema.[14] Furthermore, elevated IL-2 levels have been found in patients with heritable PAH, where they predict survival, promote expression of endothelin-1, and contribute to pulmonary hypertension.[15,16]

TNF, a major mediator of granuloma formation in sarcoidosis, has been found to drive PAH by suppressing the bone morphogenetic protein 2 (BMPR-2), which is responsible for antiproliferative signaling.[17]

Endothelial dysfunction is well recognized in sarcoidosis, possibly as a result of antibody-mediated endothelial injury.[18] There is evidence to suggest that extensive pulmonary endothelial damage may occur even before granuloma formation.[19] Pulmonary vascular remodeling seen in SAPH is propagated by serotonin-related pulmonary vascular smooth muscle hyperplasia that can be similar to that observed in patients with PAH.[20]

Granulomatous angiitis is another important manifestation of pulmonary sarcoidosis. In an autopsy study by Takemura et al,[21] a review of 40 sarcoidosis cases demonstrated granulomatous vasculitis in all cases, with occlusion of small vessels (more prominent in venules than arterioles). Obliterative pulmonary venulopathy of sarcoidosis is possibly the mechanism behind pulmonary veno-occlusive disease (PVOD), which has been described in sarcoidosis.[22,23] Plexiform lesions similar to those seen in patients with PAH have been reported but are not commonly seen in SAPH.

Granulomatous angiitis in sarcoidosis has been reported in other studies with frequency ranging from 41% to 69% of patients.[24,25] This may explain the improvement in pulmonary hemodynamic with immunosuppressive therapy noted in some patients.[26,27] The various types of arteriopathy that have been observed in SAPH are shown in Figure 2.

Imbalance in Vasoactive Substances: Pulmonary vascular homeostasis is maintained by several vasoactive substances, namely nitric oxide (NO), prostacyclin (PGI_2), endothelin (ET), and serotonin (5-HT).[28] Levels of pulmonary vasodilators (PGI_2 and NO) are reduced in patients with PAH, whereas endothelin-1, a potent vasoconstrictor with mitogenic properties, is elevated. This imbalance contributes to increased

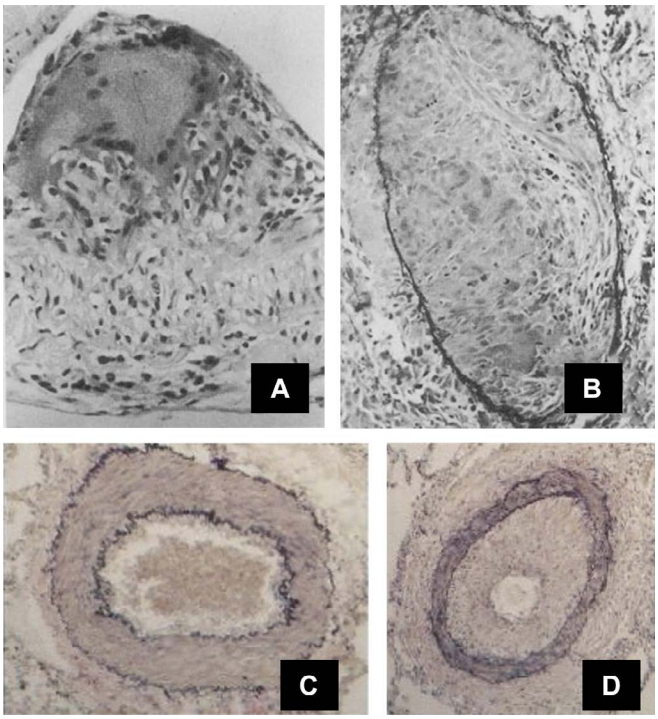


Figure 2: Various types of pulmonary vascular lesions observed in sarcoidosis-associated pulmonary hypertension. (**A**) is representative of granulomatous vascular disease. (**B**) shows venous fibrosis, much like seen in pulmonary venoocclusive disease. (**C** and **D**) demonstrate nongranulomatous pulmonary arteriopathy, like that seen in traditional group 1 pulmonary arterial hypertension. Figures 2A and 2B are reprinted with permission from Rosen et al 1994[91]; Figures 2C and 2D are reprinted with permission from Pietra 2004.[92]

pulmonary vascular resistance (PVR) in PAH. Sarcoidosis patients have a similar perturbance. Prostaglandin-endoperoxidase synthase-2 (also known as cyclooxygenase-2 [COX-2]) is a key enzyme in arachidonic acid metabolism and production of prostaglandins. This enzyme is diminished in patients with sarcoidosis, impairing prostaglandin synthesis.[29] In a study by Bachwich et al,[30] prostaglandin production was significantly reduced by alveolar macrophages in patients with sarcoidosis compared to healthy volunteers Conversely, endothelin-1 levels have been shown to be elevated in the blood and bronchoalveolar lavage in patients with sarcoidosis.[31,32] NO is a potent pulmonary vasodilator that is released in inflammatory states. However, despite granulomatous inflammation in sarcoidosis, NO levels are not increased.[33] Additionally, prolonged corticosteroid therapy (for presumed active sarcoidosis) may result in NO depletion due to altered endothelial production.[34,35]

Interplay of Interstitial Lung Disease, Lymphadenopathy and PH

Destruction of the pulmonary vascular bed by fibrocystic changes is a contributing factor in the development of SAPH. Sarcoidosis is characterized by heterogeneous distribution of fibrosis, with predilection to proximal airways. This often leads to distortion of the central vasculature and altered flow, resulting in shear stress and endothelial injury.

Additionally, fibrosis alters pulmonary vascular capacitance (ie, the ability of the vessels to dilate and recoil during the cardiac cycle) and increases pulmonary vascular pressures. The development of pulmonary hypertensive lesions (fibroblast proliferation and vascular smooth muscle hyperplasia) exacerbates regional hypoxia in lung areas distal to narrowed or occluded vessels. Hypoxia due to parenchymal lung disease is likely a prominent mechanism, given the high prevalence of SAPH in patients with advanced fibrosis and chronic respiratory failure.

These pathologic processes are usually evident on radiographic studies (corresponding to Scadding stage 4) and pulmonary function tests, which may show reduced forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO). Moreover, pulmonary vasoconstriction develops secondary to alveolar hypoxia and increased pulmonary vasoreactivity.[36] Importantly, the physiologic consequences of alveolar hypoxia are far beyond simple pulmonary vasoconstriction. Hypoxia-inducible factor (HIF)-1α), a transcription factor, is highly expressed when the oxygen-sensitive α subunit is activated in response to hypoxia. HIF-1α plays a critical role in orchestrating angiogenesis, pulmonary vascular tone regulation, and cellular proliferation.[37] Expression of HIF-1α has been shown to be upregulated in patients with sarcoidosis, especially those with abnormal lung function tests, or active disease.[38,39] Under hypoxic conditions, the HIF-1α/vascular endothelial growth factor signaling pathway becomes activated in pulmonary endothelial and vascular smooth muscle cells, promoting vasoconstriction, cellular proliferation, and angiogenesis.[40] Recent studies have shown promising results with HIF inhibition in treating idiopathic PAH.[41] Whether these results translate into benefit in SAPH is still to be elucidated. HIF-1α also mediates the Th1/Th17 inflammatory response in sarcoidosis and regulates the production of several key cytokines. Lastly, in animal models, chronic hypoxia has been associated with downregulation of BMPR-2, further promoting pulmonary vascular remodeling.[42]

Extrinsic Compression/Invasion by Mediastinal Pathology: Sarcoidosis has been reported to cause extrinsic compression of pulmonary arteries by enlarged hilar and mediastinal lymph nodes, sometimes necessitating pulmonary artery stenting.[43,44]

In some cases, patients may present with a mismatched ventilation/perfusion scan, even in the absence of parenchymal fibrosis, which can lead to a misdiagnosis of chronic thromboembolic pulmonary hypertension (CTEPH).[45]

Therefore, it is crucial to carefully evaluate these patients by an experienced

team, integrating findings from chest computed tomography (CT) scan, fluorine-18-fluorodeoxyglucose positron emission tomography (FDG PET/CT), and pulmonary angiography to assess thoracic lymph nodes and establish the correct diagnosis. Mediastinal granulomatous inflammation and fibrosing mediastinitis, accompanied by pulmonary vascular invasion, may result in SAPH and can be associated with proliferative changes in the absence of parenchymal disease. Furthermore, stenosis of the pulmonary veins resulting in postcapillary pulmonary hypertension and pulmonary edema has been described in patients with fibrosing mediastinitis secondary to sarcoidosis.[46]

Chronic Thromboembolism

Sarcoidosis is sometimes considered a prothrombotic condition as several studies have shown increased prevalence of venous thromboembolic disease in the absence of other hypercoagulable states.[47,48,49]

This is likely secondary to chronic inflammation and alterations in the coagulation and fibrinolytic systems. In addition, patients with sarcoidosis have higher prevalence of antiphospholipid antibodies, which are known to be associated with arterial and venous thrombosis.[50] This increases the risk of CTEPH and adds to the mechanisms of SAPH. CTEPH in patients with sarcoidosis has been reported in a small case series.[51]

Sarcoidosis-Related Portal Hypertension

Liver involvement is common in sarcoidosis, with evidence of hepatic granulomas in 70% of cases. These are often asymptomatic but may manifest clinically in 30% of patients.[52] Portal hypertension may complicate hepatic sarcoidosis in some patients. In a retrospective study by Fauter et al,[53] 12 patients with sarcoidosis and hepatic involvement were followed for over 10 years. Nine patients developed evidence of portal hypertension (ascites, esophageal varices, or both). The development of portal hypertension increases the risk of SAPH due to endothelial injury (high cardiac output–related shear stress), dysregulated pulmonary vascular tone (increased circulating vasoconstrictors), and pulmonary emboli from portal circulation (through portosystemic shunts).

Left-Sided Heart Disease and Pulmonary Venous Hypertension

Sarcoidosis can affect the heart in approximately 20% to 25% of patients, leading to a variety of cardiac manifestations, including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, both of which can result in postcapillary PH.[54] The prevalence of postcapillary SAPH is variable. In one retrospective study, pulmonary artery wedge pressure (PAWP) was elevated in 29% of the patients with SAPH.[55] Using cardiac magnetic resonance, one study found 15% of SAPH was related to cardiac involvement by sarcoidosis.[56] In a recent study by Mathijssen et al,[57] only 7.5% of patients had postcapillary SAPH using RHC.

Notably, the detection of heart failure with preserved ejection fraction by TTE can be challenging in sarcoidosis patients. Therefore, the use of advanced imaging modalities such as echocardiography with speckle tracking analysis, cardiac magnetic resonance imaging, or even RHC may provide more insights than TTE.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The diagnosis of SAPH requires a high index of suspicion given the nonspecific symptoms such as dyspnea, chest pain, and palpitations. Symptoms of right heart failure (elevated jugular venous pressure, edema of the lower extremities, loud P_2, right ventricular heave) are late manifestations and lack sensitivity. Exertional syncope can be seen in patients with severe SAPH; however, syncope at rest may signify underlying arrhythmias and should prompt workup for cardiac sarcoidosis.

When evaluating patients with sarcoidosis, pulmonary function tests (spirometry, lung volumes and diffusion capacity for carbon monoxide, DLCO) and a 6-minute walk distance (6MWD) test are essential to objectively assess the physiologic impairment. Besides assessing the need for supplemental oxygen, the 6MWD test can provide valuable information such as delayed heart rate recovery, which has been linked to poor outcomes in patients with PH.[58] Features suggestive of SAPH include persistent or unexplained dyspnea, clinical signs of right-sided heart failure, resting hypoxemia, DLCO $< 60\%$ predicted, and a reduced DLCO that is out of proportion to the degree of restriction (FVC/DLCO > 1.6). In a study of 363 patients with advanced sarcoidosis, the need for supplemental oxygen was the only predictor of SAPH.[59]

Serum cardiac biomarkers such as N-terminal pro–B-type natriuretic peptide (NT-proBNP) (or BNP) and the neutrophil:lymphocyte ratio (a surrogate for the degree of systemic inflammation in sarcoidosis) can also help identify patients with SAPH.[60] The extent of pulmonary fibrosis should be assessed with imaging studies, preferably chest CT. Extensive pulmonary fibrosis (ie, Scadding stage 4 involving $> 20\%$ of lung parenchyma) and enlarged pulmonary artery (indexed to body surface area, > 15.2 mm/m^2) should raise suspicion for SAPH.[61]

Screening asymptomatic patients for SAPH has the potential for early detection before the functional status and hemodynamics are severely impaired. Whether screening improves clinical outcome in those patients remains unknown. Doppler TTE is the first diagnostic modality to assess for SAPH when suspected based on symptoms, clinical presentation, and other diagnostic test findings. A maximum tricuspid regurgitant velocity (TRV_{max}) < 2.9 m/s makes SAPH unlikely, whereas $TRV_{max} > 3.4$ m/s or the presence of right ventricular dilation or dysfunction (eg, reduced tricuspid annular plane systolic excursion) highly suggest SAPH.[62] Patients with TRV between 2.9 and 3.4 m/s may also be considered for additional evaluation for PH by RHC (see Figure 3). For this group, a determination as to the relative severity of apparent right heart dilatation/dysfunction and pulmonary parenchymal disease should be made to assist in guiding the decision to proceed with RHC. We suggest using an FVC cutoff of 50% predicted as a guideline.

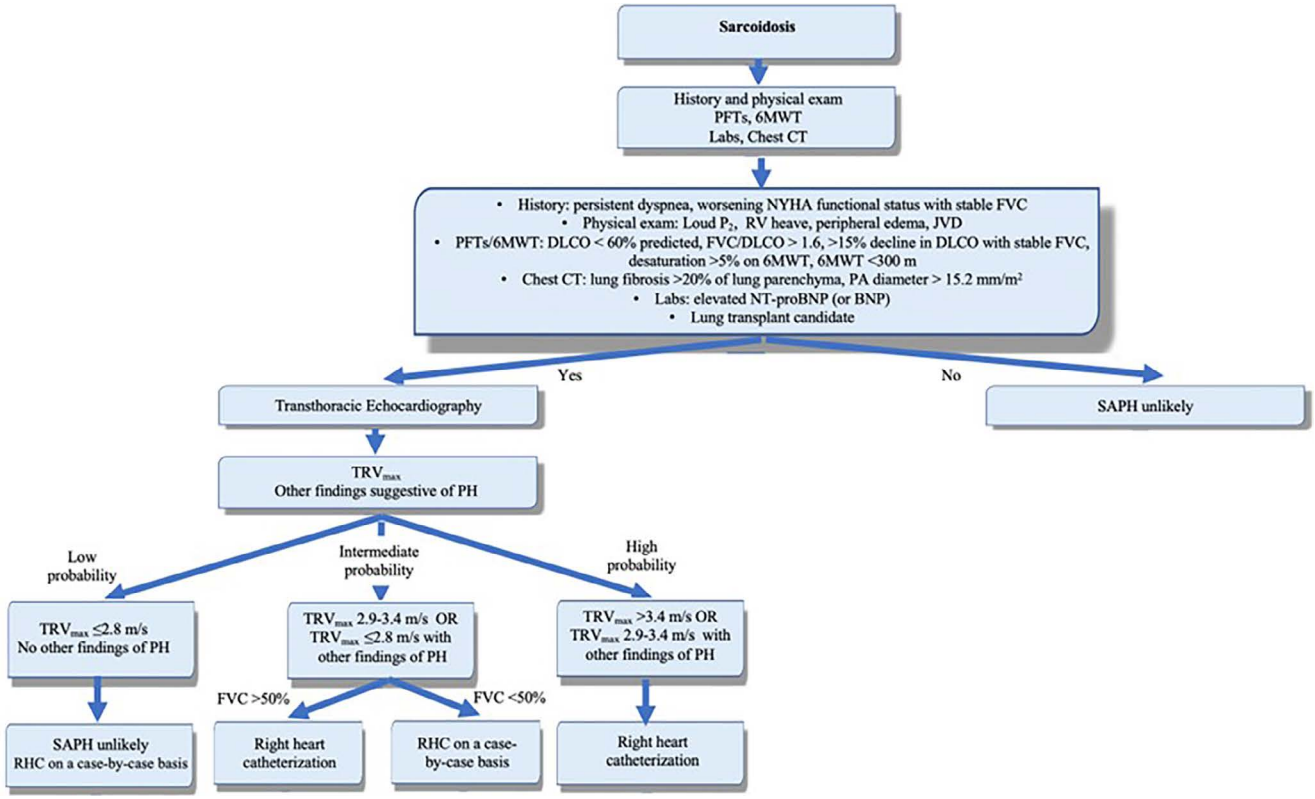


Figure 3: Proposed screening and diagnostic algorithm for the assessment of sarcoidosis-associated pulmonary hypertension (SAPH); adapted and reproduced with permission of the ERS 2024: European Respiratory Review 31 (163) 210165; DOI: 10.1183/16000617.0165-2021 Published 9 February 2022.[62] 6MWD indicates 6-minute walk distance; CT, computed tomography; DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; JVD, jugular venous distension; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PFT, pulmonary function test; RHC, right heart catheterization; RV, right ventricle; TRV, tricuspid regurgitant velocity.

Discretion is needed on a case-by-case basis, preferably at an expert center.[62] RHC remains the "gold standard" for confirming PH, defined as an elevated mPAP > 20 mmHg. Precapillary SAPH is characterized by an elevated PVR (> 2 Wood units) and a normal PAWP of 15 mm Hg or less. Patients with an elevated PAWP > 15 mm Hg are considered to have postcapillary SAPH. The PVR threshold to diagnose precapillary PH was recently lowered from 3 Wood units in light of studies that demonstrated increased mortality in PH patients with a PVR > 2.2 Wood units.[63]

If the PAWP is at the upper border of normal range (eg, 12-15 mm Hg) and clinical suspicion of left heart disease is high, provocative maneuvers (eg, fluid bolus or exercise) should be applied. If the post–fluid challenge (infusion of 7 mL/kg or 500 mL saline) reveals a PAWP > 18 mm Hg, it strongly suggests the presence of postcapillary PH. Alternatively, a postexercise PAWP exceeding 25 mm Hg is highly indicative of postcapillary SAPH. A fluid challenge is more practical as exercise equipment is not universally available, and interpretation is prone to error, especially in patients with large respiratory swings in pulmonary vascular pressures.

The findings (and tracings) from RHC should be carefully reviewed by a multidisciplinary team familiar with SAPH, preferably in the presence of a sarcoidosis specialist.

MANAGEMENT

Supportive Measures and Treatment of Comorbidities

Treatment of SAPH is challenging due to its multifactorial nature and often overlapping mechanisms as discussed earlier. Therefore, the most predominant contributing mechanism(s) to SAPH should be identified and treated accordingly. This includes correction of hypoxemia (if present) with supplemental oxygen and treatment of comorbid conditions that may exacerbate hypoxemia or worsen pulmonary vascular pressures (eg, obstructive sleep apnea). Left heart disease should be optimized according to current guidelines. Diuretics should be prescribed to alleviate symptoms of volume overload when necessary.

Immunosuppression and Vascular Stenting

SAPH due to mediastinal pathologies, such as fibrosing mediastinitis or lymph nodes causing compression on pulmonary vessels, is not uncommon. Therefore, chest CT and/or FDG PET/CT may be needed to rule out mediastinal pathologies. Stenosis of the pulmonary vasculature can also be visualized on chest CT. Pulmonary vascular stenting in such cases has been reported to improve hemodynamics. In a study by Liu et al,[64] pulmonary vascular distortion and compression were found in 11% of SAPH patients, all of whom demonstrated improvement in symptoms, pulmonary vascular resistance, and arterial oxygen saturation following stenting of the pulmonary arteries.

Uptake on FDG PET can help identify patients who may respond to corticosteroids (or other immunosuppressive

therapies) for shrinking large lymph nodes or treating inflammatory mediastinal pathology (ie, fibrosing mediastinitis due to sarcoidosis). It may also aid in identifying patients with active parenchymal sarcoidosis for whom optimizing immunomodulators may attenuate granulomatous vascular inflammation, resulting in improved pulmonary vascular pressures.[65]

In a study of 22 patients with severe SAPH by Nunes et al,[66] significant and sustained hemodynamic improvement was observed in 3 out of 10 patients who received high-dose corticosteroids.]

Pulmonary Vasodilators

Pulmonary arteriopathy, characterized by elevated PVR with minimal or no parenchymal disease and exclusion of other causes of PH, is an important mechanism of precapillary SAPH. The routine use of pulmonary vasodilators in SAPH is not recommended and should be reserved for select patients who exhibit the "pulmonary arteriopathy" phenotype, leading to PH that is seemingly "out of proportion" to the degree of underlying lung disease. Identifying this phenotype can be challenging, but generally patients may have significant PH (eg, mPAP > 35 mm Hg and/or cardiac index < 2.5 L/min/m^2) with less severe parenchymal disease on imaging (fibrosis on CT < 20%) or progressive right ventricle failure. In a study by Barnett et al,[67] patients with SAPH and less fibrotic disease (FVC > 50% predicted or stage 0 to 3) demonstrated more improvement in exercise capacity with PAH therapy compared to those with stage 4 or severe restriction.

While the use of PAH-targeted therapies can be justified in such patients, there is a significant concern regarding the potential for worsening gas exchange. Furthermore, the presence of left heart disease and/or PVOD also carries the risk of pulmonary edema when using pulmonary vasodilators.[68] On the other hand, these therapies may provide some benefits. A meta-analysis of 5 studies revealed that SAPH patients who received pulmonary vasodilators experienced significant improvement in hemodynamics, including mPAP, cardiac index, and PVR.[69] Additionally, a recent

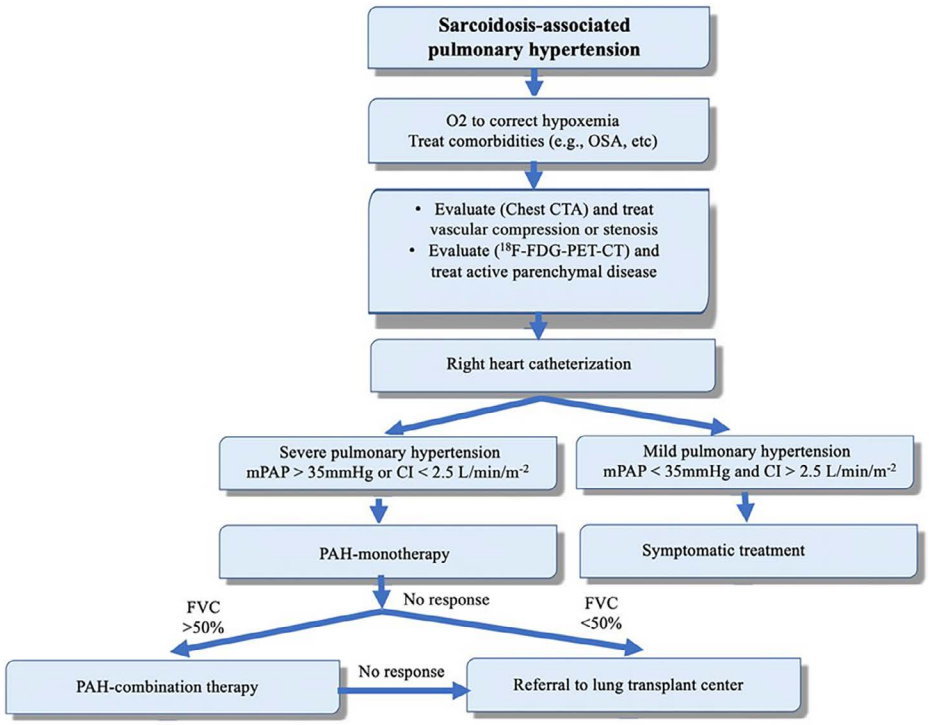


Figure 4: Proposed algorithm for management of sarcoidosis-associated pulmonary hypertension (SAPH); adapted and reproduced with permission of the ERS 2024: European Respiratory Review 31 (163) 210165; DOI: 10.1183/16000617.0165-2021 Published 9 February 2022.[62] CI indicates cardiac index; CTA, computed tomography angiography; F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography; FVC, forced vital capacity; mPAP, mean pulmonary artery pressure; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension.

study by Gayen et al[70] demonstrated that in patients with SAPH, pulmonary vasodilators may reduce hospitalization and decline in FVC, similar to the benefit observed with inhaled treprostinil in PH-interstitial lung disease (ILD). In another study, Albujoq et al[71] retrospectively evaluated 50 SAPH patients; 22 patients were treated with pulmonary vasodilators. Treatment with PAH therapy was associated with significant improvement in mPAP, BNP levels, and 6MWD.[71]

A paucity of robust data to support the use of PAH-targeted therapies in SAPH makes the selection of therapies mostly based on the severity of PH and the extent of parenchymal lung disease.[62] For example, patients with severe SAPH and mild fibrotic disease are more likely to receive intravenous prostanoids whereas patients with mild to moderate SAPH and more severe fibrotic changes tend to receive either oral therapies or inhaled prostacyclins.

Currently used PAH-specific therapies target 3 major pathways: the NO pathway (phosphodiesterase-5 inhibitors: sildenafil and tadalafil; soluble guanylate cyclase stimulators: riociguat; and inhaled NO); the endothelin pathway (endothelin receptor antagonists: bosentan, ambrisentan, macitentan), and the prostaglandin I_2 pathway (epoprostenol, treprostinil, iloprost, selexipag). Table 2 summarizes published studies evaluating PAH-specific therapies in SAPH.

Nitric oxide pathway: Phosphodiesterase-5 inhibitors (PDE5i) have been shown to have no significant impact on gas exchange in PH-ILD. This is because they exhibit a preferential vasodilatory effect in areas where NO is more available, primarily in well-ventilated areas, as oxygen is required for NO production.[72] Furthermore, PDE5i have demonstrated a favorable effect on hemodynamic measures in patients with SAPH. However, their impact on other important PH outcome variables, such as 6MWD has shown inconsistency. A small prospective open-label study conducted by Ford et al[73] evaluated tadalafil in patients with SAPH, revealing no improvement in 6MWD. Nevertheless, tadalafil was well tolerated with no

evidence of worsening ventilation/perfusion mismatch.

In another study, sildenafil was retrospectively evaluated in 19 patients with RHC-confirmed severe SAPH (median mPAP 36 mm Hg). While sildenafil resulted in significant hemodynamic improvement, including reduction in PVR by 4.9 Wood units and an improvement in cardiac index, no consistent change in 6MWD was observed.[74] However, a retrospective study that included 29 SAPH patients who were treated with sildenafil demonstrated significant improvement in 6MWD, right ventricle function by TTE, and serum BNP levels.[75] This study included patients with more severe SAPH (higher mPAP, higher PVR, and lower cardiac index) even though, similar to other studies, most patients had significant parenchymal disease (Scadding stage 3 and 4). Another agent that targets the NO pathway is riociguat, a soluble guanylate cyclase stimulator. Riociguat is contraindicated in patients with PH-ILD (not SAPH specifically) due to an increased risk of serious adverse events and mortality.[76] However, in

Table 2. Published Studies on Treatment of Sarcoidosis-Associated Pulmonary Hypertension with Pulmonary Arterial Hypertension Therapies and Relevant Characteristics and Outcomes Observed

Study	Study design	Therapy	Nol of patients	Hemodynamic effect	Clinical outcomes
Preston et al[36]	Prospective observational	iNO, CCB, epoprestenol	19	↓PVR ↓mPAP ↑CI	↑6MWD ↑functional class
Fisher et al[68]	Retrospective	Epoprestenol, treprostinil	7	↓PVR ↓mPAP ↑CI	↑functional class
Milman et al[74]	Case series	Sildenafil	12	↓PVR ↓mPAP ↑CI	⇔ 6MWD
Baughman et al[83]	Open-label	Iloprost	15	↓PVR ↓mPAP ↑CI	↑6MWD ↑functional class
Judson et al[80]	Open-label	Ambrisentan	21	—	⇔ 6MWD
Dobarro et al[69]	Retrospective	Any PAH-targeted therapy	11	↑CI	↑6MWD
Baughman et al[79]	Randomized, double-blind, placebo controlled	Bosentan	23	↓PVR ↓mPAP	⇔ 6MWD
Keir et al[75]	Retrospective	PDE5i, ERA	33	—	↑6MWD ↑TAPSE ↓BNP
Palermo et al[89]	Retrospective	Bosentan	40	↓PVR ↓mPAP	↑6MWD
Barnett et al[67]	Retrospective	Sildennafil, bosentan, epoprestenol	22	↓PVR ↓mPAP	↑6MWD
Qua et al[90]	Retrospective	Bosentan	45	—	↑6MWD
Ford et al[73]	Prospective open-label	Tadalafil	12	—	⇔ 6MWD
Bonham et al[82]	Retrospective	Epopresteol, treprostinil	26	↓PVR ↑CI	↑functionnal class ↓NT-proBNP
Boucly et al[65]	Registry	PDE5i, ERA, prostacyclin	126	↓PVR ↓mPAP ↑CI	↑functional class
Parikh et al[85]	Retrospective	Inhaled/IV prostacyclins, PDE5i, riociguat, ERA, combination therapy	74	—	↓NT-proBNP ⇔ 6MWD
Mathijssen et al[81]	Retrospective	Macitentan	6	—	↑functional class
Parsley et al[78]	Prospective open-label	iNO	8	↓mPAP ↓PVR	—
Oudiz et al[86]	Randomized, placebo-controlled trial	Bardoxolone methyl	25	—	Modest ↑6MWD
Baughman et al[77]	Randomized double-blind, placebo-controlled trial	Riociguat	16		↑6MWD Delay time to clinical worsening

Abbreviations: 6MWD indicates 6-minute walk distance; CCB, calcium-channel blockers; CI, cardiac index; ERA, endothelin receptor antagonists; iNO, inhaled nitrous oxide; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitors; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion.

a recent small (n = 16) randomized double-blind, placebo-controlled trial, riociguat was found to delay time to clinical worsening in SAPH when compared to placebo.[77] Time to clinical worsening was predefined as death, transplantation, hospitalization for progression of disease, or decrease in 6MWD of > 50 meters. Notably, 7 out of 8 patients in the riociguat group had Scadding stage 4 disease. Larger studies are needed to evaluate the efficacy and safety of riociguat in SAPH.

Inhaled NO (iNO) is a pulmonary vasodilator commonly used to assess pulmonary vasoreactivity, treat patients with PAH, and manage refractory hypoxemia in severe acute respiratory distress syndrome. The inhaled administration route ensures delivery of iNO to relatively well-ventilated lung units, reducing the risk of exacerbating hypoxemia in patients with underlying lung disease. Long-term use of iNO has been investigated in a phase 2 trial of RHC-confirmed SAPH patients. The study enrolled 8 SAPH patients, all of whom experienced significant improvement in mPAP and PVR. The drug was well tolerated, and no adverse events related to iNO were reported.[78] Other studies have also reported improvements in pulmonary hemodynamics and 6MWD with iNO in SAPH.[36] A larger trial is currently underway to validate these findings.

Endothelin Pathway: Endothelin receptor antagonists have been used in the treatment of SAPH in small case series and retrospective studies. In a retrospective study by Barnett et al,[67] SAPH patients who received PAH-specific therapies (bosentan, epoprostenol, or sildenafil) had significant improvement in their 6MWD, World Health Organization (WHO) functional class, and mPAP.

In a small randomized, double-blind, placebo-controlled study involving 23 patients treated with bosentan and 12 with placebo, bosentan was shown to significantly reduce mPAP and PVR.[79] However, no changes in 6MWD or WHO functional class were reported with bosentan. Another prospective open-label study assessed ambrisentan in 21 patients with SAPH. Ambrisentan failed to improve WHO functional class or 6MWD after 24 weeks of treatment. It is worth noting that 11 patients discontinued ambrisentan at 12 weeks, primarily due to increasing shortness of breath, which limited these findings.[80]

More recently, Mathijssen et al[81] conducted a retrospective study of macitentan in 6 patients with severe SAPH. Four patients showed improved WHO functional class and 3 had improved 6MWD. However, a major limitation was the need for increased immunosuppression due to increased sarcoidosis activity, making it unclear whether improved exercise tolerance was related to increased immunosuppressive therapy or macitentan. Additionally, 3 patients required hospitalization for volume overload during treatment. Overall, the current evidence does not support the use of endothelin receptor antagonists in SAPH.

Prostaglandin I_2 Pathway: Epoprostenol, iloprost, and treprostinil have all been used to treat patients with SAPH. In a small retrospective case series involving 7 patients treated with epoprostenol, significant improvements were observed in WHO functional classification and pulmonary hemodynamics (with a reduction in PVR of > 25%).[68] Importantly, 2 patients developed acute pulmonary edema with epoprostenol and required diuresis and reduction in the dose. Intravenous prostanoids have also been associated with a reduction in NT-proBNP.[82]

Similarly, inhaled iloprost has been showed to improve mPAP and PVR and increase the 6MWD in patients with SAPH.[83] Inhaled therapy offers an advantage, especially for patients with significant parenchymal lung disease. Currently, an ongoing open-label study is evaluating the use of inhaled treprostinil for SAPH.

Selexipag, a selective prostacyclin receptor agonist, has been used to treat SAPH in case reports and case series.[84] A randomized, placebo-controlled, trial of selexipag in SAPH was recently terminated due to slow enrollment.

Combination Therapy: Combination PAH therapy has been used in retrospective studies. However, the lack of randomized controlled trials makes it challenging to draw firm conclusions regarding the benefits of combination PAH therapy in SAPH. Parikh et al[85] published outcomes from one of the largest SAPH cohorts, consisting of 95 patients (74% with Scadding stage 4 disease). Seventy-four patients received PAH-specific therapies. Combination therapy was given to 11.6% of SAPH patients. PAH-specific therapy was not associated with death or hospitalization but did result in an improvement in NT-proBNP levels. There was no observed change in 6MWD for patients who received PAH therapy.[85] Other studies have demonstrated improvements in exercise capacity and pulmonary hemodynamics.[65]

Novel Therapies: Newer therapies for PAH have been studied in SAPH. Bardoxolone methyl, an oral antioxidant and immune modulator that inhibits the nuclear factor κB pathway, was evaluated in a randomized, placebo-controlled trial of 165 patients with PH-ILD.[86] The study included 25 patients with SAPH. After 16 weeks of treatment with bardoxolone, SAPH patients experienced a modest increase in 6MWD (17 meters with bardoxolone versus 9 meters with placebo).

Lung Transplant: In the absence of a major or disabling extrathoracic manifestations of sarcoidosis, SAPH patients who fail immunosuppression, mechanical interventions, and PAH-targeted therapy when deemed appropriate, should be considered for lung transplant. The presence of SAPH and significant lung disease (Scadding stage 4 with low FVC < 50%) is also an indication for referral for lung transplant consideration.

In summary, management of SAPH necessitates a multifaceted approach that addresses underlying pathologies and specific disease mechanisms. This includes a comprehensive evaluation to identify the most likely mechanism of PH. Patients with active granulomatous inflammation are likely to respond to immunosuppression, and those with pulmonary vascular compression or stenosis should be considered for stenting.

Patients should be carefully evaluated for postcapillary SAPH. When precapillary SAPH is confirmed, the "pulmonary arteriopathy" phenotype, characterized by less severe

Table 3. Risk Factors for Poor Outcomes in SAPH

DLCO < 35% predicted
6MWD < 300 m
Reduced 6MWD with preserved FEV_1 FVC ratio
Scadding stage 4
Precapillary SAPH (high PVR)
Elevated right atrial pressure > 15 mm Hg
Elevated NT-proBNP after treatment with PAH-specific therapies
Low cardiac index < 2.5 L/min/m^2
Presence of right-sided heart failure

Abbreviations: 6MWD indicates 6-minute walk distance; FEV_1, forced expiratory volume; FVC, forced vital capacity, NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SAPH, sarcoidosis-associated pulmonary hypertension.

parenchymal disease, should be distinguished as it tends to be more responsive to PAH-targeted therapy. Agents that target the NO pathway (especially PDE5i and iNO) and inhaled prostacyclins are well tolerated and likely beneficial. Patients treated with pulmonary vasodilators should be carefully monitored for worsening gas exchange and/or pulmonary edema (due to left heart disease or PVOD).

Timely referral for lung transplant evaluation is crucial for those with SAPH and severe parenchymal lung disease, ensuring a comprehensive and patient-centered care approach.

PROGNOSIS

The development of SAPH is associated with poor functional status, exercise-induced hypoxemia, and a 7-fold increased risk of death over 3 years.[55,87] In a study by Boucly et al[65] that included patients with severe SAPH (mPAP > 35 mm Hg), the 5-year mortality was 45% despite receiving pulmonary vasodilators. Risk factors for worse outcomes in SAPH are summarized in Table 3.[65,69,88]

CONCLUSIONS

The treatment of SAPH remains a clinical challenge with much nuance to consider due to variation in individual patient presentation. Clear direction on the use of PAH therapies in SAPH is still lacking from clinical trials conducted thus far. Given these uncertainties and the potential need for advanced therapeutics or lung transplantation evaluation, SAPH patients are likely best served by evaluation at PAH and/or sarcoidosis expert centers. Much work remains to be done to understand the exact pathogenesis of SAPH, as well as to develop therapies that clearly improve outcomes for these patients.

References

1. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1885-1889.
2. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, Kawabata Y. Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. *Acta Pathol Jpn*. 1993;43(7-8):372-376.
3. Huitema MP, Bakker ALM, Mager JJ, et al. Predicting pulmonary hypertension in sarcoidosis; value of PH probability on echocardiography. *Int J Cardiovasc Imag*. 2020;36(8):1497-1505.
4. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension insarcoidosis. *Eur Respir J*. 2008;32(2):296-302.
5. Shorr AF., Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. *Eur Respir J*. 2005;25(5):783-788.
6. Zhang S, Tong X, Zhang T, Wang D, Liu S, Wang L, Fan H. Prevalence of sarcoidosis-associated pulmonary hypertension: a systematic review and meta-analysis. *Front. Cardiovasc. Med*.2021;8:809594.
7. Sulica R, Teirstein AS, Kakarla S, Nemani N, Behnegar A, Padilla ML. Distinctive clinical, radiographic, and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. *Chest*. 2005;128(3):1483-1489.
8. Nunes H, Humbert H, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. *Thorax*. 2006;61(1):68-74.
9. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913.
10. Voelkel NF, Tamosiuniene R, Nicolls MR. Challenges and opportunities in treating inflammation associated with pulmonary hypertension. *Expert Rev Cardiovasc Ther*. 2016;14(8):939-951.
11. Steiner MK, Syrkina OL, Kolliputi N, Mark EJ, Hales CA, Waxman AB. Interleukin-6 overexpression induces pulmonary hypertension. *Circ Res*. 2009;104(2):236-244.
12. Bargagli E, Bianchi N, Margollicci M, et al. Chitotriosidase and soluble IL-2 receptor: comparison of two markers of sarcoidosis severity. *Scand J Clin Lab Invest*. 2008;68(6):479-483.
13. Grutters JC, Fellrath JM, Mulder L, et al. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. *Chest*. 2003;124(1):186-195.
14. Ferro TJ, Johnson A, Everitt J, Malik AB. IL-2 induces pulmonary edema and vasoconstriction independent of circulating lymphocytes. *J Immunol*. 1989;142(6):1916-1921.
15. Soon E, Holmes A, Treacy C, et al. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. *Circulation*. 2010;122(9):920-927.
16. Shigematsu T, Miura S, Hirokawa M, et al. Induction of endothelin-1 synthesis by IL-2 and its modulation of rat intestinal epithelial cell growth. *Am J Physiol*. 1998;275(3):G556-G563.
17. Hurst L, Dunmore B, Long L, et al. TNFα drives pulmonary arterial hypertension by suppressing the BMP type-II receptor and altering NOTCH signalling. *Nat Commun*. 2017;8:14079.
18. Tsukada N, Yanagisawa N, Mochizuki I. Endothelial cell damage in sarcoidosis and neurosarcoidosis: autoantibodies to endothelial cells. *Eur Neurol*. 1995;35(2):108-112.
19. Mochizuki I, Kubo, Hond T. Widespread heavy damage of capillary endothelial cells in the pathogenesis of sarcoidosis—evidence by monoclonal von Willebrand factor immunohistochemistry in the bronchus and lung of patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2014;31(3):182-190.
20. Marcos E, Fadel E, Sanchez O, et al. Serotonin-induced smooth muscle hyperplasia in various forms of human pulmonary hypertension. *Circ Res*. 2004;94(9):1263-1270.
21. Takemura T, Matsui Y, Saiki S, Mikami R. Pulmonary vascular involvement in sarcoidosis: a report of 40 autopsy cases. *Hum Pathol*. 1992;23(11):1216-1223.
22. Hoffstein V, Ranganathan N, Mullen JBM. Sarcoidosis simulating pulmonary veno-occlusive disease. *Am Rev Respir Dis*. 1986;134(4):809-811.
23. Portier F, Lerebourg-Pigeonniere G, Thiberville L, et al. Sarcoidosis simulating pulmonary veno-occlusive disease. *Rev Mal Respir*. 1991;8(1):101-102.
24. Takemura T, Matsui Y, Oritsu M, et al. Pulmonary vascular involvement in sarcoidosis: granulomatous angiitis and microangiopathy in transbronchial lung biopsies. *Virchows Archiv A Pathol Anat Histopathol*. 1991;418(4):361-368.

25. Rosen Y, Moon S, Huang CT, Gourin A, Lyons HA. Granulomatous pulmonary angiitis in sarcoidosis. *Arch Pathol Lab Med.* 1977;101(4):170-174.
26. Rodman DM, Lindenfeld J. Successful treatment of sarcoidosis-associated pulmonary hypertension with corticosteroids. *Chest.* 1990;97(2):500-502.
27. Gluskowski J, Hawrylkiewicz I, Zych D, et al. Effects of corticosteroid treatment on pulmonary haemodynamics in patients with sarcoidosis. *Eur Respir J*. 1990;3(4):403-407.
28. Ryan US, Ryan JW. Cell biology of pulmonary endothelium. *Circulation.* 1984;70 (5 Pt 2):III46-62.
29. Petkova DK, Clelland CA, Ronan JE, et al. Reduced expression of cyclooxygenase (COX) in idiopathic pulmonary fibrosis and sarcoidosis. *Histopathology.* 2003;43(4): 381-386.
30. Bachwich PR, Lynch JP, Kunkel SL, et al. COX-2 is reduced in sarcoidosis, likely contributing to low PGs production. *Histopathology.* 2003;43(4):381-386.
31. Reichenberger F, Schauer J, Kellner K, Sack U, Stiehl P, Winkler J. Different expression of endothelin in the bronchoalveolar lavage in patients with pulmonary diseases. *Lung.* 2001;179(3):163-174.
32. Terashita K, Kato S, Sata M, Inoue S, Nakamura H, Tomoike H. Increased endothelin-1 levels of BAL fluid in patients with pulmonary sarcoidosis. *Respirology*. 2006;11(2):145-151.
33. Choi J, Hoffman LA, Sethi JM, et al. Multiple flow rates measurement of exhaled nitric oxide in patients with sarcoidosis: a pilot feasibility study. *Sarcoidosis Vasc Diffuse Lung Dis.* 2009;26(2):98-109.
34. Wallerath T, Witte K, Schafer SC, et al. Down-regulation of the expression of endothelial NO synthase is likely to contribute to glucocorticoid-mediated hypertension. *Proc Natl Acad Sci USA*. 1999;96(23):13357-13362.
35. Iuchi T, Akaike M, Mitsui T, et al. Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. *Circ Res.* 2003;92(1):81-87.
36. Preston IR, Klinger JR, Landzberg MJ, et al. Vasoresponsiveness of sarcoidosis-associated pulmonary hypertension. *Chest*. 2001;120(3):866-872.
37. Pullamsetti SS, Mamazhakypov A, Weissmann N, Seeger W, Savai R. Hypoxia- inducible factor signaling in pulmonary hypertension. *J Clin Invest.* 2020;130(11):5638-5651.
38. Talreja J, Talwar H, Bauerfeld C, et al. HIF-1α regulates IL-1β and IL-17 in sarcoidosis. *eLife.* 2019;8:e44519.
39. Jeny F, Bernaudin JF, Valeyre D, et al. Hypoxia promotes a mixed inflammatory-fibrotic macrophages phenotype in active sarcoidosis. *Front Immunol.* 2021;12:719009.
40. Piotrowski WJ, Kiszałkiewicz J, Pastuszak-Lewandoska D, et al. Expression of HIF-1A/VEGF/ING-4 axis in pulmonary sarcoidosis. *Adv Exp Med Biol.* 2015;866:61-69.
41. Dai Z, Zhu MM, Peng Y, et al. Therapeutic targeting of vascular remodeling and right heart failure in pulmonary arterial hypertension with a HIF-2α inhibitor. *Am J Respir Crit Care Med.* 2018;198(11):1423-1434.
42. Takahashi H, Goto N, Kojima Y, et al. Downregulation of type II bone morphogenetic protein receptor in hypoxic pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol.* 2006;290(3):L450-L458.
43. Faunce HF, Ramsay GC, Sy W. Protracted yet variable major pulmonary artery compression in sarcoidosis. *Radiology*. 1976;119(2): 313-314.
44. Condado JF, Babaliaros V, Henry TS, et al. Pulmonary stenting for the treatment of sarcoid induced pulmonary vascular stenosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2016;33(3):281-287.
45. Bazmpani MA, Arsos G, Zarogoulidis P, et al. A case of sarcoidosis-associated pulmonary hypertension masquerading as chronic thromboembolic pulmonary hypertension. *Pulm Circ*. 2018;8(3):2045894018768289.
46. Yangui F, Battesti JP, Valeyre D, et al. Fibrosing mediastinitis as a rare mechanism of pulmonary oedema in sarcoidosis. *Eur Respir J.* 2010;35(2):455-456.
47. Vorselaars ADM, Snijder RJ, Grutters JC. Increased number of pulmonary embolisms in sarcoidosis patients. *Chest.* 2012;141(3):826-827.
48. Crawshaw AP, Wotton CJ, Yeates DGR, Goldacre MJ, Ho L. Evidence for association between sarcoidosis and pulmonary embolism from 35-year record linkage study. *Thorax.* 2011;66(5):447-448.
49. Swigris JJ, Olson AL, Huie TJ, et al. Increased risk of pulmonary embolism among US decedents with sarcoidosis from 1988 to 2007. *Chest.* 2011;140(5):1261-1266.
50. Ina Y, Takada K, Yamamoto M, Sato T, Ito S, Sato S. Antiphospholipid antibodies, a prognostic factor in sarcoidosis. *Chest*. 1994;105(4):1179-1183.
51. Tanddon R, Baughman RP, Stanley J, et al. The link between chronic thromboembolic pulmonary hypertension and sarcoidosis: association or visual masquerade? *Sarcoidosis Vasc Diffuse Lung Dis.* 2017;34(4):352-355.
52. Tadros M, Forouhar F, Wu GY. Hepatic sarcoidosis. *J Clin Transl Hepatol.* 2013;1(2):87-93.
53. Fauter M, Rossi G, Drissi-Bakhkhat, et al. Hepatic sarcoidosis with symptomatic portal hypertension: a report of 12 cases with review of the literature. *Front Med (Lausanne*). 2022;9:995042.
54. Birnie D, Ha AC, Gula LJ, Chakrabarti S, Beanlands RS, Nery P. Cardiac sarcoidosis. *Clin Chest Med.* 2015;36(4):657-658.
55. Baughman RP, Engel PJ, Taylor L, Lower EE. Survival in sarcoidosis-associated pulmonary hypertension: the importance of hemodynamic evaluation. *Chest.* 2010;138(5):1078-1085.
56. Rapti A, Kouranos V, Gialafos E, et al. Elevated pulmonary arterial systolic pressure in patients with sarcoidosis: prevalence and risk factors. *Lung.* 2013;191(1):61-67.
57. Mathijssen H, Huitema MP, Bakker ALM, et al. Clinical phenotypes of sarcoidosis-associated pulmonary hypertension. *Heart Lung Circ.* 2021;30(10):1502-1508.
58. Ramos RP, Arakaki JS, Barbosa P, et al. Heart rate recovery in pulmonary arterial hypertension: relationship with exercise capacity and prognosis. *Am Heart J.* 2012;163(4):580-588.
59. Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. *Eur Respir J.* 2005;25(5): 783-788.
60. Mirsaeidi M, Mortaz E, Omar H, et al. Association of neutrophil to lymphocyte ratio and pulmonary hypertension in sarcoidosis patients. *Tanaffos.* 2016;15(1):44-47.
61. Kirkil G, Lower EE, Baughman RP. Predictors of mortality in pulmonary sarcoidosis. *Chest.* 2018;153(1):105-113.
62. Savale L, Huitema M, Shlobin O, et al. WASOG statement on the diagnosis and management of sarcoidosis-associated pulmonary hypertension. *Eur Respir Rev.* 2022;31(163):210165.
63. Maron BA, Brittain EL, Hess E, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med*. 2020;8(9):873-884.
64. Liu L, Xu J, Zhang Y, et al. Interventional therapy in sarcoidosis-associated pulmonary arterial stenosis and pulmonary hypertension. *Clin Respir J.* 2015;11(6): 906-914.
65. Boucly A, Cottin V, Nunes H, et al. Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension. *Eur Respir J.* 2017;50(4):1700465.
66. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. *Thorax.* 2006;61(1):68-74.
67. Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of sarcoidosis-associated pulmonary hypertension. a two-center experience. *Chest.* 2009;135(6):1455-1461. https://doi.org/10.1378/chest.08-1881
68. Fisher KA, Serlin DM, Wilson KC, Walter RE, Berman JS, Farber HW. Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest*. 2006;130(5):1481-1488.
69. Dobarro D, Schreiber BE, Handler C, Beynon H, Denton CP, Coghlan JG. Clinical characteristics, haemodynamics and treatment of pulmonary hypertension in sarcoidosis in a single centre, and meta-analysis of the published data. *Am J Cardiol.* 2013;111(2): 278-285.
70. Gayen S, Ansari S, Lashari B, et al. Pulmonary vasodilator therapy in sarcoidosis-associated pulmonary hypertension may decrease lung

function decline and mortality. *Pulm Circ.* 2023;13(2):e12245.
71. Albujoq K, Awdish RL, Jennings JH, et al. Outcomes of directed PAH therapy in sarcoidosis. *Am J Respir Crit Care Med.* 2018;197:A1509.
72. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet.* 2002;360(9337): 895-900.
73. Ford HJ, Baughman RP, Aris R, Engel P, Donohue JF. Tadalafil therapy for sarcoidosis-associated pulmonary hypertension. *Pulm Circ.*2016;6(4):557-562.
74. Milman N, Burton CM, Iversen M, Videbaek R, Jensen CV, Carlsen J. Pulmonary hypertension in end-stage pulmonary sarcoidosis: therapeutic effect of sildenafil? *J Heart Lung Transplant.* 2008;27(3):329-334. https://doi.org/10.1016/j.healun.2007.11.576
75. Keir GJ, Walsh SL, Gatzoulis MA, et al. Treatment of sarcoidosis-associated pulmonary hypertension: a single centre retrospective experience using targeted therapies. *Sarcoidosis Vasc Diffuse Lung Dis.* 2014;31(2):82-90.
76. Nathan SD, Behr J, Collard HR, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. *Lancet Respir Med*. 2019;7(9):780-790.
77. Baughman RP, Shlobin OA, Gupta R, et al. Riociguat for sarcoidosis-associated pulmonary hypertension: results of a 1-year double-blind, placebo-controlled trial. *Chest.* 2022;161(2):448-457.
78. Parsley EL, Baughman RB, Stewart JI, et al. A phase 2 trial of INOpulse in patients with sarcoidosis associated pulmonary hypertension (SAPH) requiring supplemental oxygen. *Am J Respir Crit Care Med.* 2022;205:A5783.
79. Baughman RP, Culver DA, Cordova FC, et al. Bosentan for sarcoidosis-associated pulmonary hypertension: a double-blind placebo controlled randomized trial. *Chest.* 2014;145(4):810-817.
80. Judson MA, Highland KB, Kwon S, et al. Ambrisentan for sarcoidosis associated pulmonary hypertension. *Sarcoidosis Vasc Diffuse Lung Dis.* 2011;28(2):139-145.
81. Mathijssen H, Huitema MP, Bakker ALM, et al. Safety of macitentan in sarcoidosis-associated pulmonary hypertension: a case-series. *Sarcoidosis Vasc Diffuse Lung Dis.* 2020;37(1):74-78.
82. Bonham CA, Oldham JM, Gomberg-Maitland M, Vij R. Prostacyclin and oral vasodilator therapy in sarcoidosis-associated pulmonary hypertension: a retrospective case series. *Chest.* 2015;148(4):1055-1062.
83. Baughman RP, Judson MA, Lower EE, et al. Inhaled iloprost for sarcoidosis associated pulmonary hypertension. *Sarcoidosis Vasc Diffuse Lung Dis.* 2009;26(2):110-120.
84. Cullivan S, Natarajan A, Boyle N, et al. Real-world experience of selexipag titration in pulmonary arterial hypertension. *Br J Cardiol.* 2021;28(3):32.
85. Parikh KS, Dahhan T, Nicholl L, et al. Clinical features and outcomes of patients with sarcoidosis-associated pulmonary hypertension. *Sci Rep.* 2019;9(1):4061.
86. Oudiz RJM, Chin M, Feldman J, et al. Results of interim analysis of the efficacy and safety of bardoxolone methyl in patients with pulmonary arterial hypertension associated with connective tissue disease (the LARIAT study). *Am J Respir Crit Care Med.* 2017;195:A6896.
87. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. *Chest.* 2003;124(3): 922-928.
88. Arcasoy SM, Christie JD, Pochettino A, et al. Characteristics and outcomes of patientswith sarcoidosis listed for lung transplantation. *Chest.* 2001;120(3):873-880.
89. Palermo V, Sulica R. Bosentan for the treatment of sarcoidosis-associated pulmonary hypertension. *Am J Respir Crit Care Med.* 2011; 183:A5889.
90. Qua D, Palmero P, Sulica R. Long-term bosentan therapy improves exercise capacity and hemodynamics in sarcoidosis-associated pulmonary hypertension. *Eur Respir J.* 2012;40:942.
91. Rosen Y. Sarcoidosis. In: Dail DH, Hammar SP, eds. *Pulmonary Pathology*. New York, NY: Springer; 1994: 615-645.
92. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol*. 2004;43(12 Suppl S):25S-32S.

REGULAR ARTICLE

Pulmonary Veno-Occlusive Disease

Salma Al Kahf, MD
INSERM UMR_S 999 "Pulmonary hypertension: pathophysiology and novel therapies", Marie Lannelongue Hospital and Bicêtre Hospital, France
Assistance publique—hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Bicêtre Hospital, le Kremlin-Bicêtre, France
University of Paris-Saclay, School of Medicine, le Kremlin-Bicêtre, France

Sabina Solinas, MD
INSERM UMR_S 999 "Pulmonary hypertension: pathophysiology and novel therapies", Marie Lannelongue Hospital and Bicêtre Hospital, France
Assistance publique—hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Bicêtre Hospital, le Kremlin-Bicêtre, France
University of Paris-Saclay, School of Medicine, le Kremlin-Bicêtre, France

Marc Humbert, MD, PhD
INSERM UMR_S 999 "Pulmonary hypertension: pathophysiology and novel therapies", Marie Lannelongue Hospital and Bicêtre Hospital, France
Assistance publique—hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Bicêtre Hospital, le Kremlin-Bicêtre, France
University of Paris-Saclay, School of Medicine, le Kremlin-Bicêtre, France

David Montani, MD, PhD
INSERM UMR_S 999 "Pulmonary hypertension: pathophysiology and novel therapies", Marie Lannelongue Hospital and Bicêtre Hospital, France
Assistance publique—hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Bicêtre Hospital, le Kremlin-Bicêtre, France
University of Paris-Saclay, School of Medicine, le Kremlin-Bicêtre, France

Pulmonary veno-occlusive disease (PVOD) represents a rare yet severe etiology of pulmonary arterial hypertension (PAH). Classified within the spectrum of PAH as Group 1.5 PAH with features of venous/capillary involvement, PVOD is distinguished by its progressive fibrotic obliteration of pulmonary venules and capillary hemangiomatosis. The etiology of PVOD is multifactorial, encompassing idiopathic cases, associations with solvent or chemotherapy exposure, and heritable forms linked to biallelic mutations in the *EIF2AK4* gene. Clinically, PVOD is marked by pronounced impairment in gas exchange, notably reduced diffusing capacity of the lungs for carbon monoxide (DLCO), distinctive radiological features on chest computed tomography, and a potential risk of pulmonary edema when PAH-approved drugs are initiated. Currently, no established evidence-based medical treatment is available, and lung transplantation remains the preferred therapy for eligible patients.

Pulmonary veno-occlusive disease (PVOD) is a rare and devastating cause of pulmonary artery hypertension (PAH). PVOD is characterized by the involvement of all 3 compartments of the pulmonary microcirculation. This includes predominant venular involvement (intimal fibrosis of small preseptal venules) and capillary lesions (capillary hemangiomatosis), as well as pulmonary arterial remodeling without plexiform lesions (Figure 1). Such obstruction of the pulmonary vascular bed leads to elevated pulmonary arterial pressure and subsequent right heart failure.[1–3] PVOD can manifest as a sporadic condition (typically associated with exposure to solvent or chemotherapy) or as a heritable disorder resulting from biallelic mutations in the eukaryotic translation initiation factor 2 α kinase 4 (*EIF2AK4*) gene. A notable clinical feature of PVOD is severe impairment of gas exchange and the potential development of pulmonary edema when PAH-specific therapies are introduced.[4] Currently, no established evidence-based medical treatment is available, and for eligible patients, lung transplantation remains the preferred and definitive therapy.

Key Words—pulmonary veno-occlusive disease, pulmonary hypertension, *EIF2AK4*, chemotherapy, solvents, pulmonary edema, transplantation
Correspondence: david.montani@aphp.fr
Disclosure: The authors have no relevant personal financial relationships to disclose.

CLASSIFICATION, RISK FACTORS, AND NATURAL EVOLUTION OF PVOD

Classification of Pulmonary Hypertension

Following the recently updated guidelines from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) on pulmonary hypertension (PH), the group "PAH with features of PVOD involvement" is now incorporated into Group 1 PH (Table 1). PVOD is further divided into various subtypes, including idiopathic, heritable, and drug- or toxin-induced forms. It is noteworthy that venous and capillary involvement can also manifest in conditions like connective tissue disease, chronic respiratory disease, pulmonary Langerhans histiocytosis, and sarcoidosis, which are also poorly responsive or refractory to PAH-approved drugs. However, they are not classified as PVOD in the current

 DOI:10.21693/1933-088X-22.4.164

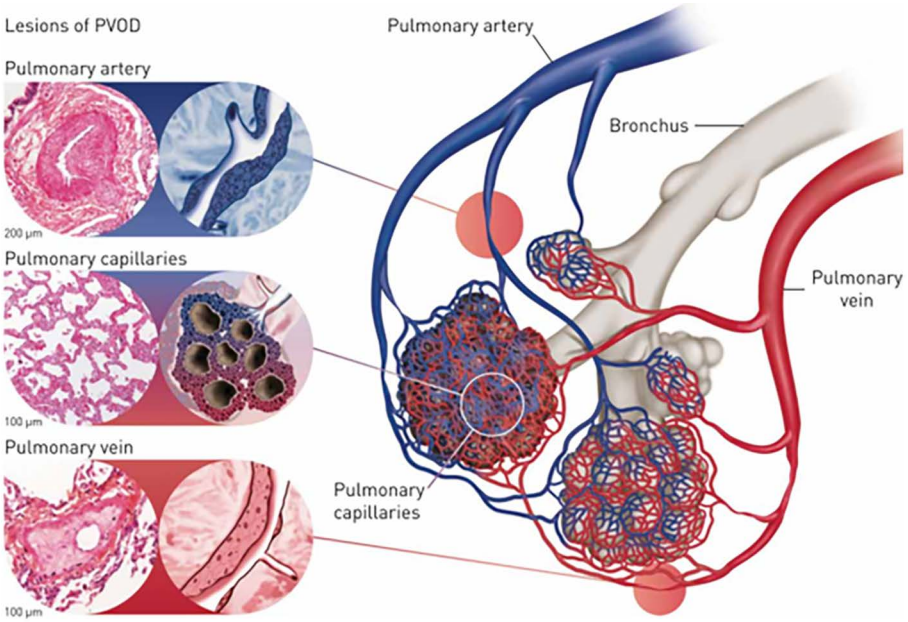


Figure 1: Pathological features of pulmonary veno-occlusive disease (reproduced from Ref. 33). All 3 compartments of the pulmonary microcirculation are affected in PVOD, although preferential involvement of the pulmonary venous system exists. Venular lesions include intimal fibrosis of small preseptal venules. Capillary lesions are characterized by exuberant proliferation of endothelial cells (capillary hemangiomatosis). Arterial lesions resemble those of pulmonary arterial h+ypertension with intimal fibrosis and medial hypertrophy, but complex plexiform lesions are absent. Reproduced with permission of the © ERS 2023: *European Respiratory Journal.* 47(5):1518–1534. https://doi.org/10.1183/13993003.00026-2016. Published 30 April 2016.

classification but within their respective groups.

Epidemiology

The precise incidence of PVOD remains uncertain, primarily due to the likelihood of many cases being misclassified as idiopathic PAH, given the similarity in clinical and hemodynamic features between these 2 conditions. PVOD's estimated annual incidence rate is 0.1–0.5 cases per million.[1,5] PVOD cases were reported across all age groups, including children. Unlike idiopathic PAH, PVOD appears to predominantly affect men, especially in instances of occupational exposure. However, because of its mode of transmission, both men and women are equally affected by heritable forms of PVOD.[4,6–10]

Pathogenesis and Risk Factors

Genetics: Autosomal recessive biallelic mutations in the *EIF2AK4* gene, coding for the general control nonderepressible 2 (GCN2) protein, was identified as the primary genetic cause of PVOD,[10,11] although the exact mechanism of how this deletion leads to PVOD remains largely unknown.[12,13] It is passed down with a complete or nearly complete penetrance; consanguinity and a family history of PH in siblings should thus raise the suspicion of heritable PVOD. Genetic counseling and testing are now integral to managing PAH, and *EIF2AK4* mutation screening should be offered to all patients with idiopathic PAH or suspected PVOD.[14,15] Indeed, it was demonstrated that genetic testing may correct the diagnosis of PAH for PVOD.[16]

While no specific guidelines for screening relatives with biallelic *EIF2AK4* mutations exist, a yearly, noninvasive evaluation may be considered. This evaluation could include symptom assessment, electrocardiogram, NT-proBNP levels, diffusing capacity of the lung for carbon monoxide (DLCO), echocardiography, cardiopulmonary exercise testing (CPET), and high-resolution computed tomography (HRCT).[6] Current evidence suggests that relatives carrying a single *EIF2AK4* mutation are not at an increased risk for PVOD.[17]

Chemotherapy: Various drugs, especially chemotherapeutic agents, were described as potential triggers for PVOD with various levels of evidence. Alkylating or alkylating-like agents were particularly implicated in chemotherapy-induced PVOD, and the most reported causal agents were cyclophosphamide (43.2%), mitomycin-C (MMC) (24.3%), and cisplatin (21.6%).[18,19]

Organic Solvent Exposure: PVOD is significantly associated with occupational exposure to organic solvents, especially trichloroethylene (TCE).[4,5] The latter, a chlorinated solvent,[4,5] is mainly used in the mechanical, textile, and plastic industries. Organic solvents have also been used in pesticides and herbicides, with potential exposures among farmers. In a rat model exposed to TCE, it was demonstrated that the latter causes a breakdown of the endothelial barrier, which is responsible for increased endothelial permeability and subsequent pulmonary perivascular edema.[20]

Tobacco Exposure: Cumulative tobacco exposure was reported to be higher in PVOD compared with idiopathic PAH.[6] This increased risk could be explained by the alteration of vascular permeability and endothelial barrier dysfunction described after cigarette smoke exposure.[21] In a case-control study comparing PVOD patients and patients with PAH, all patients with significant exposure to trichloroethylene had concurrent tobacco exposure.[8]

Other Forms of PH Associated With Venous and Capillary Involvement: It is increasingly recognized that significant venular involvement is often found in connective tissue disease-associated PAH, particularly systemic sclerosis,[22,23] and that they are often less responsive or even refractory to PAH-approved drugs, like patients with PVOD. Significant venous/capillary involvement was also reported to complicate other inflammatory disorders such as sarcoidosis, pulmonary Langerhans cell granulomatosis, or interstitial lung diseases.[24–27] Regarding their categorization, it is more appropriate to classify them according to the group of the underlying disease regardless of venular or capillary involvement.

Table 1. Classification of Pulmonary hypertension ESC/ERS guidelines on PH[3]

GROUP 1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Nonresponders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
GROUP 2 PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to postcapillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease
3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
GROUP 5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1
5.3 Metabolic disorders
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

Abbreviations: HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

EVALUATION AND APPROACH TO CLINICAL DIAGNOSIS OF PVOD

Several distinctive features distinguish PVOD from PAH: resting hypoxemia with severe desaturation on exertion, very low DLCO, radiological signs on HRCT, and occult alveolar hemorrhage if bronchoalveolar lavage is performed. Since histological confirmation of PVOD is not feasible, a noninvasive diagnostic approach using clinical, functional, CT, hemodynamic, and genetic findings is to be adopted.

Clinical Features

PVOD and PAH share a joint clinical presentation characterized by

progressive dyspnea, fatigue, palpitations, chest pain on exertion, hemoptysis, or syncope. Notably, PVOD patients often experience more severe dyspnea and impaired exercise capacity than those with PAH with similar hemodynamic parameters.[28,29] Physical signs include typical signs of PH and right heart failure. Cyanosis is more frequently observed in PVOD due to frequent concomitant hypoxemia, whereas clubbing or Raynaud's phenomenon occur in both PVOD and PAH in similar proportions.[4] Other signs suggestive of PVOD may include pulmonary edema and pleural effusions.[30,31] Pulmonary edema after the initiation of PAH-approved drugs strongly suggests a diagnosis of PVOD.

Right Heart Catheterization

PH is diagnosed through right heart catheterization (RHC), with a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest. In the case of PVOD, pulmonary hemodynamics are characterized by a pattern of precapillary PH (mPAP ≥ 20 mmHg, normal pulmonary arterial wedge pressure [PAWP] ≤ 15 mmHg, and pulmonary vascular resistance [PVR] ≥ 2 WU). Despite the primary anatomical involvement of postcapillary venules in PVOD, the PAWP typically remains within the normal range.[4,7,32,33] Normal PAWP is explained by the predominant impact on small venules and capillaries, with relatively spared larger veins.[33] PAWP, in this case, is thus not a reflection of pulmonary capillary pressure. Acute vasoreactivity testing, usually performed systematically in the workup of PH before PVOD is suspected, is not very helpful in the management of PVOD patients. It does not predict long-term response to calcium channel blockers, even if it yields a positive result,[34] nor is it indicative of the potential development of pulmonary edema under PAH-specific therapy. Furthermore, the initiation of a calcium channel blocker may lead to life-threatening pulmonary edema.

Doppler Echocardiography

Transthoracic echocardiography is a valuable diagnostic tool for assessing patients with suspected PH.[3] In the context of PVOD, typically associated with hypoxemia and radiological abnormalities, echocardiography can be particularly useful for ruling out intracardiac or intrapulmonary shunts as well as for diagnosing left-sided heart disease.

Radiographic Findings

HRCT of the chest has become a fundamental component in the noninvasive diagnostic approach of PVOD specifically, in addition to revealing more general signs of PH. The triad of findings suggestive of PVOD is centrilobular ground-glass opacities, smooth bilateral interlobular septal thickening, and mediastinal lymphadenopathy (Figure 2).[6,31] For patients suspected of having PVOD, ventilation-perfusion lung scans do not reveal abnormalities specific to PVOD: segmental or subsegmental defects or, occasionally, diffuse and patchy perfusion defects are observed in the same proportion as in idiopathic PAH.[35] It is important to note that radiological abnormalities may be absent or mild at diagnosis in approximately 25% of PVOD patients.[6] When the diagnosis is uncertain, HRCT should be repeated, as it can reveal a worsening of radiological signs over time or after the initiation of PAH-approved drugs.

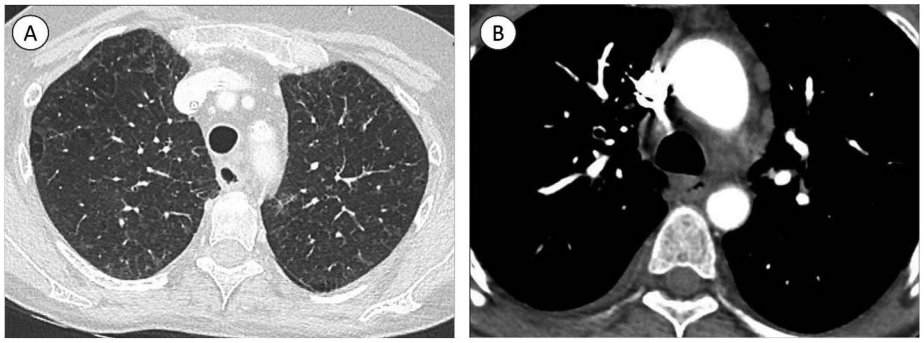


Figure 2: High-resolution CT scan of the chest in patients with PVOD. (**A**) Centrilobular ground-glass opacities and septal lines. (**B**) Mediastinal lymph node enlargement.

Pulmonary Function Test, Gas Exchange, and Exercise Testing

While spirometry and lung volume tests generally yield normal results, PVOD patients typically exhibit a reduced DLCO compared with the relatively preserved DLCO in patients with idiopathic or heritable PAH.[6,7] This can be explained by a reduced capillary blood volume due to a compromised pulmonary vascular bed and a poorer membrane diffusion due to interstitial edema. Arterial blood gas also reveals significant resting hypoxemia in PVOD.[4] Data on the 6-minute walk distance (6MWD) are limited, but they usually show severe impairment accompanied by significant desaturation.[4] Compared with other PAH patients, patients with PVOD exhibit greater ventilatory inefficiency (as demonstrated by higher minute ventilation to carbon dioxide output slope) and more severe functional impairment (revealed by lower peak oxygen consumption and earlier anaerobic ventilatory threshold).[29,36]

Bronchoalveolar Lavage

Bronchoalveolar lavage is not recommended as part of the diagnostic workup of PH and may pose a significant risk in PVOD patients who are frequently hypoxemic. Nonetheless, when it is conducted, occult alveolar hemorrhage with a significantly increased percentage of hemosiderin-laden macrophages can be found.[37] This can be explained by the increased transmural capillary pressure secondary to the remodeling of the postcapillary vasculature. However, with this finding, PVOD can only be suggested after having ruled out left-sided cardiac pathology, such as mitral valve stenosis.

Histopathological Diagnosis

A histological diagnosis before autopsy or lung transplantation should not be pursued, given the substantial risk of performing lung or transbronchial

biopsy in the setting of significant PH with compromised hemodynamics and low functional capacity, associated with the risk of bleeding. Therefore, it is recommended to follow a diagnostic approach based on clinical features and noninvasive tests alone.

When histological information is accessible, notably on lung explants or postmortem analysis, PVOD patients showcase extensive constrictive remodeling by intimal fibrotic thickening of postcapillary venules and small veins, capillary hemangiomatosis, and significant muscularization of precapillary arterioles with no plexiform lesions (Figure 1).[13] The unique histopathological pattern of PVOD parallels the radiological findings on HRCT: subpleural basal lines on HRCT align with increased collagen deposition in septal veins. Centrilobular ground-glass opacities correlate with the centrilobular distribution of capillary angioproliferation, the accumulation of intra-alveolar hemosiderin-laden macrophages, and edematous fluid. Finally, histological examination of lymphadenopathy reveals a vascular transformation of the sinus, characterized by increased wall thickness of the sinuses.[38]

MANAGEMENT AND EVOLUTION OF PVOD

General and Supportive Measures

Hypoxemia should be addressed by administering oxygen to prevent further worsening of PH from hypoxic pulmonary vasoconstriction. Diuretics can help optimize patients' fluid status. In line with the most recent ESC/ERS guidelines, anticoagulation is not systematically recommended in PAH patients.[3] Since PVOD patients may be at an increased risk of alveolar hemorrhage, and no known benefit of anticoagulation was demonstrated to date, it seems reasonable to avoid routine anticoagulation.

PAH-Approved Therapies

Several therapeutic classes are currently used to treat PAH: prostacyclin and prostacyclin-receptor agonists, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 inhibitors/soluble guanylate cyclase stimulators. In patients with PVOD, the effectiveness and safety of PAH-approved drugs remain controversial. Some improvements were reported in the 6MWD and PVR.[28] However, considerable concern about the potential development of life-threatening pulmonary edema exists. Additionally, for a significant proportion of PVOD patients, the initiation of PAH-approved drugs leads to a deterioration of gas exchange.[6,28,39,40] The initiation of PAH-approved drugs should, therefore, be undertaken at expert centers, preferring a monotherapy regimen for selected patients, accompanied by very close monitoring.[3]

Other Therapies

While current guidelines do not endorse the use of immunosuppressive therapy in PAH, evidence indicates the participation of inflammation in the pathophysiology of both PVOD and PAH.[5,41,42] It was suggested in isolated cases that mycophenolate and prednisolone helped stabilize symptoms, enhance oxygenation, and improve gas exchange and hemodynamic parameters in PVOD, possibly by downregulating the underlying inflammatory process[43] Immunosuppression was notably suggested in systemic lupus erythematosus and mixed connective tissue disease, with a possibly improved clinical outcome. However, it is not effective for systemic sclerosis-associated PAH. Therefore, currently, the use of immunosuppressive therapy in PVOD without substantial confirmatory data cannot be encouraged. In addition, *EIF2AK4* loss-of-function mutations, which lead to an absence of GCN2, a protein that participates in the integrative stress response,[12,44] may represent a potential target for future innovative therapies.

Lung Transplantation

The only definitive treatment for PVOD is a bilateral lung or heart-lung transplantation. Posttransplant survival in PVOD cases seems to be comparable with that of idiopathic PAH. Due to the difference in epidemiological characteristics, patients with heritable forms are more often eligible for transplantation than those with sporadic forms, who are older and often have comorbidities.[4] Overall, the prognosis of PVOD is poor, and the disease inevitably progresses with an event-free survival rate (considering death or transplantation) estimated to be around 65% at 1 year and 35% at 3 years.[4] Given the risk of rapid deterioration and the absence of effective treatment, it is recommended to discuss early listing for transplantation at the time of diagnosis, particularly when no program for urgent listing transplantation exists.

CONCLUSION

PVOD stands as a rare and intricate form of PAH, marked by its association with genetic and environmental risk factors and a notably grim prognosis. Diagnosing PVOD can be challenging, but high diagnostic certainty can be attained through a battery of noninvasive tests. Given the disease's progressive and ultimately fatal course, along with the absence of established and effective medical treatments, an expeditious referral for lung transplantation remains the sole definitive therapeutic option. Ongoing research to understand the role of the *EIF2AK4*/GCN2 pathway in maintaining pulmonary vascular homeostasis may hold promise for uncovering innovative strategies for managing PVOD.

References

1. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. *Am J Respir Crit Care Med.* 2000;162:1964–1973.
2. Montani D, Price LC, Dorfmuller P, Achouh L, Jaïs X, Yaïci A, Sitbon O, Musset D, Simonneau G, Humbert M. Pulmonary veno-occlusive disease. *Eur. Respir. J.* 2009; 33: 189–200.
3. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43:3618–3731.
4. Montani D, Girerd B, Jaïs X, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med.* 2017;5:125–134.
5. Montani D, Lau EM, Dorfmüller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J.* 2016;47:1518–1534.
6. Montani D, Achouh L, Dorfmüller P, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore).* 2008;87:220–233.
7. Holcomb BW, Loyd JE, Ely EW, Johnson J, Robbins IM. Pulmonary veno-occlusive

disease: a case series and new observations. *Chest.* 2000;118:1671–1679.
8. Montani D, Lau EM, Descatha A, et al. Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease. *Eur Respir J.* 2015;46:1721–1731.
9. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest.* 2010;137:376–387.
10. Eyries M, Montani D, Girerd B, et al. *EIF2AK4* mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet.* 2014;46:65–69.
11. Best DH, Sumner KL, Austin ED, et al. *EIF2AK4* mutations in pulmonary capillary hemangiomatosis. *Chest.* 2014;145:231–236.
12. Manaud G, Nossent EJ, Lambert M, et al. Comparison of human and experimental pulmonary veno-occlusive disease. *Am J Respir Cell Mol Biol.* 2020;63:118–131.
13. Nossent EJ, Antigny F, Montani D, et al. Pulmonary vascular remodeling patterns and expression of general control nonderepressible 2 (GCN2) in pulmonary veno-occlusive disease. *J Heart Lung Transplant.* 2018;37:647–655.
14. Girerd B, Montani D, Jaïs X, et al. Genetic counselling in a national referral centre for pulmonary hypertension. *Eur Respir J.* 2016;47:541–552.
15. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J.* 2019; 53:1801899.
16. Hadinnapola C, Bleda M, Haimel M, et al. Phenotypic characterization of *EIF2AK4* mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. *Circulation.* 2017;136: 2022–2033.
17. Lechartier B, Girerd B, Eyries M, Beurnier A, Humbert M, Montani D. Screening for pulmonary veno-occlusive disease in heterozygous *EIF2AK4* variant carriers. *Eur Respir J.* 2022;60(2):2200760.
18. Ranchoux B, Günther S, Quarck R, et al. Chemotherapy-induced pulmonary hypertension: role of alkylating agents. *Am J Pathol.* 2015;185:356–371.
19. Perros F, Günther S, Ranchoux B, et al. Mitomycin-induced pulmonary veno-occlusive disease: evidence from human disease and animal models. *Circulation.* 2015;132:834–847.
20. Caliez J, Riou M, Manaud G, et al. Trichloroethylene increases pulmonary endothelial permeability: implication for pulmonary veno-occlusive disease. *Pulm Circ.* 2020;10:2045894020907884.
21. Rounds S, Lu Q. Cigarette smoke alters lung vascular permeability and endothelial barrier function (2017 Grover Conference Series). *Pulm Circ.* 2018;8:2045894018794000.
22. Günther S, Jaïs X, Maitre S, et al. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum.* 2012;64: 2995–3005.
23. Launay D, Montani D, Hassoun PM, et al. Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis. *PloS One.* 2018;13:e0197112.
24. Hoffstein V, Ranganathan N, Mullen JB. Sarcoidosis simulating pulmonary veno-occlusive disease. *Am Rev Respir Dis.* 1986;134:809–811.
25. Hamada K, Teramoto S, Narita N, Yamada E, Teramoto K, Kobzik L. Pulmonary veno-occlusive disease in pulmonary Langerhans' cell granulomatosis. *Eur Respir J.* 2000;15:421–423.
26. Kokturk N, Demir N, Demircan S, et al. Pulmonary veno-occlusive disease in a patient with a history of Hashimoto's thyroiditis. *Indian J Chest Dis Allied Sci.* 2005;47:289–292.
27. Kay D, Kadri F, Fitzpatrick G, Alnuaimat H, Reddy R, Ataya A. Anti-synthetase syndrome-associated pulmonary veno-occlusive disease. *Pulm Circ.* 2020;10:2045894020935289.
28. Montani D, Girerd B, Jaïs X, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med.* 2017;5:125–134.
29. Laveneziana P, Montani D, Dorfmüller P, et al. Mechanisms of exertional dyspnoea in pulmonary veno-occlusive disease with *EIF2AK4* mutations. *Eur Respir J.* 2014;44:1069–1072.
30. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126:14S–34S.
31. Resten A, Maitre S, Humbert M, et al. Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. *AJR Am J Roentgenol.* 2004;183:65–70.
32. Heath D, Segel N, Bishop J. Pulmonary veno-occlusive disease. *Circulation.* 1966;34: 242–248.
33. Montani D, Lau EM, Dorfmüller P, et al. Pulmonary veno-occlusive disease. *Eur Respir J.* 2016;47:1518–1534.
34. Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. *Eur Heart J.* 2010;31: 1898–1907.
35. Seferian A, Helal B, Jaïs X, et al. Ventilation/perfusion lung scan in pulmonary veno-occlusive disease. *Eur Respir J.* 2012;40: 75–83.
36. Pérez-Olivares C, Segura de la Cal T, Flox-Camacho Á, et al. The role of cardiopulmonary exercise test in identifying pulmonary veno-occlusive disease. *Eur Respir J.* 2021;57:2100115.
37. Rabiller A, Jaïs X, Hamid A, et al. Occult alveolar haemorrhage in pulmonary veno-occlusive disease. *Eur Respir J.* 2006;27: 108–113.
38. Thomas de Montpréville V, Dulmet E, Fadel E, Dartevelle P. Lymph node pathology in pulmonary veno-occlusive disease and pulmonary capillary heamangiomatosis. *Virchows Arch Int J Pathol.* 2008;453: 171–176.
39. Palmer SM, Robinson LJ, Wang A, Gossage JR, Bashore T, Tapson VF. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. *Chest.* 1998;113:237–240.
40. Humbert M, Maître S, Capron F, Rain B, Musset D, Simonneau G. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. *Am J Respir Crit Care Med.* 1998;157:1681–1685.
41. Perros F, Cohen-Kaminsky S, Gambaryan N, et al. Cytotoxic cells and granulysin in pulmonary arterial hypertension and pulmonary veno-occlusive disease. *Am J Respir Crit Care Med.* 2013;187:189–196.
42. Corrin B, Spencer H, Turner-Warwick M, Beales SJ, Hamblin JJ. Pulmonary veno-occlusion–an immune complex disease? *Virchows Arch A Pathol Anat Histol.* 1974;364:81–91.
43. Bergbaum C, Samaranayake CB, Pitcher A, eta l. A case series on the use of steroids and mycophenolate mofetil in idiopathic and heritable pulmonary veno-occlusive disease: is there a role for immunosuppression? *Eur Respir J.* 2021;57:2004354.
44. Wilson GJ, Bunpo P, Cundiff JK, Wek RC, Anthony TG. The eukaryotic initiation factor 2 kinase GCN2 protects against hepatotoxicity during asparaginase treatment. *Am J Physiol Endocrinol Metab.* 2013;305:E1124–1133.

PH Roundtable: Use of Off-Label PAH Therapies

Murali Chakinala, MD, Washington University, St Louis, Missouri led a discussion with Mardi Gomberg, MD, George Washington University Hospital, Washington, DC; Elizabeth Klings, MD, Boston University Chobanian & Abedisian, School of Medicine, Massachusetts; Josanna Rodriguez-Lopez, Massachusetts General Hospital, Boston; and Susie McDevitt, NP, University of Michigan Health System, Ann Arbor.

Murali Chakinala: Today's topic is off-label use of PAH medications. But first, it's important that our readers understand that off-label use of PAH medications should not be taken lightly, and their use in individual cases should only be undertaken after thorough evaluation and careful discussion of the potential risks and benefits with a knowledgeable prescriber.

I thought we'd start with a general background on what off-label really means.

Mardi, I'd like to throw the first couple of questions to you. Could you explain what "off-label" therapy really means? And how often does it happen in general practice, not just in PH? I think people would be surprised by how often we are using off-label therapy.

Mardi Gomberg: Thanks, Murali. I think off-label is, in the purest of senses, when you're using a medication for an indication that it was not initially approved for, or at a dose that it was not initially approved for, or at a frequency that it was not initially approved for. When we design clinical trials, we try to the best of our ability to use what we know of the pharmacology of the medication, and how long it lasts within the body and the pharmacokinetics to design a study that's going to get the most efficacy from that medication, if it is going to work.

What we've learned over time is that sometimes when we design a study, in practice, we don't use it based on how it's labeled, or how the clinical trial initially designed it to be used. That would be, I think, the most frequent time that we use things off-label, but when it comes to using it for a different indication, a lot of times there's overlap within disease processes, and we often don't have approved therapies for the other disease.

Within pulmonary hypertension, an example would be chronic thromboembolic pulmonary hypertension (CTEPH). Before we had riociguat approved for CTEPH, I think all of us here on this roundtable utilized all of our PAH therapies for these patients. Scientifically this made sense because we knew the pathophysiology was similar in the small vessels that weren't affected. Our patients did well, we had great results, but the treatment was technically off-label, and not for what the medication was originally approved.

As for how often do we use drugs off-label, my guess is that a lot of times it's "off-label" based on drug frequency of administration, especially in a rare disease. Having worked with PCORI, I know there's a lot of times when we approve a drug for once a month administration, but we could actually use it once every 2 months. Over time with patients providing input, and having the science to back it up, we often get the labels changed so that we can work within what's clinically indicated, and not just the specifications in the original label.

Murali: That's a great intro, Mardi.

I think it happens a lot more than we think. Liz, let's discuss the more extreme examples; that is, expanding the indication for a drug on an off-label basis. What are some of the things that go into the conversation you have with a patient in that situation?

Elizabeth Klings: Thank you for that question, Murali. I really think it depends on the disease process that you were using an off-label therapy for. What do I mean by that? I think that, as Mardi alluded to, there are within pulmonary hypertension a number of diseases which are quite rare, and very difficult to study in isolation without other forms of pulmonary hypertension. Yet, there may be benefit for using PAH therapy. Then there are other conditions where things may be more dicey.

I think when I talk to a patient who doesn't have maybe pure pulmonary arterial hypertension or fits into a patient group that would've been included in a clinical trial, I do explain to them that sometimes when we use these therapies, they may not be as effective for you specifically. It is also possible that they may cause other problems to occur, such as developing more issues with fluid overload, and congestive heart failure, and that sometimes we need to manage that as well as the therapy.

I try not to focus on the off-label usage, because I often will draw upon my own clinical experience with some of the rare disease-related cases of pulmonary hypertension, and what benefits that I've observed hemodynamically, as well as clinically, in my patients, and presented as part of that as well.

Murali: Josanna, Liz said something that I think is real important. Could you talk specifically about some of the toxicities of PAH medications that you most worry about when using drugs in unstudied populations? In general, is your approach to risk aversion and tolerability of these adverse effects different with off-label usage versus when you're using the drugs as they were studied and intended for?

 DOI:10.21693/1933-088X-22.4.170

Josanna Rodriguez-Lopez: Thank you, Murali. That's a great question. I think it depends on what disease we're talking about. Is it a PAH patient that happens to have also heart failure, or some lung disease, or is it a completely off-label patient with mostly group 2 PH, and you're trying a drug? I think the conversation with the patient is this: "These medications may not have been as well studied in patients like you. We have to monitor very closely for side effects, and also because they haven't been studied as well in patients like you, we may not know if they're going to help, and we have to be really vigilant for the possibility that you could get worse on them, and we have to be able to identify that."

For instance, in a patient who happens to have also some heart failure, you really want to pay attention once you start a pulmonary vasodilator: are they gaining weight, are they getting more volume overloaded? Also discuss with the patient when to call you, what to look for. I would say, probably, you would be more likely to stop a medication early if you're seeing any signs of worsening, or bad outcomes, or side effects.

Murali: I totally agree. To me, the other one I worry about is when there is some underlying parenchymal lung disease and worsening oxygenation through worsened VQ mismatch.

Mardi: I just want to caution, I rarely use PAH therapies off-label. There are studies with PH in left heart disease have not been successful with PAH therapies, multiple times over and over. As a cardiologist, I don't see a lot of PH-ILD, but in the past when used, it was very rare that they had improvement with our agents. It's also really hard to get covered by insurance.

Another example is group 5 PH in patients with ESRD on hemodialysis. I do think sometimes, especially in these patients who really have pulmonary vascular disease, where we don't have any known therapies or trials and we want to get them to transplant, we use PAH therapies off-label. This use is only when their hemodynamics are significantly abnormal even after achieving euvolemia with dialysis. It is still a difficult process and not always successful, more often than not. Off-label use is not easy and requires personalized care.

Off-label also encompasses stuff like the case reports of imatinib early on, which was clearly off-label compassionate use, which is a very different off-label use. That then set the stage for us today, where we're looking at a new inflammatory pathway in PAH.

Murali: Mardi, I think those are great points. I think your admonishments are well received. I want to come back to that a little later when we go over some of the specific situations where we might try it, and you've done a great job already introducing it. Liz, did you want to say something else?

Liz: Yes, I agree with Mardi and want to clarify what I said earlier. When I talk about different disease states, I actually do not use these drugs routinely in my practice for left side of congestive heart failure no matter how much our cardiologists try to push me to use them, to be honest, because that never really goes well. The scenarios where I do use off-label therapy are in group 5 PH, and particularly in patients who have pure precapillary PH related to sarcoidosis, and in patients who have pure precapillary PH related to sickle cell disease.

In both scenarios, you can unmask left-sided heart failure, but in both scenarios, based on the case series that have been published as well as my own clinical experience, patients can get symptomatic improvement, hemodynamic improvement, and echocardiographic improvement. In both of these diseases, there is a very mixed population, and in many of our sarcoid patients, this is actually a form of PH-ILD and reacts differently to vasodilators than other forms of PH-ILD. What I mean by that, is this group of patients seem to be more responsive to vasodilating therapy. I often will use inhaled treprostinil as my first agent in patients with sarcoid and extensive ILD. Those are the 2 groups of patients where I do use off-label therapy.

Josanna: I'm going to agree with both of you. Obviously, I don't think anybody in this panel is here to try to promote use of off-label PAH therapy in group 2 PH. I think that part of the problem is how difficult it is with our classification system. And it's so hard to know, if this a real group 1 PAH patient or not, and is their heart failure not easily identified? In reality, patients don't read the textbook, and they have all sorts of comorbidities, so it can actually be quite challenging sometimes to even know, are you treating group 1 PAH, or is this more of a mixed picture? In those patients who have a lot of comorbidities, I definitely have the more thoughtful discussion about the risks of trying PH therapy.

Susie McDevitt: I'll add to that, Murali. Just from our center's perspective, I think if you look at clinical trial inclusion-exclusion criteria, and you look at the real patients we're taking care of every day, some could argue a lot of that is off-label use based on comorbidities and everything you guys are mentioning. For us, it's really about the hemodynamic profile, whether precapillary pulmonary hypertension is out of proportion, however we define it, and we don't have good criteria for any of the groups. Also looking at that with the right ventricle, and really trying to optimize all those underlying medical conditions first in a very systematic approach with very close follow-up with these patients.

We feel very strongly that these patients need transparency about the limited rationale or limited evidence we have. We do trial quite a bit. When you think about all the populations we don't have evidence for that we're probably all using the medication for, there's a lot in group 3, and group 5, and even some in group 2. I would say we do try to use the therapies, but we try to optimize everything. I'm sure you guys do as well.

Murali: You're all making some fantastic points, and I'm crossing off questions already because you're bringing them up in our conversation! You can already

sense, even on our panel, there's some variability from practice to practice about the extent of off-label use of PAH medications. Some centers are more conservative, and some are a little more liberal. It may depend on the types of patients they're seeing. For example, Liz has a good number of sickle cell patients.

I think an underlying theme is that any time that off-label use is going to be considered in patients that don't fit into our silos of PH groups, they need a very thorough evaluation. We need to know everything about them, their hemodynamics, RV function, and comorbidities. And someone with an understanding of the pharmacology of these medications is carefully selecting the patients who might get a net benefit.

Sometimes that's a decision you can't make in one encounter. You have to follow these patients over months, and tweak things like diuretics, dialysis, immunosuppression, etc. We've tuned them up as much as possible, yet there is still significant pulmonary vascular disease. Maybe now we would consider off-label therapy.

Liz: I think the other big piece, and Josanna referred to this, and you just did as well, is the need to see people frequently. You can't just start these medications, and then have the patient come back in 3 to 6 months and expect everything to be fantastic. There is a need for a very specialized approach and individualized approach to the patient.

Murali: Maybe just one more general question before we might get into some specific clinical scenarios. Susie, maybe you can comment. There's the off-label piece of the story, but then there's also the unfortunate financial aspect to consider. A lot of times, off-label use of inexpensive or generic drugs is not a big deal. No one's going to get in your way. We know PAH medications are different. They require prior authorizations and are expensive. Could you discuss the extra work and potential nuances of prescribing off-label PAH in terms of coverage and assistance programs?

Susie: Sure. I think we would all agree that in our programs and all across the world, we're spending exorbitant amount of time on paperwork, prior authorizations, grants assistance, charitable grant assistance, etc. We've got to do something about this. The labor that is involved is amazing. Now we're talking about patients that don't fit exact criteria on the label for the medication. The workload is tremendous, we would agree.

We have just creatively come up with mechanisms and verbiage that we put in our medical documentation just basically stating this is significant precapillary pulmonary hypertension, out of proportion to underlying group 2, group 3 PH. We've been pretty successful with that. Every now and then, we will need to get a little more on the phone, or do the actual meetings with the insurance companies and the medical directors. We've been pretty successful with that. I don't know if you guys have found the same thing.

We recently had our first denial in the other direction. We had a denial for a mean pulmonary artery pressure of 24 with a PVR greater than 3, and they've completely denied medication because it's not the old definition of greater than 25. We'll see where this is all going to go in the future as more medications come out; it gets more complex as the costs go up. So I think it's just going to be more work. We have really learned to use this significant precapillary pulmonary hypertension out of proportion. What are the other programs doing?

Murali: Yes, I think that's a great point. The legwork that has to be done is definitely greater. Oftentimes these are appealed, and then unfortunately, sometimes some of the assistance programs, especially the drug company–sponsored programs aren't options, as people aren't eligible when it's off-label. They're not allowed to provide support in those situations. It can be tough to get a drug approved. Liz, you had a comment?

Liz: Yes, it's interesting. I told my nurse a couple weeks ago that it's like the "Secret Society of Pulmonary Hypertension Clinicians." A patient shows up from some outside facility, and my first question is, "Where are you getting your meds from?" Because half the time they're not, and nobody outside the PH world actually gets that, but I think that with the group 5 patients, if you submit the right heart cath data, they get approved.

I don't have to write any letters; showing significant precapillary PH gets it approved, even if I say it's pulmonary hypertension related to sarcoidosis. Where it doesn't is with inhaled treprostinil related to sarcoid. You have to say that's ILD-related. I would have to say it's gotten less challenging for the group 5 patients, but it can be worked on.

Murali: Great points! Maybe now in the remainder of our time, we can focus on some specific clinical scenarios we encounter. You guys have been touching on this already, but I'd like to delve into a few clinical scenarios that might trigger you to off-label use.

Josanna, I'll start with you. You work at a very busy and active CTEPH center. We only have 1 drug approved for CTEPH. We have 2 fantastic interventions that help the majority of patients. Can you talk about patients who either have persistent PH after interventions or inoperable CTEPH and you've already got them on Rio, but you're still not satisfied with their treatment response. We don't have any other on-label options at this point, but we do have some evidence from trials. How do you approach that patient, and how successful have you been in treating those CTEPH patients beyond riociguat?

Josanna: Yes, that's a great question. I think that, thankfully, as you said, we have a lot of options now as far as treating CTEPH, and hopefully getting people well enough that they don't need PH therapy, but there are people who will have residual disease after PTE that I may treat while I get them to BPA; or after all the interventions still have residual pulmonary vascular disease that's not treatable by any other interventions. I agree, we use Rio as

our first-line therapy, but there will be patients where that's not enough. I have used macitentan. I feel like the (MERIT) study showed improvement. It didn't show any worrisome issues, and for the most part, we have been able to get that approved, although not for everyone. There are some insurance companies that will say, "It's not approved, we don't want to give it," but if you write an appeal letter and show the study, for the most part, I've been able to get people on it. It's not a huge portion of patients, but it can be quite helpful to have an additional second agent in patients. With those patients, really, at the end, we are now dealing with small vessel vasculopathy that's not a mechanical issue anymore. It's really very similar to PAH. It also makes theoretical and scientific sense to use these drugs in that scenario.

Liz: Prior to riociguat getting FDA-approved for treatment of CTEPH, as Josanna and Mardi alluded to, we were using every class of drugs to treat PAH for this population. I think that I do use macitentan based on the MERIT study as my second line agent, if riociguat is not enough.

I think that, in real life, our patients don't fall neatly into the groups. The WHO groups are becoming more outdated as we learn more about this disease. I would say, in the general CTEPH scenario, macitentan would be my second choice of drugs.

Mardi: I would say that the ones that I had 20 years ago, they were all on IV vasodilators because they were really sick, they weren't surgical candidates, and many did extremely well. I don't think riociguat is as potent as IV prostanoid and if you're failing riociguat, and you're a lung transplant candidate, then it should be lung transplant. I don't have a particular agent that I favor, because I look at the hemodynamics, and treat accordingly. I think it's great that we now have procedures for these patients that are effective.

I remember a study from UCSD from 2008 or 2009 when they looked at patients started on PAH therapies before they got their thrombectomies. They didn't do any better with the initiation of medications and it just delayed the surgery. Just to clarify if patients are surgical candidates that should be offered.

What's unfortunate now is it's harder to get approval for other agents to add to riociguat without the supporting clinical trials.

Josanna: You're right. If somebody presents an overt RV failure, you're probably going to reach for a parenteral agent.

Susie: I can also say BPA patients need to be optimized before BPA. They often need more therapy than just Rio.

Murali: I've also had some success getting parenteral treprostinil approved in CTEPH patients. There are a couple of reports that can be cited, mainly out of Vienna, including the more recent CTREPH trial. So at least there's a study that can be submitted to an insurance company. That's a lot of good advice on CTEPH.

Maybe we can spend a little bit of time on group 5. Mardi, let me go to you first. Group 5 is obviously a very heterogeneous group. Of course, the ticket that gets you into the door to that category is because we either don't know why pulmonary hypertension develops, or they have multiple mechanisms, sometimes in an individual patient, that leads them to developing PH.

Clearly, this harkens back to our earlier conversation that any group 5 patient you're going to treat needs a very thorough evaluation with all issues outlined. Talk a little bit about some of the group 5 patients that you might treat with PAH medications on an off-label basis. What are the key features that might sway you?

Mardi: I think I'll start on sarcoid. At the last PH World Symposium, there was discussion about which group should sarcoid patients sit in. I think sarcoid needs to be in every group: it's 1, 2, 3, 4, and 5. To stick it in 5 is part of the problem, because we all have had patients with a little bit of group 3 and a little bit of group 2, who have had a clot in the past, but they're really predominantly group 1 pulmonary vascular disease. I think it's appreciating that some of group 5 have a predominant vascular component, and those are the ones that need to be treated. Roxanna Sulica, I think, had the first case series, but there's been lots of data.

Trying to do a sarcoid trial has failed miserably because there is such a mix of patients and it's hard to get people in a study who aren't already on off-label PAH therapy. Again illustrating that group 5 is probably not the best way to group these patients, because it ends up confusing things, and making it harder to get therapies that may help them. I'm not sure that's going to get fixed anytime soon, but I think it affects us in the US more than Europe because of our approval processes. If you're in group 5, the answer becomes "no" instead of, if you're group 1 PAH with associated concomitant disease, "yes."

Stuff like all the hemoglobinopathies, I think that for the most part they are not severe pulmonary vascular disease, with perhaps mild pathology. I think there's always going to be a spectrum, a bell-shaped curve, where some people are going to be at the 95% end, and they do have pulmonary vascular disease, but most patients don't have significant disease.

I think ESRD really needs to be studied, because whether it's the high flow from the fistula or just chronic renal insufficiency, we do know chronic renal insufficiency is a bad prognostic indicator in PAH at presentation, during follow-up, and on admission to the hospital. We also know that patients with high flow over time, whether that's congenital heart disease, or portal pulmonary, some patients can develop vasculopathy in the lungs. We should be looking for things to treat them. It's a high-risk population; I treat them, the dialysis patients, when I'm trying to get them to kidney transplant. Our colleagues at UVA had a case series just showing that if you did dialysis 4 times a

week, and really monitored fluid removal to a new dry weight verified by right heart catheterization hemodynamics, they were able to get a renal transplant. I think that that's what needs to be done more.

I think we probably should try to measure hemodynamics on dialysis sooner, and not wait till they're 10 years out because the left atrial compliance fails, and when left atrial compliance fails, then no matter what you do with your volume status, you can't fix the abnormality. I think that that's when I tend to use PAH medications in ESRD. But there's so much that we need to learn from that, because I do think that it really relates to what ends up leading to their mortality. The patients can't tolerate dialysis because their RV fails and they can't generate systemic pressures. We probably need to look at it like we did with scleroderma, where everybody got screening echoes and maybe a right heart cath every so often, but I think a lot of work needs to be done. That was a very long answer, but it's probably because group 5 is the one that needs the most work. So, it's not really crazy to think that group 5 should just go away, and we should just try to phenotype people better.

Murali: I think that you made a lot of great points about the ESRD patients, and we've also had some very nice results when some of these tough patients switch to nightly home hemodialysis, and you really get that fluid off and get the dry weight down. We've seen some remarkable improvements in their hemodynamics sometimes after just a few weeks. We empty the tank with all the other issues that could be contributing to PH and need to be addressed. There's such a high prevalence of sleep apnea in that population that often goes unrecognized because the only physicians they're seeing are their dialysis team, and they're overlooking it, even if they're not of the typical body habitus to have sleep apnea. I think doing all of that, ruling out CTEPH, evaluating the fistula, are essential things before we reach for a PAH drug to work on the pulmonary vasculature. Like you, it's the ones that I'm trying to get into transplant, or we're starting to see worrisome RV changes that are going to threaten their ability to be dialyzed. That's when we'll think about trying PAH medications, but it's a select group of patients. It's not a lot, yet there's such a large dialysis population out there. We have to funnel it down to those few cases.

Liz: I have a couple of comments. I agree with Mardi, that there is a lot of variation amongst group 5 diseases, and my approach to them. I actually will start with the end-stage renal disease. I would agree with both of you that really the only scenario where I would even consider PH therapy in this population is to try to get somebody to renal transplant.

From my experience and from working with our renal transplant group, this is predominantly postcapillary PH due to significant left heart disease. There is a very rare patient in that group that really should be considered for PH therapy.

I want to say something in contradiction to what Mardi said about the pulmonary hypertension of sickle cell disease. I think you will occasionally see isolated precapillary disease with a vasculopathy, in the context of so much postcapillary PH in our sickle cell population, very similar to what we see in sarcoidosis. We know this from limited autopsy studies that have been done, usually in 30 patients or less. They've looked at the lungs in these patients no matter how they die. They have medial hypertrophy of their vessels. They have plexiform lesions, and they have thrombosis. This is a PH that probably belongs in 4 of the 5 WHO groups. There's not significant interstitial lung disease in this population, although the term pulmonary fibrosis gets misused in these patients. There is also a significant proportion who have sleep-disordered breathing, including obstructive sleep apnea, from group 3 PH. In our patients who have significant precapillary pulmonary hypertension, I do treat them with meds. My go-to agents are combination therapy with an endothelial receptor antagonists, with macitentan as my agent of choice these days, combined with riociguat.

We recently completed a phase 2 safety trial of riociguat versus placebo in patients with sickle cell disease, the results of which are under review right now. This was actually not for pulmonary hypertension per se, but for abnormal echocardiography or systemic hypertension or proteinuria. The reason to do this was because of the issues of the Walk-PHaSST clinical trial of sildenafil in this population. Suffice to say that riociguat was safe in this randomized placebo-controlled trial of a hundred patients.

I have occasionally, over the years, needed to use intravenous therapy for hemoglobinapthy with severe precapillary PH in this population. One other thing you need to remember is that the chronic anemia of these patients leads them to have a baseline elevated cardiac output of 7 to 9 liters per minute. That goes back to right heart cath data published in the 1950s. This needs to be kept in mind that this is often a disease where the output is preserved, at least relatively, so the PVR elevations are actually often quite mild.

I agree with what was said about sarcoid, that there is a subgroup of the sarcoid population who have isolated pulmonary vascular disease, they don't have significant interstitial lung disease or significant left-sided heart disease, and that is a group that is most responsive to PAH therapy.

Murali: Those are great points, Liz, and I can't let you slip that in there without making a general comment. You mentioned the Walk-PHaSST trial. It's a perfect example of the cautions we have to apply when using off-label. We thought there was a biological basis for one of our therapies to benefit a group of patients, but we actually saw the increased adverse events. So that's why we have to study these patients whenever possible. And when the data is there, it has to help inform us which way to go. So thanks for bringing that up!

Mardi: For sickle cell disease, the group at NIH had a lot of positive experience treating the PAH, for sure. But most of the sickle cell I see tends to be pulmonary venous hypertension, or high-output failure, and you don't know that until you thoroughly examine, and do the right testing, which I think Murali had mentioned earlier.

Liz: Definitely. I have people who have combined pre and post, for sure, and there's so much underrecognized diastolic dysfunction in this population.

Murali: In our remaining time, I'm going to dare and touch that "third rail" by bring up the group that we cringe at dealing with and that's the HFpEF-PH patients, the folks with combined pre- and postcapillary PH. Some of you have touched on this already, but, Susie, let me turn to you. You work at a center with a huge cardiology focus. Are there some patients who fit that HFpEF-PH definition that you are treating with off-label therapy? Who are they and what's your experience been? And let's assume they don't have a concomitant group 1 risk factor, like scleroderma with some diastolic dysfunction.

Susie: Yes, great question. This is probably one of the largest groups that we all see in our programs, and the largest groups that we have after their right heart cath. For us, it's a slippery slope, difficult and challenging. If it's true combined pre- and postcapillary, and that PVR is pretty elevated, that's when we would "dip our toe." If they come back with PVRs of 3 or 4, we may not dip our toe. At least now we have guideline-directed medical therapy, so we can be working on other things in the background, but I would say, it's really a tricky population.

We're probably case-by-case, for sure. If we've optimized the volume status as best as we can, and we still have that significantly elevated PVR and RV dysfunction on echo, then we would cautiously consider off-label therapy. We would start with a PDE5 inhibitor and they would have very close follow-up, watching for volume optimization. What's our success rate with that? I think they don't symptomatically subjectively feel a lot better in our experience, I don't know if you guys feel the same. We are looking forward to the new clinical trials coming out in this area because we feel like it's such an area that we need more data and more evidence, but we do dip our toe if that PVR is out of proportion, and we will trial, and just cautiously follow. I would say we have some patients who've had success and some subjective benefit, and some who've not.

Mardi: I would say if you have those patients, you should put them in the CADENCE trial of sotatercept or any of the other clinical trials in PH-left heart disease. (Note: I am the chair of the steering committee for CADENCE). Because we need to get the answers, right?

It's not an easy population because the patients often have so many different comorbidities. It's hard because we don't have therapies, and they have true elevation of pressures, whether if it's on exertion or even just at rest, and they are limited. Even when they're euvolemic, they're still limited. There's a definitely a gap in our knowledge of how to treat it. We haven't done a great job with our current existing therapies, and I agree with you. Some of it might be subjective improvements, which is good, but on the whole, I haven't seen dramatic improvements when I've done it in the past, so I try to stay away from it.

Murali: Susie, I loved your answer, and I also want to emphasize, at least we are making some progress with this patient population. I think a lot of our colleagues still take a nihilistic approach to the HFpEF population, in general. We have good data now with SGLT2 inhibitors, an ARNI, and emerging data with GLP-1 agonists. We need to be educating our colleagues, even the cardiologists, that these agents have become the standard of care, and they should be tried first before we start monkeying around with PDE5 inhibitors and ERAs, where there's even a chance they'll end up in the hospital due to medication-related fluid retention and volume overload.

Well, ladies, I want to thank you for an informative and spirited discussion, on a very difficult and complicated topic. I think you made some great points. There was a lot of consensus but with some variability in opinions because of the lack of data. Nevertheless, some general points and approaches are echoed by everybody. I really appreciate you taking time today to have this conversation!

ORIGINAL CASE REPORT

Lung Transplantation for Pulmonary Veno-Occlusive Disease Without Hemodynamic Changes: A Case of Radiographic Findings Preceding Vascular Changes

Martin Y. Rofael
Department of Medicine, University of California Irvine, Irvine, CA

Travis Henry
Department of Radiology and Biomedical Imaging, Duke University, Durham, NC

Alyssa A. Perez
Department of Medicine, University of California San Francisco, San Francisco, CA

Lorriana E. Leard
Department of Medicine, University of California San Francisco, San Francisco, CA

Jasleen Kukreja
Department of Surgery, University of California San Francisco, San Francisco, CA

Kirk D. Jones
Department of Pathology and Laboratory Medicine, University of California San Francisco, San Francisco, CA

Teresa De Marco
Department of Medicine, University of California San Francisco, San Francisco, CA

Nicholas A. Kolaitis
Department of Medicine, University of California San Francisco, San Francisco, CA

We present a case of pulmonary veno-occlusive disease, with classic findings on cross-sectional imaging, but the absence of any hemodynamic changes. Given the high clinical suspicion for pulmonary veno-occlusive disease, this patient was referred for lung transplantation despite the absence of hypoxemia, and despite the normal pulmonary vascular resistance. His clinical picture progressed rapidly without the development of significant hemodynamic abnormalities. Fortunately, he was transplanted before fulminant respiratory failure, with the explant confirming granulomatous pulmonary veno-occlusive disease as the diagnosis. Early referral for transplantation is needed when pulmonary veno-occlusive disease is suspected, even in the absence of hemodynamic changes.

CASE PRESENTATION

A 52-year-old male nonsmoker presented with progressive dyspnea, cough, and wheezing over the preceding 7 months. He reported no fevers, chills, night sweats, weight loss, joint stiffness, or rashes. History was notable for biopsy-proven neurosarcoidosis, diagnosed 9 years prior, for which he was in remission and off immunosuppression. Aside from the history of sarcoidosis, there were no risk factors for cardiac disease or diastolic dysfunction. Physical examination was remarkable only for minimal bilateral lower extremity edema. He had no hypoxemia. Spirometry and diffusing capacity for carbon monoxide ($D_{L,CO}$) were normal. He walked 400 m without desaturations on his 6-minute walk test.

Laboratory investigation was notable for an elevated erythrocyte sedimentation rate of 52 mm/h (normal 0-10 mm/h) and a C-reactive protein of 11.6 mg/L (normal < 5.1 mg/L). His B-type natriuretic peptide (BNP) was normal at 6 pg/mL. Vitamin D, 25-hydroxy; Vitamin D, 1,25-dihydroxy; and both serum and cerebral spinal angiotensin converting enzyme were normal. Infectious workup was unrevealing.

Chest computed tomography (CT) scan revealed interlobular septal thickening, ground glass opacities (GGOs), lymphadenopathy, peri-bronchial cuffing, and pleural effusions, highly suggestive of pulmonary veno-occlusive disease (PVOD) (Figure 1A). Transthoracic echo (TTE) revealed mild left ventricular hypertrophy, and normal left ventricular function with an ejection fraction of 60% to 65%. There was no diastolic dysfunction. Right ventricular systolic function was also normal, with an estimated pulmonary artery systolic pressure of 36 mm Hg. Positron emission tomography CT showed no active sarcoidosis. Multiple large bilateral mismatched defects were noted on ventilation-perfusion scan (Figure 1B).

Given concern for PVOD, the patient underwent right heart catheterization (RHC), which showed mean pulmonary artery pressure of 28 mm Hg, pulmonary capillary wedge pressure (PCWP) of 15 mm Hg, pulmonary vascular resistance (PVR) of 1.69 Wood units, and cardiac output (CO) of 7.67 L/min, measured by averaging 3 separate thermodilution values. When measured by indirect Fick, the CO was 6.60 L/min, yielding a PVR of 1.97. There was no significant change after vasodilator therapy. The PCWP measurement was confirmed by measurement of a PCWP saturation, which showed a jump in saturation

Key Words—lung transplantation, pulmonary veno-occlusive disease
Correspondence: nicholas.kolaitis@ucsf.edu

 DOI:10.21693/1933-088X-22.4.176

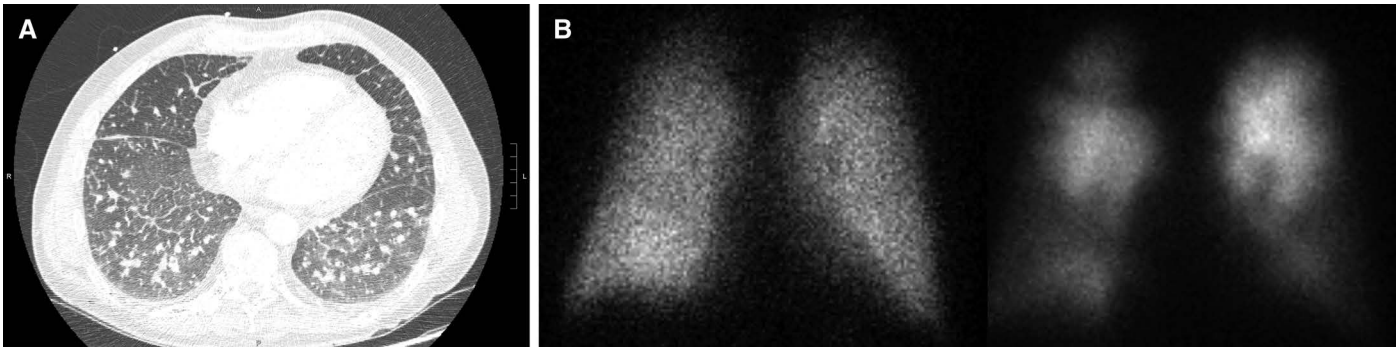


Figure 1: (**A**) Chest computed tomography with centrilobular ground glass nodules and interlobular septal thickening. (**B**) Ventilation (left)–perfusion (right) scan with multiple large bilateral mismatched defects.

from 74.8% in the pulmonary artery to 96.2% in the pulmonary capillary wedge position. Pulmonary angiography demonstrated no filling defects. The patient underwent endobronchial ultrasound-guided transbronchial needle aspiration of a station VII lymph node, without evidence of infection, malignancy, or granulomas. While the RHC was not consistent with an elevated PVR, the clinical picture was felt to represent PVOD, with imaging findings preceding hemodynamic changes. Therefore, the patient was referred simultaneously for surgical lung biopsy and lung transplant evaluation.

His symptoms rapidly progressed, and evaluation 6 weeks from initial presentation revealed worsening hypoxemia requiring 4 L/min at rest and 15 L/min with exertion. A TTE at the time showed right ventricular enlargement, and a pulmonary artery systolic pressure >60 mm Hg. Given the rapidity of progression, he was hospitalized for expedited lung transplant evaluation. Repeat RHC showed a showed mean pulmonary artery pressure of 35 mm Hg, PCWP of 12 mm Hg, PVR of 2.8 Wood units, and CO of 7 L/min by thermodilution and 6.7 L/min by indirect Fick. His BNP increased 12-fold to 74 pg/mL. After completion of his workup, he was rapidly listed for transplant without tissue confirmation of PVOD, and underwent bilateral lung transplant 2 weeks later. Pathologic examination of the explanted lung showed diffuse obliteration of pulmonary veins within interlobular septa, nonnecrotizing granulomas, and perivenous fibrosis (Figure 2).

DISCUSSION

We present this case of a patient with a history of neurosarcoidosis in remission, who presented with progressive dyspnea, and a chest CT suggestive of PVOD. Notably, the imaging findings of PVOD preceded any hemodynamic manifestations, which has only been described once before.[1] Unlike the previously reported case, this patient developed rapidly progressive hypoxemia and required emergent lung transplant. Explanted lung pathology confirmed granulomatous PVOD.

Sarcoidosis is a granulomatous disorder of unknown etiology that can involve any organ. Sarcoidosis can lead to pulmonary hypertension (PH), most often as pulmonary arterial hypertension secondary to advanced pulmonary fibrosis, and rarely as PVOD.[2-4] PVOD is a subset of PH characterized typically by intimal proliferation, thrombosis, and obliteration of the intralobular veins.[5] PVOD has multiple etiologies including autoimmune disorders, chemotherapy, and as an inherited condition.[4] Symptoms of PVOD are nonspecific. Radiographic findings include GGOs, interlobular septal thickening, lymphadenopathy, and less likely pericardial and pleural effusions.[6] Ventilation-perfusion scans may show mismatches, which are not seen with pulmonary angiograms.[7] Pulmonary function tests often show a severely reduced $D_{L,CO}$.[2] The presence of postcapillary blockage can lead to alveolar hemorrhage in

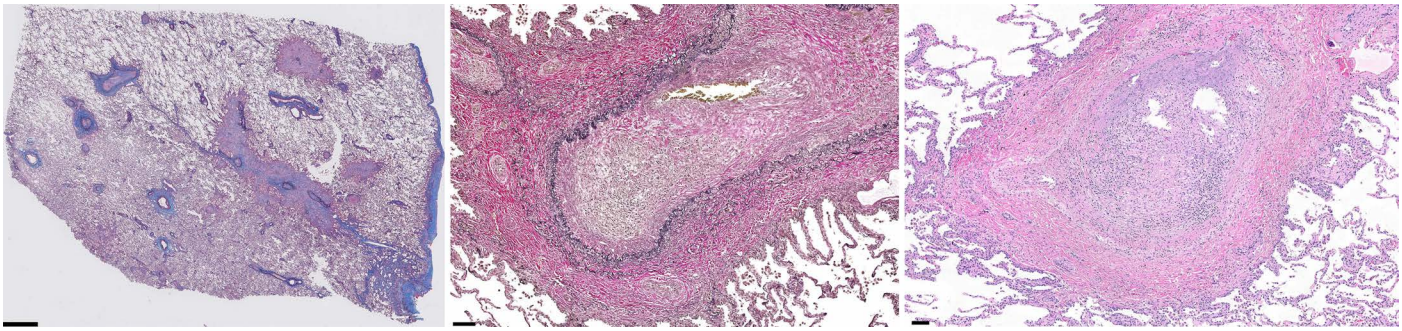


Figure 2: Low-power view (left) shows complete obliteration of interlobular pulmonary veins by non-necrotizing granulomas and fibrosis (Elastichrome, scale bar = 2 mm). The pulmonary veins show filling and obliteration of lumens by nonnecrotizing granulomas (middle: Verhoeff-Van Gieson, scale bar = 100 microns, and right: hematoxylin and eosin, scale bar = 100 microns).

PVOD, so transbronchial lung biopsies are not recommended.[8] Mainstay pulmonary arterial hypertension therapies, such as vasodilators, may conversely lead to increased capillary congestion leading to life-threatening pulmonary edema.[8,9] PVOD has a poor prognosis and lung transplant is the best available treatment.[10]

Sarcoidosis-associated PVOD is characterized by noncaseating granulomas involving intralobular veins and fibrointimal changes of small venules causing luminal obliteration.[4,11-13] In a postmortem study of 40 patients with sarcoidosis, 65% had granulomatous invasion of pulmonary venules.[14] Despite this, the frequency of clinically significant pulmonary arterial hypertension and PVOD is low. Studies suggested that PH from sarcoidosis can be from pulmonary fibrosis, or in the absence of it, as is the case with granulomatous infiltration of the pulmonary vascular system.[4]

The decision to treat sarcoid-related PVOD with steroids is controversial. Reports suggest that pulse steroids may not change progression of disease.[13] Others suggest that steroids may stabilize symptoms, though recurrence may occur with tapering.[4,11,12] One study noted that response to steroids, disease burden, and normalized pulmonary pressures on RHC occurred only in patients without fibrotic changes, suggesting that the nonfibrotic phenotype may respond to steroids.[4] Before we listed this patient for transplantation we had a multidisciplinary conversation with our internal sarcoidosis expert, as well as 2 sarcoidosis experts at other academic centers. All 3 sarcoidosis experts independently agreed that steroids would not have been helpful. As such, the patient was not given a trial of steroids given the concern that it would delay transplantation, would likely not change the clinical course, and would pose increased risks of infection posttransplantation. Although steroids may be reasonable to consider in other less advanced patients without significant pulmonary fibrosis, our patient's explant demonstrated severe intimal fibrosis in the postcapillary venules, confirming that steroids would have had little benefit even if they had been given.

In prior reports of sarcoidosis-associated PVOD, pulmonary hypertension was noted on TTE or RHC and correlated with symptoms well before diagnosis of PVOD. In our case, chest CT scan strongly suggested PVOD, despite an initially normal BNP, $D_{L,CO}$, TTE, and PVR on RHC. Guidelines recommend chest CT scan as part of the PH workup, and the combination of GGOs, interlobular septal thickening, and mediastinal lymphadenopathy is 95% sensitive and 89% specific for PVOD.[15] Random zonal predominance and preferential centrilobular distribution of GGOs are more specific, while pericardial and pleural effusions are less specific.[6] Our patient's symptoms, and PVOD imaging findings, preceded objective changes in pulmonary vascular pressures. Evidence of PH on his TTE and RHC were very late findings, after significant and rapid clinical worsening. Our high clinical index of suspicion for PVOD led to early referral for transplant evaluation, and without this early referral the patient would likely have died before completing his transplant evaluation.

This case highlights that sarcoidosis-related PVOD may occur even in the absence of markers of active sarcoidosis and should always be considered in any patient with a history of sarcoidosis, no matter how remote. It also highlights the need for early referral for lung transplantation in patients with suspected PVOD, even when hemodynamic changes are not present.

References

1. Beshay S, Humbert M, Barrios R, Sahay S. Progression of pulmonary veno-occlusive disease without pulmonary hypertension. *Pulm Circ.* 2022;12(1):e12046.
2. Rapti A, Kouranos V, Gialafos E, et al. Elevated pulmonary arterial systolic pressure in patients with sarcoidosis: prevalence and risk factors. *Lung.* 2013;191(1):61-67.
3. Huitema MP, Bakker ALM, Mager JJ, et al. Prevalence of pulmonary hypertension in pulmonary sarcoidosis: the first large European prospective study. *Eur Respir J.* 2019;54(4).
4. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. *Thorax.* 2006;61(1):68-74.
5. Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. *Mod Pathol.* 1991;4(2):269-282.
6. Resten A, Maitre S, Humbert M, et al. Pulmonary hypertension: CT of the chest in pulmonary venoocclusive disease. *AJR Am J Roentgenol.* 2004;183(1):65-70.
7. Bailey CL, Channick RN, Auger WR, et al. "High probability" perfusion lung scans in pulmonary venoocclusive disease. *Am J Respir Crit Care Med.* 2000;162(5):1974-1978.
8. Palmer SM, Robinson LJ, Wang A, Gossage JR, Bashore T, Tapson VF. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. *Chest.* 1998;113(1):237-240.
9. Montani D, Achouh L, Dorfmuller P, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore).* 2008;87(4):220-233.
10. Huertas A, Girerd B, Dorfmuller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: advances in clinical management and treatments. *Expert Rev Respir Med.* 2011;5(2):217-229; quiz 230-211.
11. Crissman JD, Koss M, Carson RP. Pulmonary veno-occlusive disease secondary to granulomatous venulitis. *Am J Surg Pathol.* 1980;4(1):93-99.
12. Dwyer N, Smith R, Challis D, Reid D, Kilpatrick D. Granulomatous angiitis leading to a pulmonary veno-occlusive disease-like picture. *Eur Respir J.* 2009;33(3):666-669.
13. Portier F, Lerebours-Pigeonniere G, Thiberville L, et al. Sarcoidosis simulating a pulmonary veno-occlusive disease [in French]. *Rev Mal Respir.* 1991;8(1):101-102.
14. Takemura T, Matsui Y, Saiki S, Mikami R. Pulmonary vascular involvement in sarcoidosis: a report of 40 autopsy cases. *Hum Pathol.* 1992;23(11):1216-1223.
15. Mineo G, Attina D, Mughetti M, et al. Pulmonary veno-occlusive disease: the role of CT. *Radiol Med.* 2014;119(9):667-673.

2023 PH Professional Network (PHPN) Symposium: Abstracts

EFFECT OF PULMONARY HYPERTENSION ON CLINICAL AND ECONOMIC OUTCOMES OF PATIENTS ADMITTED WITH ACUTE MYOCARDIAL INFARCTION IN THE UNITED STATES, A NATIONWIDE STUDY

M. El Labban
Mayo Clinic Health System, Mankato, Minnesota, MN

S. Khan
Mayo Clinic Health System, Mankato, Minnesota, MN

I. Bou Aki
Mayo Clinic Health System, Mankato, Minnesota, MN

H. Guleid
Mayo Clinic Health System, Mankato, Minnesota, MN

Category: Clinical Science
Subcategory: Diseases and Conditions Associated with PH

Background: Acute myocardial infarction (AMI) is one of the leading causes of morbidity and mortality. Pulmonary hypertension (PH) is often missed as a diagnosed comorbidity in patients admitted with AMI. We aimed to study the effect of PH (all categories) on the outcomes of patients admitted with AMI with further subclassifications into ST elevation myocardial infarction (STEMI) and non-STEMI.
Methods: Using the National Inpatient Sample Database from 2017 to 2020, a retrospective study of adult patients with principal diagnosis of AMI with secondary diagnosis with or without PH according to ICD-10 codes. Several demographics, including age, race, and gender, were analyzed. The primary endpoint was mortality, while the secondary endpoints included mechanical intubation, length of stay in days, and patient charge in dollars. Multivariate logistic regression model analysis was used to adjust for confounders, with a *P* value <0.05 considered statically significant.
Results: The study included 1830229 patients admitted with an AMI, of which 37895 of which had PH. The mean age for patients with and without PH was 72.8 and 66.7 years, respectively. In the PH group, 50% were females compared with 37% in the non-PH group. Around 70% in both groups were White. Statistically significant comorbidities noticed in the PH group included sepsis (4% versus 2%), diabetes mellitus (47% versus 40%), hypertension (89% versus 81%), acute kidney injury (36% versus 19%; $P < 0.01$). In-hospital mortality rate was higher in the PH group with statistical significance (7.2% versus 4.6%, $P < 0.01$). The adjusted odds ratio (aOR) was 0.99 without statistical significance. In the STEMI group, mortality rate was higher in the PH group with statistical significance (15.7% versus 7.8%, $P < 0.01$) similar to the non-STEMI group (5.9% versus 3.3%, $P < 0.01$). The odds ratio if in-hospital mechanical ventilation was only statistically significant in the STEMI group (aOR = 1.32, $P = 0.01$). The length of stay was longer in the PH group across the 3 groups (AMI: 6.5 versus 4.35 days, aOR = 0.87, $P < 0.01$; STEMI 6.6 versus 3.9, aOR = 0.87, $P < 0.01$; non-STEMI 6.5 versus 4.5 days, aOR = 0.88, $P < 0.01$). Patients in the PH group had a higher total charge in the 3 groups (Figures 1 and 2).
Conclusion: Patients admitted with AMI with associated PH were found to have worse clinical outcomes and a higher economic burden. Practicing clinicians should be aware of the significance of associated PH as a comorbidity in the setting of AMI.

Table 1: Demographic Characteristics			
Characteristics	Without PH	With PH	p value
AMI-PH, no(%)	1,792,334 (98)	37,895 (2)	
Female, no(%)	663,163 (37)	18,947(50)	<0.01
Age (y)	66.7	72.8	
Race,no(%)			<0.01
White	1,326,327 (74)	26,526 (70)	
Black	197,156 (11)	5,305 (14)	
Hispanic	143,386 (8)	3,031 (8)	
Asian or Pacific Islander	53,770 (3)	1,136 (3)	
Native American	8,961 (0.5)	265 (0.7)	
Other	53,770 (3)	1,136 (3)	
Charlson Comorbidity Index score, no. (%)			
1	448,083 (25)	1,894 (5)	
2	448,083 (25)	5,684 (15)	
>=3	896,167 (50)	30,316 (80)	
Median annual income in patient's zip code, US$, no. (%)			0.13
1 - 43,999	537,700 (30)	11,747 (31)	
44,000 - 55,999	501,853 (28)	10,989 (29)	
56,000 - 73,999	430,160 (24)	8,715 (23)	
74,000+	322,620 (18)	6,442 (17)	
Insurance type, no. (%)			<0.01
Medicare	1,057,477 (59)	29,179 (77)	
Medicaid	179,233 (10)	3,031 (8)	
Private Insurance	483,930 (27)	4,926 (13)	
Self-pay	71,693 (4)	757 (2)	
Hospital bed size, no. (%)			0.13
Small	304,696 (17)	7,200 (19)	
Medium	555,623 (31)	11,747 (31)	
Large	932,013 (52)	18,947(50)	
Hospital region, no. (%)			0.02
Northeast	322,620 (18)	7,200 (19)	
Midwest	394,313 (22)	8,715 (23)	
South	716,933 (40)	14,021 (37)	
West	358,466 (20)	7,957 (21)	
Teaching hospital			<0.01
Rural	125,463 (7)	2,273 (6)	
Urban Nonteaching	448,083 (25)	7,957 (21)	
Urban teaching	1,218,787 (68)	27,663 (73)	
Comorbidities, no. (%)			
Sepsis	35,846 (2)	1,515 (4)	<0.01
DMII	716,933 (40)	17,810 (47)	<0.01
HTN	1,451,790 (81)	33,726 (89)	<0.01
AKI	340,543 (19)	13,642 (36)	<0.01
BMI>40	286,773 (16)	6,442 (17)	<0.01
AMI:Acute Myocardial Infarction, PH: Pulmonay Hypertension, DMII: Diabetes Milletus II, HTN: Hypertension, AKI: Acute Kidney Injury, BMI: Body Mass Index			

Figure 1: Demographics.

In-hospital mortality rates and odds						
	Total	Without PH	With PH	p value	Adjusted Odds Ratio	p value
AMI, no (%)	85,834 (4.7)	82,506, (4.6)	2635 (7.2)	<0.01	0.99	0.98
STEMI, no (%)	39,190(7.9)	38,682(7.8)	760 (15.7)	<0.01	1.04	0.6
NSTEMI, no (%)	45,444(3.4)	42,799(3.3)	1,936(5.9)	<0.01	1.12	0.03

In-hospital mechanical ventilation odds		
	PH-Adjusted Odds Ratio	p value
AMI	1.08	0.15
STEMI	1.32	0.01
NSTEMI	1.13	0.055

Mean Length of Stay				
	Without PH	With PH	Adjusted Odds Ratio	p value
AMI, days	4.35	6.5	0.87	<0.01
STEMI, days	3.9	6.6	0.87	<0.01
NSTEMI, days	4.5	6.5	0.88	<0.01

Total Charges				
	Without PH	With PH	Adjusted Odds Ratio	p value
AMI, ($)	95,213	119,083	13,229	<0.01
STEMI, ($)	111,963	159,452	18,587	<0.01
NSTEMI, ($)	88,906	113,450	15,040	<0.01

Figure 2: Results.

PERSISTENCE AND PREDICTORS OF PERSISTENCY FOR PULMONARY ARTERIAL HYPERTENSION PATIENTS ON SELEXIPAG IN CANADA: A RETROSPECTIVE CLAIMS DATABASE STUDY

L. Mielniczuk
University of Ottawa, ON, Canada

S. Provencher
Université Laval, QC, Canada

J. Swiston
University of British Columbia, BC, Canada

J. Weatherald
University of Alberta, AB, Canada

C. Zhang
Janssen Business Technology Commercial Data Sciences, NJ

S. Golden
IQVIA Solutions Canada Inc., ON, Canada

Brad Millson
IQVIA Solutions Canada Inc., ON, Canada

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a serious, progressive disease that usually leads to right heart ventricular failure and death. Although treatment guidelines include recommendations for combination drug therapy with selexipag (prostacyclin receptor agonist), research examining real-world persistence and potential predictors of persistency in the Canadian population is sparse.
Methods: This retrospective claims database analysis included PAH patients (inferred) with ≥1 selexipag claim from Ontario Drug Benefits (ODB), Régie de l'assurance maladie du Québec (RAMQ), or Canadian Private Drug Plan (PDP) databases between April 2016 and July 2021. Selexipag persistence was calculated from index date (first selexipag claim) until discontinuation (no further selexipag claims) or censoring (no further claims in any database or persistent at the end of the study period). Persistence was estimated by Kaplan-Meier (KM) analyses. Four feature selection models (stepwise Cox proportional hazards, Boruta, Coxnet, and Random Survival Forest) were used to rank 28 potential predictors of persistence, including clinical and demographic variables. The top 12 (average model rank) were included in a Cox proportional hazards model for selexipag persistence.
Results: Of 311 patients identified throughout the observation period (PDP = 101, 32%; ODB = 181, 58%; and RAMQ = 29, 9%), 70% were female and 71% were aged 50–79 years. During the study period, 129 patients (41%) discontinued selexipag, including 16 (5%) who switched to intravenous prostacyclin. Another 69 patients (22%) were censored, and 113 (36%) were persistent on selexipag at the end of the study. From the KM

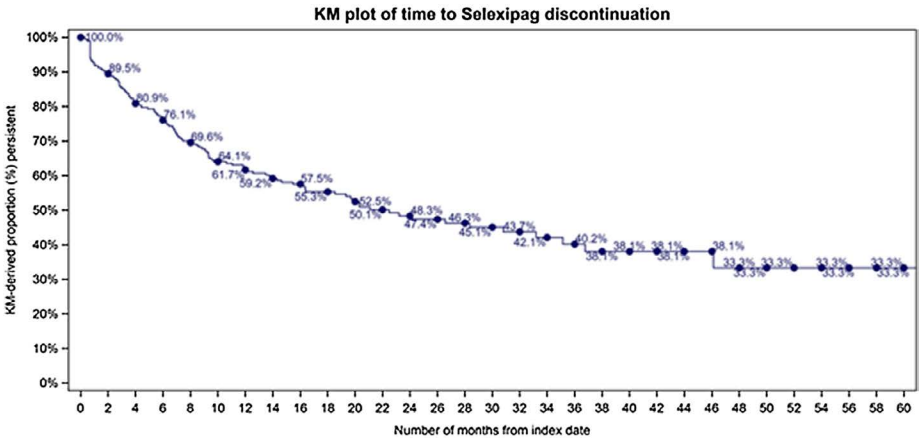


Figure 1: Kaplan-Meier derived selexipag persistence for pulmonary arterial hypertension patients between April 2016 and July 2021 discontinuations.

analysis, 62% of patients were persistent on selexipag after 1 year, 48% after 2 years, and 33% after 4 years (Figure 1). None of the predictors tested reached statistical significance level (0.05). However, 3 predictors had *P* values <0.1: baseline use of double oral combination therapy (heart rate [HR] = 0.63; 95% confidence interval [CI] = 0.38, 1.04), sildenafil monotherapy (HR = 1.92; 95% CI = 0.97, 3.58), and riociguat monotherapy (HR = 2.31; 95% CI = 0.89, 5.23).

Conclusion: This is the first Canadian retrospective claim database study to examine the persistence and predictors of persistency of PAH patients on selexipag. Persistence on selexipag in this cohort was 62% at 1 year and 33% at 4 years. However, none of the predictors of selexipag persistence tested in this study reached significance in this population. Further research into predictors of selexipag persistence is needed to help improve potential treatment outcomes and therefore benefits for PAH patients.

INPATIENT PROSTACYCLIN ACTIVITY OVER A 1-YEAR PERIOD AT A PULMONARY HYPERTENSION CENTER OF COMPREHENSIVE CARE

K. Loi
Community Medical Centers, Fresno, California

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Prostacyclins are high-risk, high-alert medications that have been shown to actually or potentially cause significant harm to the patient, even when used as intended. As a result, inpatients receiving prostacyclins require care from specially trained nurses and pharmacists. With the recent newer prostacyclin dosage formulations coming to market, in this study, we seek to provide baseline data on inpatients who receive prostacyclins at our Pulmonary Hypertension Center of Comprehensive Care.

Methods: Hospital encounters with inpatient medication orders for prostacyclins between January 1 and December 31, 2022, were identified by electronic health record. Prostacyclin route of administration, average length of stay, and average discharge dose were extracted from the electronic health record patient encounter.

Results: This study included 62 hospital encounters by 36 patients. Of 62 hospital encounters, 35 (56%) received parenteral prostacyclin, 14 (22%) received inhaled prostacyclin, and 13 (21%) received oral prostacyclin. Three patients made up 20 (32%) of the 62 hospital encounters over the 1-year period. Four (7%) of 62 encounters were for ≤1 day, and all 4 were on parenteral prostacyclin. The mean (+SD) discharge dose was 54.9 ± 17.7 ng/kg/min, and mean length of stay was

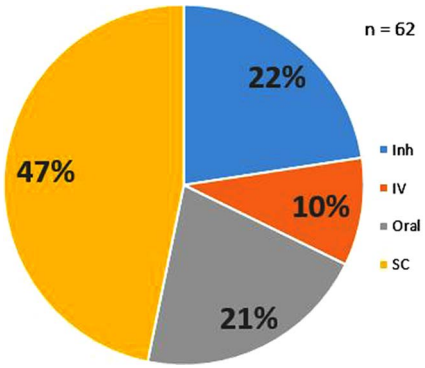


Figure 1: Hospital encounters with a prostacyclin order by route.

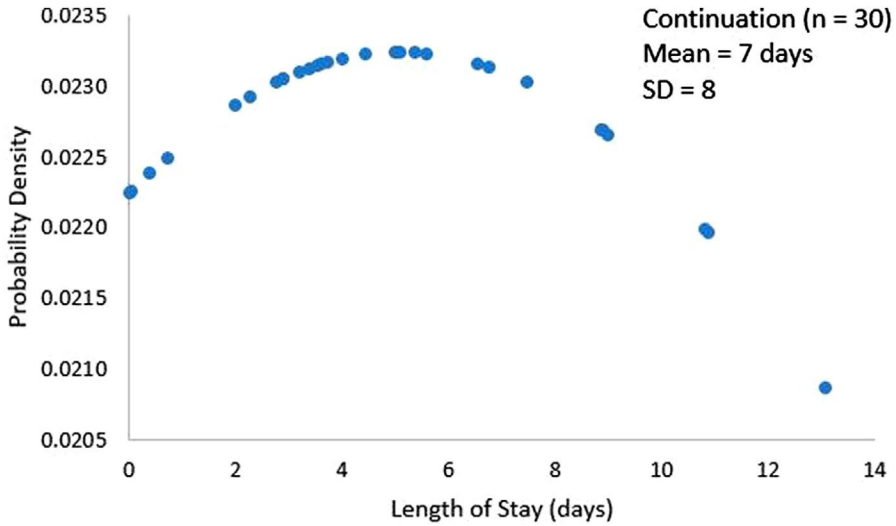


Figure 2: Mean length of stay for continuation of parenteral prostacyclin encounters.

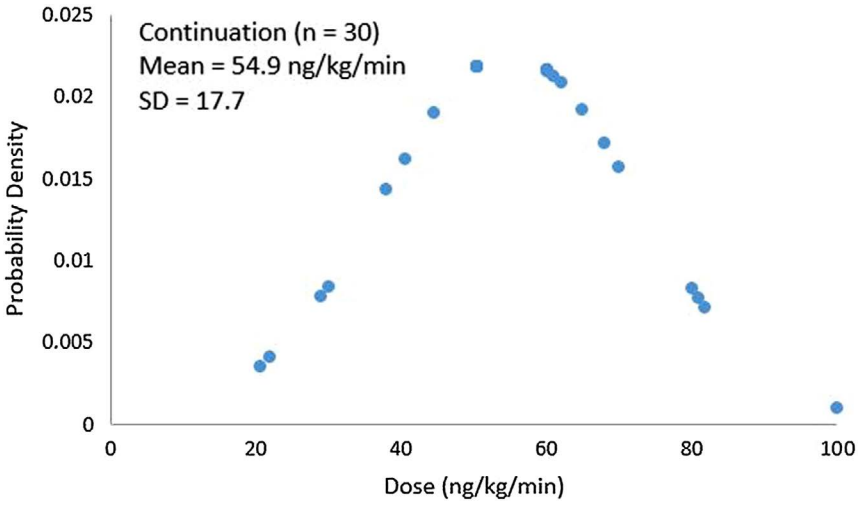


Figure 3: Mean discharge dose for continuation of parenteral prostacyclin encounters.

7 days for established patients on parenteral prostacyclin. The mean discharge dose was 20 ng/kg/min, and mean length of stay was 11 days for new patients on parenteral prostacyclin (Figures 1–3).

Conclusion: Over a 1-year period, 36 patients on prostacyclin therapy presented to the hospital 62 times. Three patients made up 20 (32%) of the 62 hospital encounters over the 1-year period. The mean length of stay for patients on parenteral prostacyclin therapy is between 7 and 11 days. Additional research will be done evaluating the difference in length of stay and cost of care between patients receiving parenteral, inhaled, and oral prostacyclin therapy.

A CASE SERIES OF COMMON VARIABLE IMMUNODEFICIENCY RELATED LUNG DISEASE WITH PRECAPILLARY PULMONARY ARTERIAL HYPERTENSION (PAH): REVIEW OF CLINICAL PRESENTATIONS AND TREATMENT CONSIDERATIONS

A. Parsons
Henry Ford Hospital, Detroit, MI

D. J. Franco-Palacios
Henry Ford Hospital, Detroit, MI

Category: Case Report
Subcategory: Diseases and Conditions Associated with PH

Background: Common variable immunodeficiency (CVID) is a rare and poorly understood immunologic disease with varying criteria for diagnosis. CVID is associated with various pulmonary manifestations including lymphoid interstitial pneumonitis, bronchiectasis, granulomatous-lymphocytic interstitial lung disease (GLILD), and severe pulmonary arterial hypertension (PAH). The ideal treatment option for this rare, complex form of PAH is unknown given the sparsity of clinical data, and thus, treatment is guided by case reports. Our case series highlights the diagnosis of CVID-related PAH, varying treatment options for their PAH, and the outcomes for 3 patients with different clinical manifestations.

Methods: Retrospective chart review was performed on 3 patients previously known to the Pulmonary Hypertension program at Henry Ford Hospital in Detroit, Michigan. Our patients had CVID and were receiving active treatment or have probable CVID based off Ameratunga criteria. All included patients were demonstrated to have severe precapillary PAH by right heart catheterization (RHC) or highly likely to have pulmonary hypertension (PH) by their echocardiogram data by the 2022 European Respiratory Society guidelines, which is consistent with previous PAH described in CVID patients.

Results: Our 3 patients had the following demographics: 2:1 F/M ratio, male patient was diagnosed at age 46, and our female patients' age of diagnosis was average 28 years old. Our female patients were on oxygen therapy for a mean of 8 years prior to the diagnosis of PH. Our patients had the following echocardiographic data: median estimated pulmonary artery (PA) pressure of 83 mmHg, mean maximal tricuspid valve regurgitation velocity of 4.235 m/s, median tricuspid annular plane systolic excursion when available was 1.245 cm. Our patients' RHC data (n = 2) showed median mean PA pressure (mPAP) of 48 mmHg, median pulmonary capillary wedge pressure of 6 mmHg, median cardiac index of 2.57 L/min/m^2, median pulmonary vascular resistance of 24.49 WU. Pulmonary function testing showed severe reduction in forced expiratory volume in the first second (median 33% of predictive) and diffusing capacity after correction for alveolar volume for all patients. Median diffusing capacity for carbon monoxide (DLCO) was 24.2 mL/mmHg/min, roughly 25% of predicted, and median adjusted DLCO/alveolar volume was 4.88 mL/mHg/min/L, roughly 70% of predicted. All patients had New York Heart Association functional class III/IV dyspnea prior to PH treatment and had pulmonary symptoms, including hypoxia requiring continuous oxygen and/or frequent respiratory infection for a mean of 13 years prior to diagnosis of PAH. Regarding treatment options, all patients had variable courses for both their CVID treatment and PH treatment. Ultimately, 2 of our patients received intravenous immunoglobulin therapy for their CVID, and 1 patient was additionally treated with rituximab infusions and mycophenolic acid 2 times per day, with worsening of GLILD off mycophenolic acid and stabilization when resumed. One patient had progression to bilateral lung/liver transplantation performed in 2013 due to bronchiectasis and end-stage liver disease related to CVID. One patient with PAH symptoms was controlled with inhaled treprostinil alone

15 puffs 4 times per day, and 1 patient was on inhaled treprostinil 9 puffs 4× per day and ambrisentan 10 mg combination. **Conclusion:** CVID has a wide spectrum of presentations and likely varying pathophysiologic mechanisms leading to the development of PAH. Our cases highlight these variable clinical manifestations and the eventual development of severe precapillary PH, which is consistent with the little data published to date. More research is needed into the possible mechanisms of CVID-PAH, and more awareness is needed to reduce the mean time to diagnosis. Patients with frequent respiratory infections should have screening with serum immunoglobulins if the clinical picture fits a description of CVID. We believe a myriad of factors lead to pulmonary vascular remodeling in CVID not limited to chronic hypoxia, portal hypertension, systemic inflammation, granulomatous inflammation, lymphocytic infiltration, or a combination of them. No treatment generalizations can be made from our patients, each appearing to have a different manifestation of CVID leading to PAH; however, our series highlights that great care should be taken to solve the underlying pulmonary mechanisms which are driving the severe PAH.

A PHASE 3 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF LIPOSOMAL TREPROSTINIL (L606) IN SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION OR PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASE

P. Kan
Pharmosa Biopharm Inc., Taipei City, Taiwan

Category: Clinical Science
Subcategory: Diseases and Conditions Associated with PH

Background: Pharmosa Biopharm Inc. is developing L606, a novel sustained formulation, as an inhalation combination product in the treatment of patients with pulmonary arterial hypertension (PAH) or pulmonary hypertension associated with interstitial lung disease (PH-ILD). L606 is composed of treprostinil-encapsulated liposomes which alleviate upper airway irritation and reduce dose frequency to twice a day. In addition, a mesh-vibrating nebulizer offers a simple, convenient, and portable inhalative delivery that is a clinically meaningful improvement over the current nebulized therapy. In the Phase 1 study, L606 showed a sustained and prolonged release profile as compared with Tyvaso and is expected to reduce the time spent at subtherapeutic levels as well as frequency of inhalations per day. L606 was found to be safe and was well tolerated in healthy volunteers. This Phase 3, open-label, 2-part, multicenter study aims to demonstrate the short-term and long-term safety and efficacy of repeated doses of L606 in subjects with PAH or PH-ILD.
Methods: A single-arm, open-label, multicenter study was designed to recruit 60 patients with PAH or PH-ILD. Subjects will be recruited into 2 cohorts with different target populations: Cohort A—subjects with PAH or PH-ILD on a stable Tyvaso dose who are willing to transition to L606; and Cohort B—subjects with PAH who are not receiving a prostacyclin at the time of study entry. Subjects in Cohort A will sequentially participate in a 2-week main study and extension phase (up to 12 months). Subjects in Cohort B will sequentially participate in a 12-week main study and extension phase (up to 12 months). In Cohort A only, a subset of approximately 15 subjects will also participate in a pharmacokinetics (PK) substudy to evaluate steady-state plasma treprostinil PK after administration of Tyvaso and L606. The safety assessments include adverse effects, physical and vital signs examination, clinical laboratory tests, 12-lead electrocardiogram, and echocardiogram. Efficacy assessments includes the 6-minute walking test, Borg Dyspnea Score, PH symptoms, New York Heart Association functional class, and N-terminal prohormone B-type natriuretic peptide levels. In this study, we also evaluate the steady-state PK of L606 as compared with Tyvaso, quality of life, and treatment satisfaction with L606 in patients with PAH or PH-ILD.
Results: The enrollment of this study is currently ongoing.
Conclusion: We hypothesize that L606 will achieve similar systemic exposure but safer and more convenient than Tyvaso in patients with PAH or PH-ILD.

IMPLEMENTATION OF A PHARMACY SPECIALIST ROLE TO IMPROVE CHRONIC, PULMONARY HYPERTENSION MEDICATION MANAGEMENT AND PATIENT EXPERIENCE

G. Leung
University of Kentucky Healthcare, Lexington, KY

Category: Clinical Science
Subcategory: Diseases and Conditions Associated with PH

Background: A multidisciplinary approach is recommended to individualize care for patients with pulmonary hypertension (PH). Previous publications described the role of a pharmacist, however, were limited to specialty pharmacies, inpatient settings, and timeframe immediately postdischarge.
Methods: An ambulatory clinic-focused PH pharmacist was incorporated into the team. A proactive, new medication follow-up and side effect management process was created. This is a retrospective cohort analysis for the time period October 15, 2021, to July 20, 2022. Pharmacist-driven, phone follow-up encounters were included. Calls unrelated to chronic PH disease management were

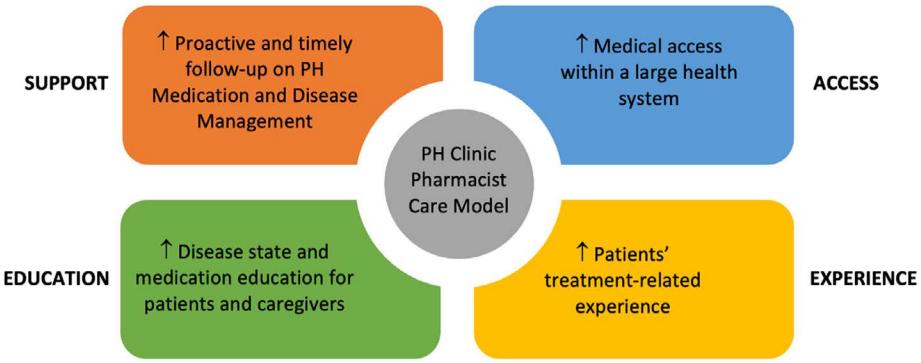


Figure 1: Summary of clinical pharmacist effect on the care of ambulatory pulmonary hypertension patients.

Clinic Visit and Pharmacist Follow-up Calls	
Total number of clinic visits, n=91	**115**
Clinic visits since referral per patient, median (Q1,Q3) Range: Min-Max	2 (1,2) Range: 0-5
Total number of pharmacist phone follow-up encounters, n=91	**265**
Pharmacist follow-up visits per patient, median (Q1,Q3) Range: Min-Max	2 (1,3) Range: 1-11
Pharmacist follow-up within 30 days of clinic appointment, n (%)	60 (65.9)

Figure 2: Clinic visit and pharmacist phone follow-up encounters.

Side Effect Management Encounters (n=28)	
Side Effect Resolved, n (%)	25 (89.3)
In progress, n (%)	1 (3.6)
Complicated by COVID infection, n (%)	1 (3.6)
Lost to follow-up, n (%)	1 (3.6)
Medication Titration Encounters (n=18)	
At goal, n (%)	14 (77.8)
Not at goal*, n (%)	2 (11.1)
In progress, n (%)	1 (5.6)
Lost to follow up, n (%)	1 (5.6)
Diuretic Management Encounters (n=28)	
Euvolemia, n (%)	22 (78.6)
Uncontrolled hypervolemia^, n (%)	5 (17.9)
Lost to follow up, n (%)	1 (3.6)

**1 patient passed away, 1 patient abruptly discontinued medication independently*
^4 patients required admission and 1 patient was noncompliant to medication adjustments and laboratory follow-up

Figure 3: Pharmacist medication management outcomes for the total cohort.

excluded. Outcomes included number of clinic visits, pharmacist phone follow-up encounters, patients with pharmacist follow-up within 30 days of clinic appointment, type of pharmacist follow-up, and pharmacist medication management outcomes, ie, side effect resolution, medication titrated to goal, and euvolemic status.

Results: Ninety-one patients received pharmacist follow-up; 265 pharmacist follow-up phone encounters were completed (median, 2 per patient). These patients completed 115 traditional clinic visits during the study period, yielding a >2:1 ratio of pharmacist interactions to physician visits. In addition, 60% of patients had a pharmacist follow-up within 30 days of clinic visit. For medication management, 25 of 28 patients (89%) reached an acceptable level of side effect improvement, 14 of 18 patients (78%) with pharmacist-driven titration plans reached goal doses, and 22 of 28 patients (78.6%) reached euvolemia (Figures 1–3).

Conclusion: The integration of a PH ambulatory pharmacist has led to side-effect mitigation, achievement of goal medication doses, and improved volume status in patients. Medication-related issues are proactively addressed sooner than may have been addressed at a traditional clinic practice model.

ASSESSING THE READABILITY OF PULMONARY HYPERTENSION DRUG PRODUCT PATIENT PACKAGE INSERTS

L. Frierdich
PharmD

G. Leung
University of Kentucky Healthcare, Lexington, KY

J. S. Smith
University of Kentucky Healthcare, Lexington, KY

K. Meyer
University of Kentucky College of Pharmacy, Lexington, KY

K. Morgan
University of Kentucky College of Pharmacy, Lexington, KY

R. Canode
University of Kentucky College of Pharmacy, Lexington, KY

Category: Clinical Science
Subcategory: Quality of Life

Background: The currently recommended reading level for patient education materials is at a fifth grade level. Despite this, it has been shown that many patient package inserts for drug products contain information that is of a much higher reading level. Patients with lower health literacy levels may find these materials to be unreadable or may even misinterpret the information leading to poor outcomes.
Methods: Three patient package inserts for drug products within the nitric oxide pathway were included in this analysis. Four student pharmacists independently appraised each of the patient package inserts using the Simple Measure of Gobbledygook (SMOG) criteria and Fry readability formula. Data are checked randomly by the research group to ensure precision and accuracy. Descriptive statistics were used for the display of results.
Results: Preliminary data suggested the reading level of patient package inserts within the nitric oxide pathway to be between the 11th and 13th grade reading levels.
Conclusion: Based on preliminary data, the research group strongly recommends that patient package inserts for pulmonary arterial hypertension drug products be updated to increase compliance to recommended reading level and improve readability. Results and conclusion will be finalized and presented at the Pulmonary Hypertension Professional Network Symposium 2023.

ENHANCING KNOWLEDGE, ATTITUDES, AND WILLINGNESS TO DISCUSS CLINICAL TRIALS AND REGISTRIES WITH PULMONARY ARTERIAL HYPERTENSION PATIENTS: A QUALITY IMPROVEMENT PROJECT

L. Lea
University of Phoenix, San Francisco, CA

Category: Basic Science
Subcategory: Databases and Registries

Background: Research clinical trials (RCTs) and registries are necessary to advance science and bring novel therapies to patients, particularly in rare disease. Success of an RCT or registry depends heavily upon the success of patient recruitment. However, despite multiple efforts to improve patient involvement in clinical research, participation in RCTs remains low. The lack of clinical trial diversity is also evident in the literature. Diverse subsets of clinical trial participants improve equity of care and are essential in determining the efficacy and safety of new therapies for the populations who will ultimately be using them. Despite that most patients regardless of race or ethnicity have expressed interest in participating in RCTs if approached by a trusted clinician, these conversations are not happening on a consistent basis, if at all. Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disease characterized by an elevation of pulmonary artery pressure and pulmonary vascular resistance, leading to right ventricular failure and death. PAH is classified as a rare disease, with an estimated 40000–100000 patients globally. Adequate enrollment strategies are even more important in rare diseases given that available data are already limited due to the small number of patients available for participation. Subsequently, obtaining sufficient and diverse datasets in rare diseases can take years, which can delay access to potentially life-saving therapies and hinder the generalizability of the data to diverse populations of patients. Recent literature has identified that PAH patients would be willing to participate in clinical trials but are not consistently being approached by their clinicians. Nurses and nurse practitioners (NPs) spend a substantial amount of time with their patients and thus are in a prime position to discuss the option of RCTs and registries. However, nurse professionals often lack the awareness and education to feel empowered to have these discussions. Misunderstanding, lack of confidence or awareness of clinical trials and registries available for patients may prevent nurses and NPs from discussing clinical trials and registries as an option for their patients, thereby creating a missed opportunity for speedy enrollment with a diverse and representative population. Targeted education around enhancing the patient-provider discussion around clinical trials and registries may increase the number of conversations occurring with PAH patients and thus help improve the problem of lack of diversity in clinical trials.
Methods: Ten to 20 nurse professionals who belong to the Pulmonary Hypertension Association Pulmonary Hypertension Resource Network (PHPN) email listserv will be invited to participate in a survey and virtual educational intervention. Participants must be 18 or older and be actively caring for patients with PAH. The survey is an adapted tool from the IMPACT study, which has been validated for use with oncology nurses and has been adapted for the purposes of this project.
Results: Results will be updated upon project completion. Anticipated completion date is February 2023.
Conclusion: Conclusions will be updated upon project completion. Anticipated completion date is February 2023.

MINDFULNESS MEDITATION FOR PULMONARY HYPERTENSION PROGRAM FOR SYMPTOM SELF-MANAGEMENT: QUALITATIVE THEMATIC ANALYSIS FROM PATIENTS' PERSPECTIVE

T. Von Visger
The State University of New York at Buffalo, NY

Y. Zhou
The State University of New York at Buffalo, NY

N. Alanazi
The State University of New York at Buffalo, NY

Y. P. Chang
The State University of New York at Buffalo, NY

Category: Clinical Science
Subcategory: Quality of Life

Background: Patients with pulmonary hypertension (PH) face many challenges in symptom self-management. Despite pharmacologic advancement, patients experience dyspnea, anxiety, depression, and poor quality of life, leading to suboptimal medical treatment adherence and clinical outcomes. Preliminary evidence demonstrates that complementary health approaches (CHAs) positively affect symptom reduction in PH. However, in-person participation has proven to be physically challenging and can contribute to an increased risk of infection exposure, particularly during the COVID-19 pandemic. A technology-assisted mindfulness meditation for PH (MMPH) program can potentially improve intervention adherence through better acceptance and acceptability. In-depth knowledge of how patients accept, embrace, and adopt Web-based-delivered CHA is needed.
Methods: A qualitative design was used. Participants included 12 patients with PH who completed an MMPH intervention program in a randomized pilot trial (October 11 to December 8, 2022). The MMPH program included 8 weekly 60-minute intervention sessions, including mindfulness concepts, application to the PH experience, and mindful practices (breathing, movement, positioning, and meditation) designed for the virtual delivery method. It incorporated 3 technology-delivery methods: Zoom (Weeks 1 and 4), videos, and the MMPH app daily use. The interviews were conducted individually over Zoom (October 11 to December 8, 2022). Example interview questions were (1) "Describe your experience with the MMPH study," and (2) "What do you like and do not like about the MMPH Zooms, videos, and app?" Recorded interview sessions were transcribed verbatim. We analyzed the interview transcripts for thematic content through open coding/labeling of ideas that emerged employing constant comparison.
Results: Participants were predominantly females (83%), aged 35–72, and 2–46 years living with PH. Six major themes emerged, reflecting what participants determined as remarkable about the intervention (Table 1). These themes included overall positive experiences in symptom management, enhanced understanding of mindfulness, incorporating mindfulness into daily practice, perceived facilitators of mindfulness app, barriers to app use, and distinguishing features of MMPH video use.

"It's a great program. It does relax you. It makes you feel better."

"The idea is to notice what you are thinking, to know that, and to go back to your breath. If you have to do that 10 times in a 10-minute sit, that's what the practice is."

"I noticed that, if I started practicing mindfulness and paying attention to what I was doing in the breathing exercises, my anxiety lessened, and I've noticed my stress levels have gone down. So it helped me."

Table 1. Participants Perceptions of MMPH Intervention

Theme No.	Qualitative themes	Theme definitions	Participants count (N = 12)
#1	MMPH study impression	Positive comments and feelings about the program	●●●●●●●●●●●●
#2	MMPH study effect on mindfulness knowledge	Descriptions about increased awareness of thoughts, body sensations	●●●●●●●●●●●●
#3	MMPH study effect on mindfulness integration	Descriptions of self-care practices by integrating mindfulness knowledge	●●●●●●●●●●●●
#4	MMPH app facilitators	Preference descriptions of app features; aspects of the app that enhance app use	●●●●●●●●●●
#5	MMPH app barriers	Descriptions of app design, functionality, or user interface that lessen app use	●●●●●●●●●
#6	MMPH video as a mindfulness anchor	Descriptions of how visual learning serves as an anchor in mindfulness practice	●●●●●●●●●●●●

Abbreviation: MMPH = mindfulness meditation for pulmonary hypertension.

"Yeah, for one reason, the voice on the video is so calming. I can't even begin to tell you. It's almost like a warm blanket wrapped around you. It's just so calming."

"It's the visual aspect. Seeing it, seeing a person, my mind doesn't wander as much when I watch a video compared to listening to audio."

Conclusion: Our MMPH intervention demonstrates acceptability and feasibility for participants with PH. Patients perceive its benefit in psychological stress and symptom reduction, with exemplars of real-life integration into their routine PH self-management practice.

PARENTERAL TREPROSTINIL INDUCTION FACILITATES RAPID ACHIEVEMENT OF THERAPEUTIC DOSES OF ORAL TREPROSTINIL: RESULTS FROM THE EXPEDITE STUDY

V. Franco
The Ohio State University Wexner Medical Center, Columbus, OH

J. Kingrey
INTEGRIS Health, Oklahoma City, OK

C. Miller
Piedmont Healthcare, Atlanta, GA

R. Zolty
University of Nebraska Medical Center, Omaha, NE

R. Oudiz
Harbor-UCLA Medical Center, Torrance, CA

J. Elwing
University of Cincinnati College of Medicine, Cincinnati, OH

L. Melendres-Groves
University of New Mexico School of Medicine, Albuquerque, NM

J. S. Smith
University of Kentucky College of Medicine, Lexington, KY

A. Ravichandran
Ascension St. Vincent Health, Indianapolis, IN

J. Tarver
AdventHealth Cardiovascular Institute, Orlando, FL

D. Cella
United Therapeutics Corporation, Research Triangle Park, NC

C. Thrasher
United Therapeutics Corporation, Research Triangle Park, NC

S. Seaman
United Therapeutics Corporation, Research Triangle Park, NC

M. Broderick
United Therapeutics Corporation, Research Triangle Park, NC

V. Balasubramanian
University of California San Francisco, Fresno, Fresno, CA

Category: Clinical Science
Subcategory: Diseases and Conditions Associated with PH

Background: Oral treprostinil slows disease progression and improves exercise capacity in pulmonary arterial hypertension (PAH), yet titration can be lengthy. Data from clinical studies and real-world analyses suggest that prostacyclin-naïve patients achieve a mean daily oral treprostinil dose around 6 mg by Week 16 (W16), while those on prior parenteral treprostinil reached higher doses at the same timepoint. EXPEDITE (NCT03497689), an open-label multicenter study, assessed the efficacy of rapid parenteral treprostinil induction to rapidly achieve higher doses of oral treprostinil in patients with PAH.

Methods: Parenteral treprostinil was titrated over 2–8 weeks. Subjects transitioned to oral treprostinil, which was titrated through W16. The primary endpoint was percent of subjects reaching a daily oral treprostinil dose ≥12 mg at W16. Secondary endpoints included changes in clinical measurements from baseline (BL) to W16. BL was defined as prior to parenteral treprostinil initiation.

Results: Twenty-nine eligible prostacyclin-naïve subjects were included in these analyses. Patients had to have a REVEAL 2.0 Risk Score <10 with either World Health Organization (WHO) functional class (FC) II or III symptoms and could be on 0, 1, or 2 PAH therapies. At W16, the mean daily oral treprostinil dose was 16.4 mg with 79% of subjects meeting the primary endpoint. WHO FC improved in 68% of subjects ($P < 0.0001$); 46% achieved FC I, and 39% achieved FC II. From BL to W16, median NT-proBNP improved from 415 to 212 ng/L, with a median change of –134 ng/L ($P = 0.0041$). Median 6-minute walk distance improved from 363 to 395 m, with a median change of +25 m ($P = 0.0078$). Median right atrial area improved from 20.3 to 17.5 cm^2, with a median change of –2.9 cm^2 ($P = 0.0102$). Statistically significant improvements were also seen in Borg Dyspnea Score ($P = 0.0009$) and the emPHasis-10 quality of life (QOL) questionnaire ($P = 0.0001$). Favorable trends were seen in risk stratification, additional echocardiography parameters, PAH symptoms, and treatment satisfaction.

Conclusion: Short-course parenteral treprostinil allowed for over twice the dose oral treprostinil previously reported in de novo initiations. Significant improvements were seen in clinical parameters, risk status, echocardiography, and QOL. These results support rapid parenteral treprostinil induction as a useful approach to quickly reach effective doses of oral treprostinil.

Sponsored by United Therapeutics.

THE IMPLEMENTATION OF A PULMONARY HYPERTENSION PROGRAM AT A COMMUNITY HEALTH SYSTEM

A. Smith
Ohio Health, Columbus, OH

L. Castle
Ohio Health, Columbus, OH

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary hypertension (PH) is a complex, resource intensive disease state. As the incidence increases and more patients require treatment in community health systems, standardization of program development and implementation will be essential for optimal patient care. Prior to program implementation, in fiscal year 2020, our health system had roughly 3000 patients with a diagnosis of PH who were hospitalized for a variety of medical problems over 4100 times. **Methods:** The development of a PH program at our institution began in September 2020 with a presentation to hospital administrators. A PH work group was created that included an advanced heart failure cardiologist as program medical director, pulmonary and critical care physician, administrator, clinical pharmacist, respiratory therapist, advanced practice provider, nurse navigator, and both inpatient and outpatient nursing representation. This interdisciplinary group met monthly throughout the program development and implementation process. **Results:** Focused education was completed with core team members including inpatient nursing staff and providers within the advanced heart failure, pulmonary, critical care, and hospital medicine service lines. Emergency departments across the health system were made aware of resources available to care for this patient population. The pharmacy department was trained on how to safely process PH therapies including the risk evaluation and mitigation strategy, home dosing, and medication compounding. Lectures provided for inpatient and outpatient nursing, physicians, and rehabilitation providers were recorded for future reference. Oral pulmonary vasodilator therapy was added to the hospital formulary in September 2021. In December 2021, a protocol was developed for delivery of inhaled epoprostenol to treat patients with decompensated PH. A comprehensive prostacyclin therapy guideline and nursing policy was implemented for continuous infusion prostacyclin therapy in December 2022. As part of this initiative, a comprehensive order set was built into the electronic medical record to ensure safe patient management. In January 2023, a PH clinic was established for ongoing collaboration of care between advanced heart failure cardiology and pulmonology. A multidisciplinary case conference is conducted monthly for case review and quality improvement. Future initiatives for this program include creation of a perioperative management guideline, development of a pharmacist-directed medication titration program, construction of a PH dashboard within the electronic medical record, and application for Pulmonary Hypertension Association accreditation. **Conclusion:** As the incidence of PH increases, due in part to heightened awareness as a serious medical problem, many patients will be evaluated and treated within community health systems. This framework for PH program development can be used to implement new programs resulting in improved access to quality care.

FINDING THE "NEW BEST NORMAL": HEALTH CARE RE-ENTRY AND ADHERENCE

M. Granato
Pulmonary Hypertension Association (PHA), Silver Spring, MD

E. Joseloff
Pulmonary Hypertension Association (PHA), Silver Spring, MD

D. Layton
Pulmonary Hypertension Association (PHA), Silver Spring, MD

A. Laughlin
Pulmonary Hypertension Association (PHA), Silver Spring, MD

K. Rose
The Blackstone Group Inc., New York, NY

M. Horn
Horn Research & Consulting, Wilmette, IL

Category: Case Report
Subcategory: Effect of COVID and Telemedicine on PH Management

Background: The COVID-19 pandemic has created obstacles to established approaches to managing pulmonary hypertension (PH) patients' care, including impeding in-facility appointments, testing, and prescribing behaviors. We commissioned an independent research and consulting firm to conduct an online quantitative study of PH patients that measured behaviors, awareness, and attitudes to establish benchmarks for use in detecting subsequent changes in patient care. In this study, we also aimed to uncover prospective drivers of and barriers to care use and medication adherence among PH patients. **Methods:** We developed a quantitative questionnaire to distribute to Pulmonary Hypertension Association constituents (with sample files of n = 7883 patients and n = 8000 friends). The questionnaire included questions regarding past care use during the previous 3 months and projected care use over the next 3 months. We sent an initial email and up to 2 follow-up emails inviting the sampled individuals to take part in the online study, resulting in n = 530 completed questionnaires. We

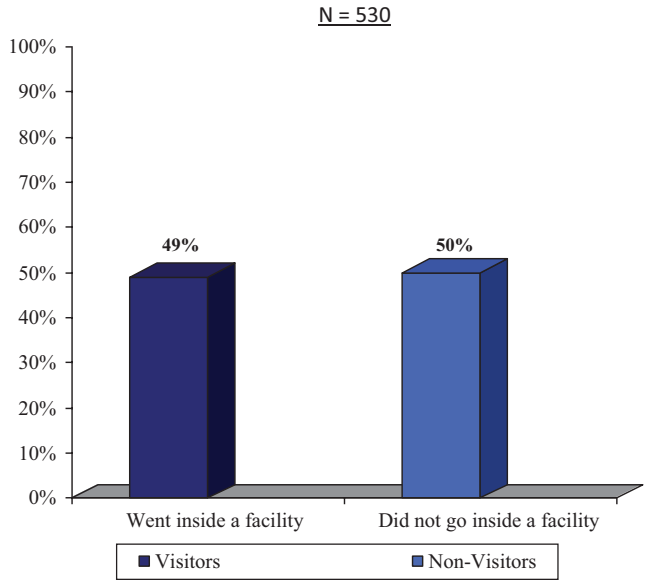


Figure 1: Whether participant went inside a health care treatment facility to receive care for pulmonary hypertension (PH) or chronic thromboembolic PH (CTEPH) in the past 3 months.

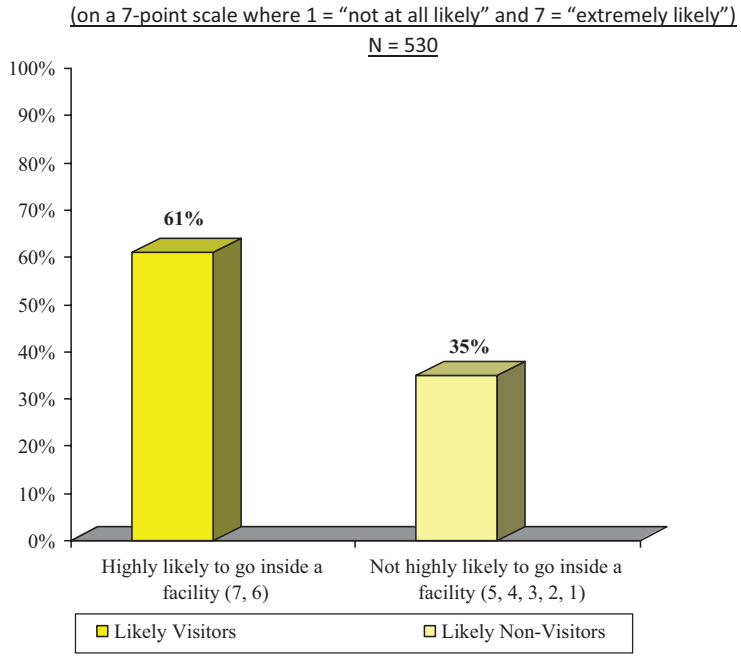


Figure 2: Rating of participants' likelihood to go inside a health care treatment facility to receive care for pulmonary hypertension (PH) or chronic thromboembolic PH (CTEPH) in the next 3 months.

were able to define various care use segments to consider in analyzing the data for patterns of statistically significant differences in PH patients' care behaviors including past in-facility visits, past telehealth participation, likelihood to make an in-facility visit, likelihood to participate in telehealth, in-facility care use, past care demand, and projected care demand.

Results: The questionnaire results showed that, among the 530 respondents, 49% had recently entered a health care treatment facility to receive care, and 61% qualified as likely visitors in the next 3 months. The most cited reason for those who were not likely to enter a facility in the next 3 months was that visits were not medically necessary, or they had no set appointment. The results also showed that 28% of respondents had received care for PH in the past 3 months via telehealth, and 44% said they were highly likely to use telehealth in the next 3 months. We further analyzed the results through segmentation analysis into drivers of care use behavior such as in-facility visits (persistents, periodics, potentials, and absentees) and the number of different medications participants' health care providers had prescribed (5+, 3–4, 1–2, and 0). The number of different medications was revealed to be a constant driver of care use behavior; 56% of respondents who were persistents (visitors + likely visitors) had 5+ different medications versus 11% of respondents who were absentees (nonvisitors + likely nonvisitors). Also, only 17% of respondents who were persistents had 0 medications versus 50% of absentees who had the same (Figures 1–5).

Conclusion: The COVID-19 pandemic did not show a major influence on PH patient in-facility care use, and PH patients will continue to return to care. The results of the study lead us to conclude that individual patients are not the main decision maker regarding seeking in-facility or telehealth care, but the care management system (and health care providers' medication prescribing

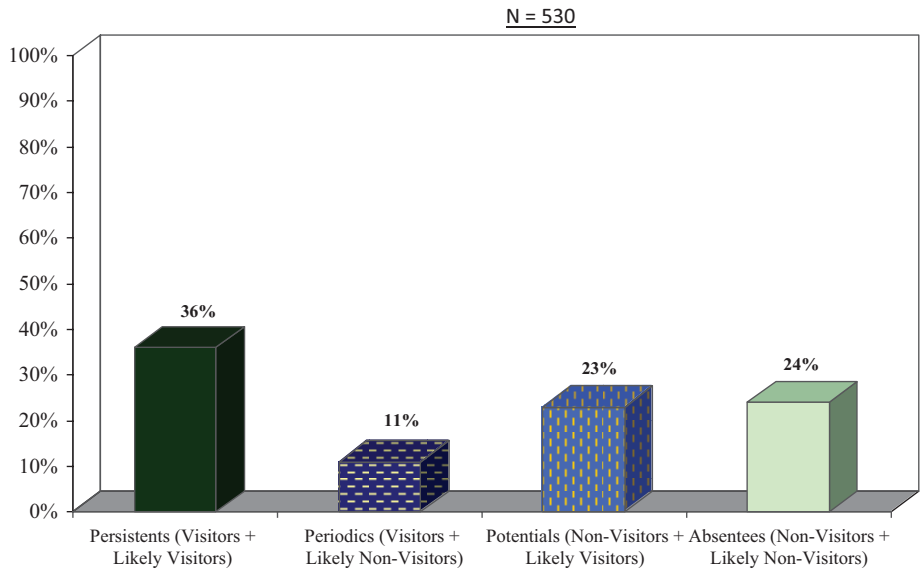


Figure 3: In-facility care use segments (did/did not go inside a health care facility in the past 3 months + highly likely/not highly likely to go inside a health care facility in the next 3 months).

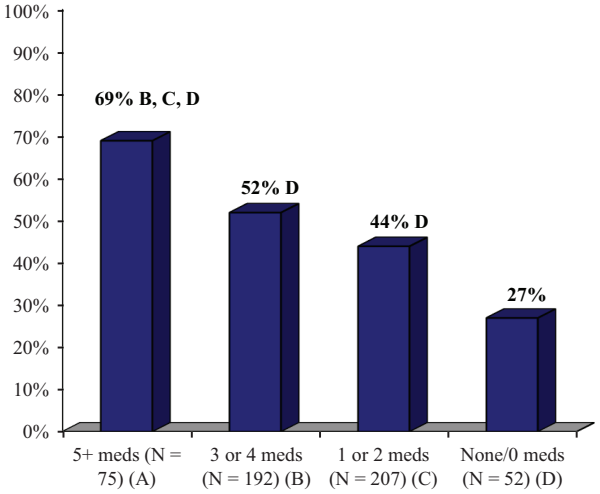


Figure 4: Percent of participants in the visitors care use segment: by number of different pulmonary hypertension (PH) or chronic thromboembolic PH (CTEPH) medications for which participant has a current prescription.

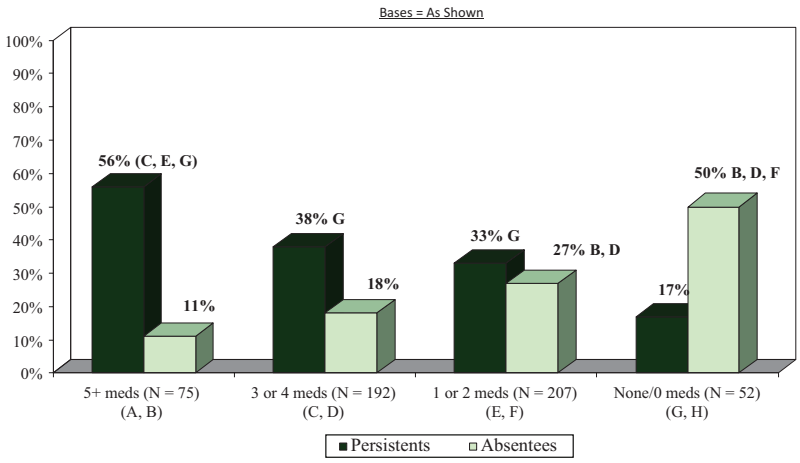


Figure 5: Percent of participants in selected in-facility care use segments (persistents and absentees): by number of different pulmonary hypertension (PH) or chronic thromboembolic PH (CTEPH) medications for which participant has a current prescription.

behaviors) were correlated with in-facility and telehealth care usage. The health care system is just beginning to come to terms with the major changes in care delivery resulting from the COVID-19 pandemic. For PH and chronic thromboembolic PH patients specifically, care has evolved to encompass in-facility visits, telehealth, and/or adjunctive methods, such as smartphone apps and wearables. While adoption of and reliance on various care delivery methods will continue to change, future investigation will be needed to explore the optimal mix of care delivery methods for PH.

HELPING ACUTE PULMONARY EMBOLISM (PE) PATIENTS PHACE THE FUTURE: DEVELOPMENT OF AN ACUTE PE FOLLOW-UP CLINIC

A. Felder
Baylor Scott & White Heart Hospital, Plano, TX

M. Connelly
Baylor Scott & White Heart Hospital, Plano, TX

T. Dudeck
Baylor Scott & White Heart Hospital, Plano, TX

Category: Clinical Science
Subcategory: Diseases and Conditions Associated with PH

Background: Current literature suggests that the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic disease (CTED) is underestimated for multiple reasons. One of those reasons is a lack of follow up after acute pulmonary embolism (PE). In turn, this leads to a missed opportunity to detect a developing disease process or underlying disease that may have contributed to the sentinel PE event. In early 2021, our PH care team recognized a low incidence of CTEPH and CTED diagnoses in relation to our pulmonary arterial hypertension World Health Organization Group 1 patient population. We also received some referrals for patients who had persistent symptoms following an acute PE event >3 years prior. To increase local awareness of the disease process and improve our effectiveness in identifying such patients, we developed an acute PE follow-up protocol with the collaboration of our inpatient pulmonary embolism response team (PERT) colleagues.

Methods: Beginning in July 2021, we developed a plan for outpatient follow up for acute PE patients but lacked an efficient referral process and noticed poor patient adherence to the follow-up plan. Barriers included lack of an efficient referral process, poor patient and caregiver understanding, and inability to contact patients following discharge. We collaborated with our inpatient PERT colleagues to develop a workflow that allowed for improved patient adherence to the follow-up plan. The key elements of improving our process included creating an Epic order for consultation, creating of an information packet explaining the follow-up process, standardizing follow-up appointments, and working with our care management team to streamline communication with each patient.
Results: As a result, we appreciated a significant increase in patient adherence to the follow-up plan and were able to identify many more patients with CTEPH and CTED than prior years. Some other unexpected but favorable outcomes included identification of hypercoagulable conditions and coordinating hematology consultation, diagnosis of other disease processes that contributed to the venous thromboembolism, assisting with medication refills, and financial assistance to avoid a treatment gap, securing or discontinuing supplemental oxygen therapy, and receiving referrals from outside health care systems as local awareness increased.
Conclusion: Likewise, we identified some challenges including managing care for patients who do not live near our geographic

location, obtaining approval for repeating a ventilation perfusion scan and/or echocardiogram imaging on occasion, and developing new anticoagulation protocols. We now have a streamlined process in place for each acute PE patient and have started working with the local Emergency Departments to identify patients who may not be identified using our current process. Overall, developing this process has allowed our PH team to meet a need for this often-overlooked patient population.

RISK FACTORS ASSOCIATED WITH PEDIATRIC PULMONARY HYPERTENSION WITHIN THE NATIONAL 2016 KIDS' INPATIENT DATABASE (KID)

A. Kohanzadeh
Albert Einstein College of Medicine, Bronx NY

B. Wajsberg
Albert Einstein College of Medicine, Bronx NY

J. Choi
Albert Einstein College of Medicine, Bronx NY

Q. Gao
Albert Einstein College of Medicine, Bronx NY

M. Kravitz
Montefiore Medical Center, Bronx NY

N. J. Sutton
Montefiore Medical Center, Bronx NY

C. J. Yang
Montefiore Medical Center, Bronx NY

Category: Clinical Science
Subcategory: Pediatrics

Background: Pediatric patients with untreated obstructive sleep apnea (OSA) are at risk for development of pulmonary hypertension (PH), a rare but serious outcome. By identifying clinical and demographic risk factors associated with PH, primary care providers can better direct prompt screening and specialty referral in high-risk children, such as those with OSA.
Methods: Retrospective cross-sectional cohort study analyzing weighted discharges from the 2016 Kids' Inpatient Database (KID). Demographic, procedural, and continuous variables were examined. Mean and median levels of continuous variables were estimated and compared between patients with and without PH using the 2-sample *t* test or Wilcoxon rank sum test. Bivariate analysis was conducted, followed by a multivariable logistic regression model to investigate risk factors associated with PH among the overall cohort using odds ratios (ORs) and 95% confidence intervals (CIs). PH was the primary outcome and was identified via diagnostic ICD-10 codes recorded in the KID.
Results: A total of 6081132 weighted discharges were included. The mean age was 3.8, and 48.9% were males. The prevalence of PH was 0.21% (12777 patients). There were 37631 patients with OSA, and the prevalence of PH among this cohort was 3.3%. Risk factors associated with PH included chronic lung disease of prematurity (OR = 21.3; 95% CI = 19.3, 23.4), congenital heart disease (OR = 16.0; 95% CI = 14.8, 17.2), Down syndrome (OR = 11.2; 95% CI = 10.1, 12.3), asthma (OR = 2.0; 95% CI = 1.8, 2.2), OSA (OR = 4.9; 95% CI = 4.4, 5.5), central sleep apnea (OR = 2.1; 95% CI = 1.4, 3.3), hypertension (OR = 4.9; 95% CI = 4.4, 5.4), sickle cell disease (OR = 3.9; 95% CI = 3.4, 4.5), obesity (OR = 1.3; 95% CI = 1.1, 1.5), Asian or Pacific Islanders (OR = 1.2; 95% CI = 1.1, 1.4), Blacks (OR = 1.2; 95% CI = 1.1, 1.3), Native Americans (OR = 1.3; 95% CI = 1.0, 1.7), enrollment in government-sponsored health insurance (OR = 1.4; 95% CI = 1.4, 1.5), patient age (OR = 1.014; 95% CI = 1.010, 1.02), hospital admission in the Western US region (OR = 1.2; 95% CI = 1.1, 1.3), and male gender (female gender was protective [OR = 0.93; 95% CI = 0.89, 0.98]; Figure 1).
Conclusion: The prevalence of PH among patients with OSA was 3.3%, which is over 10 times greater than the overall prevalence of PH in the 2016 KID (0.21%). Several risk

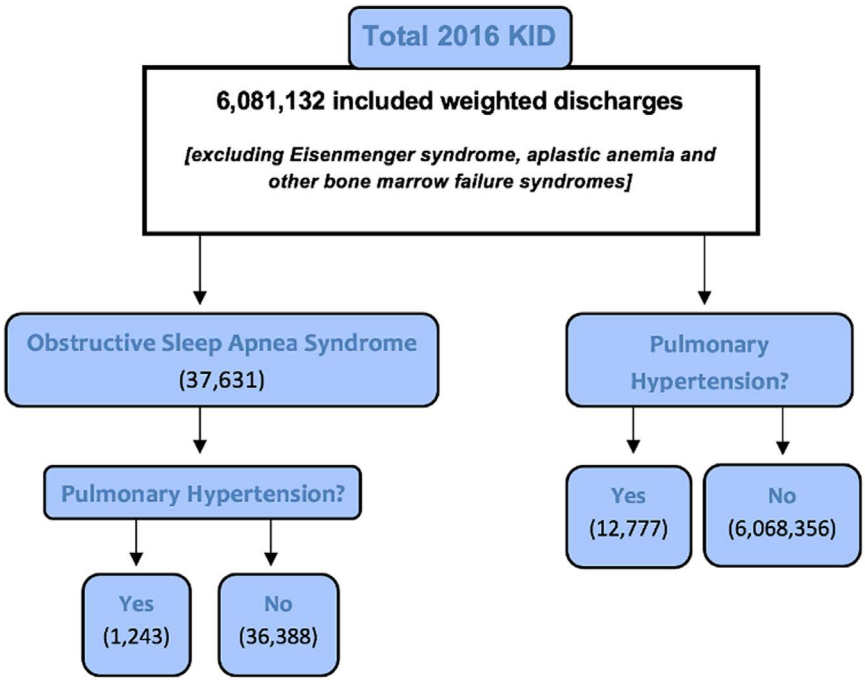


Figure 1: 2016 Kids' Inpatient Database (KID) pulmonary hypertension and obstructive sleep apnea weighted discharges.

factors were independently associated with PH. Considering that the KID only includes in-patient admission data, future multi-institutional prospective studies are needed to further evaluate the relationships between specific clinical and demographic risk factors, such as OSA, obesity, insurance status, and other potential risk factors for development of pulmonary hypertension.

PREDICTION OF PULMONARY HYPERTENSION ASSOCIATED WITH BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS USING MIRNAS IN EARLY TRACHEAL ASPIRATE SAMPLES

R. Siddaiah
Penn State Health Hershey Medical Center, Hershey, PA

L. Dobge
Penn State Health Hershey Medical Center, Hershey, PA

X. Wang
Penn State Health Hershey Medical Center, Hershey, PA

A. Donnelly
Penn State Health Hershey Medical Center, Hershey, PA

V. Aluquin
Penn State Health Hershey Medical Center, Hershey, PA

H. Stephens
Penn State Health Hershey Medical Center, Hershey, PA

Category: Clinical Science
Subcategory: Pediatrics

Background: Pulmonary hypertension (PH) associated with bronchopulmonary dysplasia (BPD) is a severe complication of preterm birth associated with high mortality. However, because the clinical signs and symptoms of BPD-PH overlap with that of BPD, a high level of suspicion needs to be employed to perform tests to diagnose BPD-PH. Hence, the current clinical practice is to screen for BPD-PH via echocardiogram at 36 weeks in preterm infants with BPD. Identifying at-risk preterm infants will help early diagnosis. We have previously identified a panel of 20 miRNAs in tracheal aspirate (TA) differentially expressed in BPD-PH. The objective of the study is to analyze the predictive value of target specific miRNA panel in early TA samples in extreme preterm infants.
Methods: We collected TA samples from 22 preterm infants born <28 weeks of gestation within the first 7 days of age. The samples were frozen at –80°C until analysis. The samples were then thawed, RNA extracted using Norgen miRNA purification kit, and miRNA was analyzed using small RNA-sequencing libraries prepared from 5–25 ng total RNA, the resulting high throughput sequencing data using the QIAseq miRNA Library kit (QIAGEN). Of the original 20 miRNAs, only 16 were expressed in the 7-day-old samples in our new cohort. Logistic regression was calculated for the 16 miRNAs (hsa-miR-29a-3p, hsa-miR-542-3p, has-miR-624-5p, hsa-miR-183-5p, hsa-miR-3131, hsa-miR-501-3p, hsa-miR-101-3p, has-miR-101-5p, hsa-miR-3128, hsa-miR-128-3p, hsa-miR-628-3p, hsa-miR-24-3p, hsa-miR-1255b-5p, hsa-miR-205-5p, hsa-let-7i-3p, and has-let-7i-5p) to calculate receiver operating characteristic (ROC) area under the curve.

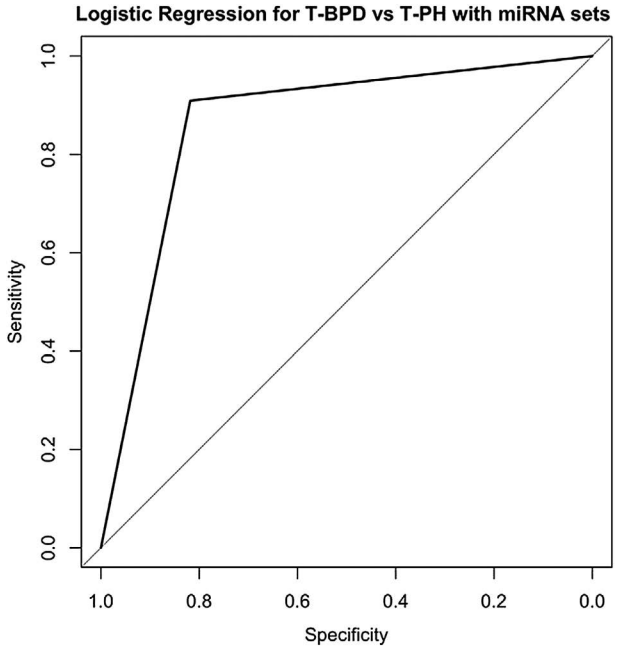


Figure 1: Predictive value of 16 mIRNAs in early tracheal aspirates in extreme preterm infants show receiver operating characteristic (ROC) area under curve = 0.86 and sensitivity of 83% and specificity of 82%.

Results: Of the 22 infants, 11 of them were diagnosed with BPD-PH at 36–40 weeks of gestation based on their echocardiogram findings, and 11 of them with Grade 2–3 BPD (2019 National Institute of Child Health and Human Development [NICHD]/Neonatal Research Network [NRN] classification). Logistic regression calculation (Table 1) of the 16 miRNAs comparing infants who went on to develop BPD-PH versus BPD at 36 weeks of PMA revealed area under the curve ROC = 0.86 with sensitivity and specificity of 83% and 82%, respectively (Figure 1), of predicting BPD-PH in those with high risk of developing BPD.
Conclusion: A panel of 16 miRNAs expressed in early TA samples has significant predictive value in identifying extreme preterm infants that are at high risk for developing BPD-PH at 36 weeks PMA. This panel once validated in a larger cohort has the potential as a clinical tool to closely monitor high-risk infants for pulmonary vascular disease and intervene as needed with target oxygen saturations, optimize nutrition and fluid goals, and early echocardiogram to screen for BPD-PH.

PULMONARY HYPERTENSION-RELATED AGE-ADJUSTED MORTALITY RATES AND TRENDS BY URBANIZATION CATEGORY IN THE UNITED STATES

D. Moretta
Loma Linda University Medical Center, Loma Linda, CA

Category: Clinical Science
Subcategory: Databases and Registries

Background: Pulmonary hypertension (PH) is a progressive disease and is associated with high mortality regardless of the subtype. Despite therapeutic advances, the overall age-adjusted PH mortality rate increased significantly from 1999 to 2019. However, rural-urban disparities in PH-related mortality and trends have not been studied.
Methods: We analyzed adjudicated death certificate data from the Centers for Disease Control and Prevention Wide Ranging Online Data for Epidemiological Research Multiple Cause of Death Database for PH-related deaths in the US from 2005 to 2019. We identified PH-related deaths using ICD-10 codes. We divided the cohort into large metropolitans (>1 million), medium/small metropolitans (50000–999999), and rural (<50000) areas. Poisson regression modeling was used to calculate mortality rate ratios and to analyze temporal trends from 2005 to 2019.
Results: There were 346452 PH-related deaths between 2005 and 2019. Of these, 46.9% of decedents were from large metropolitans, 34.4% from medium/small metropolitans, and 18.7% from rural areas. The age-adjusted mortality rates (AAMRs) from PH per 1 million population were 60.3 in large metropolitans, 73.4 in medium/small metropolitans, and 72.2 in rural areas. From 2005 to 2019, AAMRs increased 26.6% in large metropolitans, 35.0% in medium/small metropolitans, and 33.6% in rural areas. The absolute difference in PH-related AAMRs per 1 million population almost doubled from 2005 to 2019 between large metropolitans and medium metropolitans (9.1 to 18.4) and between large metropolitans and rural areas (9.9 to 19.4; Figure 1).
Conclusion: Between 2005 and 2019, there was an increase in PH-related deaths within all urbanization categories. However, the absolute difference between large metropolitans and rural/medium/small metropolitans nearly doubled over time. The disparities noted are likely due to demographic differences; varying risk factors; and a combination of social, economic, and geographic barriers to health care. Further investigations focused on the causes for these differences are needed to reduce the disparities and decrease the burden of deaths from PH. As an extension of these data, we will be investigating demographic differences (sex, age groups, and race) in PH-related mortality rates/trends between urbanization categories.

	Number of Deaths	Age-Adjusted Mortality Rate per 1,000,000 (95% CI)	Mortality Rate Ratio (95% CI)	% Rate Change from 2005-2019
Overall	346452	66.5 (66.2-66.7)	-	+29.4 (22.4-36.4)*
Large Metropolitan	162426	60.3 (60.0 to 60.6)	Reference	+26.6 (19.6-33.6)*
Medium/Small Metropolitan	119250	73.4 (73.0 to 73.9)	1.21 (1.18-1.25)*	+35.0 (28.0-40.6)*
Rural	64776	72.2 (71.7 to 72.8)	1.20 (1.17-1.23)*	+33.6 (26.6-39.2)*

*P = <0.001

Figure 1:

CORRELATION OF WORLD HEALTH ORGANIZATION FUNCTIONAL CLASS AND PATIENT-REPORTED OUTCOME MEASURES IN ADULTS WITH PULMONARY ARTERIAL HYPERTENSION

M. Wilson
Advent Health, Orlando, FL

K. El-Kersh
University of Nebraska Medical Center, Omaha, NE

K. Highland
Cleveland Clinic, Cleveland, OH

M. Broderick
United Therapeutics Corporation, Research Triangle Park, NC

B. Wu
United Therapeutics Corporation, Research Triangle Park, NC

S. Seaman
United Therapeutics Corporation, Research Triangle Park, NC

P. Classi
United Therapeutics Corporation, Research Triangle Park, NC

H. Dubrock
Mayo Clinic, Rochester, MN

Category: Clinical Science
Subcategory: Quality of Life

Background: The World Health Organization Functional Classification (WHO-FC) measures pulmonary arterial

hypertension (PAH) symptom severity and physical activity limitations. Patient-reported outcome (PRO) instruments are increasingly used to monitor other aspects of patient health such as treatment satisfaction, overall wellbeing, and disease burden. In this study, we aimed to understand the correlation between WHO-FC and PRO measures in patients with PAH.
Methods: In this study, we analyze data for adults with PAH on oral treprostinil enrolled in the ADAPT Registry. Assessments were obtained for select PRO measures at registry enrollment: Treatment Satisfaction Questionnaire for Medication (TSQM), emPHasis-10, and Short-Form-12v2 Health Survey (SF-12). WHO-FC was assessed by clinician or patients using the Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR). Authors of previous work have shown high agreement between clinician-assessed WHO-FC and PH-FC-SR. WHO-FCs completed within 30 days of registry enrollment were used. Pearson or Spearman correlation coefficients were used to assess strength of association.
Results: Eighty-six patients met inclusion criteria for this analysis. Patients had a mean ± SD age of 55.4 ± 13.4, 67 (78%) were female, and 67 (78%) were white. Thirteen (15%) patients were WHO-FC Class I, 43 (50%) Class II, and 30 (35%) Class III. For all 4 domains of TSQM, mean scores worsened with higher WHO-FCs. Mean ± SD emPHasis-10 scores worsened from WHO-FC Class I (18.2 ± 11.4) to Class II (23.0 ± 12.1) to Class III (34.1 ± 11.2). WHO-FC and emPHasis-10 overall scores were strongly correlated ($\rho = 0.45$; $P < 0.01$). SF-12 physical aggregate scores worsened with higher WHO-FCs, but mean ± SD SF-12 mental aggregate scores were similar across WHO-FC Class I (51.9 ± 10.5), Class II (50.5 ± 10.7), and Class III (49.8 ± 12.3). WHO-FC was strongly correlated with aggregate SF-12 physical score ($\rho = -0.58$; $P < 0.01$), but there was no correlation with aggregate SF-12 mental score ($\rho = -0.07$; $P = 0.60$).
Conclusion: WHO-FC strongly correlates with emPHasis-10 and SF-12 aggregate physical scores, but there are aspects of patient health that it does not reflect, such as mental health. Holistic patient health may not be adequately monitored in routine care for patients with pulmonary arterial hypertension.

CASE STUDY: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

R. Gadioma
New York Presbyterian Weill Cornell, NY

L. Andwood
New York Presbyterian Weill Cornell, NY

Category: Case Report
Subcategory: Diseases and Conditions Associated with PH

Background: The case study to be presented is on chronic thromboembolic pulmonary hypertension (CTEPH). This describes a patient our team is following and workup which led to definitive treatment of the disease condition.
Methods: We reviewed several cases and chose 1 to be presented.
Results: The patient underwent pulmonary endarterectomy with success.
Conclusion: The case chosen for this case study continues to be followed in clinic.

INPATIENT TRANSITIONS OF PARENTERAL PROSTACYCLINS AND SELEXIPAG: A 6-YEAR, ACADEMIC MEDICAL CENTER EXPERIENCE

M. Guido
University of Cinncinnati Health, Cincinnati, OH

D. Kuebel
University of Cinncinnati Health, Cincinnati, OH

J. Stone
University of Cinncinnati Health, Cincinnati, OH

J. Elwing
University of Cinncinnati Health, Cincinnati, OH

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: The University of Cincinnati Medical Center, a Pulmonary Hypertension Center of Comprehensive Care, uses thorough medication guidance to outline the medication use process of parenteral prostacyclins and other pulmonary arterial hypertension (PAH)-targeted pharmacotherapy in the inpatient setting. These guidelines include a specific appendix that contains recommended transition processes between select medications. All transitions to or from a parenteral prostacyclin are completed during an inpatient admission. Prostacyclin infusions are only administered in designated units. Medical Step Down is the preferred unit for medication transitions with the Medical Intensive Care Unit as an alternative based on bed availability or severity of illness. All nurses in these units complete initial and ongoing education and competency related to disease state and administration of targeted pharmacotherapy. PAH providers and pharmacists use these transition processes as a general guide for developing individualized patient transition plans. Each process includes information specific to the medications included in the transition, a transition checklist, and a transition process. The transition checklist includes necessary items for medication administration. Examples include (but are not limited to)

required type of intravenous (IV) access, calculation references (such as for parenteral to oral treprostinil), dose rounding, and dosing weight selection. The transition process describes information such as time between transition steps, medication overlap (if required), whether central line priming is required, typical duration of transition (in hours), recommendations for long-term intravenous access (such as tunneled catheters), and general line/site care (such as withdrawal of medication from central line prior to removal).
Methods: Selexipag has been approved for inpatient administration since 2016. We reviewed all inpatient transitions, including planned admissions and unplanned transitions, from a data query of the electronic medical record. Patients were included if they completed a transition between selexipag and parenteral treprostinil or epoprostenol (either to or from). A single patient was included multiple times if he or she experienced >1 medication transition (ie, from IV epoprostenol to selexipag, then later from selexipag back to IV epoprostenol).
Results: From July 2016 to December of 2022, 49 patients were transitioned between selexipag and a parenteral prostacyclin. Median (IQR) transition time was 36 (24–48) hours. The most frequent transition periods were 24 (n = 12) and 36 (n = 12) hours, and most (77.6%) occurred over <48 hours. The shortest transition occurred over 12 hours (n = 4), and the longest transition was a duration of 156 hours (n = 2). Thirty-two of the 49 patients (65.3%) transitioned from a parenteral prostacyclin to selexipag. Of those patients, 16 (50%) transitioned from epoprostenol and 16 (50%) to treprostinil. Seventeen patients (34.7%) transitioned from selexipag to a parenteral prostacyclin; 23.5% (n = 4) to epoprostenol, and 76.5% (n = 13) to treprostinil. Most patients were discharged from the hospital; however, 3 patients died during the hospital stay after completing the transition. Of the 46 patients who were discharged, 69.6% (n = 32) were discharged with selexipag, and 30.4% (n = 14) were discharged with parenteral prostacyclin (71.4% with treprostinil and 28.6% with epoprostenol).
Conclusion: A guideline-based approach is effective to support inpatient transitions between oral and parenteral prostacyclin pathway medications in patients with PAH.

DIRECT PROSTACYCLIN TRANSITION IN PEDIATRIC PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

K. Merrill
Seattle Children's Hospital, Seattle, WA

A. Davis
Seattle Children's Hospital, Seattle, WA

E. Jackson
Seattle Children's Hospital, Seattle, WA

M. Riker
Seattle Children's Hospital, Seattle, WA

C. Kirk
Seattle Children's Hospital, Seattle, WA

D. Yung
Seattle Children's Hospital, Seattle, WA

Category: Case Report
Subcategory: Pediatrics

Background: Pediatric patients with pulmonary arterial hypertension (PAH) are commonly treated with the prostacyclin analog treprostinil in intravenous, subcutaneous, inhaled, or oral form or the prostacyclin receptor agonist selexipag. Patients who transition between these medications often follow recommendations for gradual up and down titrations that take place over several days in the hospital or several weeks as an outpatient. However, hospital resources are limited, and long transitions are inconvenient for patients and families. Our center has previously had experience with rapid 1-day transitions, so we hypothesized that direct prostacyclin transitions in pediatric PAH patients would be safe and effective.
Methods: Eight pediatric patients with PAH transitioned directly between prostacyclins with no overlapping doses. Direct medication transitions occurred in the Cardiac Intensive Care Unit, at home, and in Cardiology Clinic. Equivalent doses for selexipag were estimated using information extrapolated from experience and published materials.
Results: All patients completed direct transition as planned and remained on transition dose for at least 1 week. In most cases, selexipag was up titrated at home after establishing initial transition dose. Please see Figure 1 for transition data.
Conclusion: In selected patients, direct prostacyclin transition in pediatric patients with PAH is safe, effective, convenient for families and reduces the use of hospital resources.

Age (years)	Weight (kg)	From	To	Location
15	58	SQ treprostinil 116 ng/kg/min	IV treprostinil 116 ng/kg/min	Clinic
4	13	IV treprostinil 34 ng/kg/min	Selexipag 400 mcg BID	CICU
2	16	SQ treprostinil 76 ng/kg/min	Selexipag 800 mcg BID	CICU
14	85	SQ treprostinil 50 ng/kg/min	Selexipag 1600 mcg BID	CICU
15	55	Inhaled treprostinil 6 breaths (_ mcg) QID	Selexipag 200 mcg BID	Home
14	56	Oral treprostinil 6 mg TID	Selexipag 1000 mcg BID	Home
12	38	Selexipag 1600 mcg	SQ treprostinil 40 ng/kg/min	CICU
14	85	Selexipag 1600 mcg	SQ treprostinil 50 ng/kg/min	Home

Figure 1: Transition data.

PATIENTS LIVING WITH PULMONARY ARTERIAL HYPERTENSION (PAH) PROVIDE ESSENTIAL INSIGHTS FOR DRUG DEVELOPMENT

L. Loungani
Enzyvant Therapeutics, Inc., Cary, NC

Category: Case Report
Subcategory: Quality of Life

Background: The voices of patients and patient representatives are essential in improving health outcomes, including drug development. A patient advisory meeting was held to gain insights into experiences with pulmonary arterial hypertension (PAH) and to inform early-stage clinical research and development, disease management, and patient advocacy programs.
Methods: A virtual patient advisory meeting was conducted with 6 US patients (4 women, 2 men), ages 24–69, living with PAH. Participants reported a range of functional classes (FCs), including 1 person in FC 1, 3 people in FC 2, and 2 people in FC 3. Diagnoses included idiopathic PAH and familial PAH. The meeting included interactive polls, a chatroom, and featured a live illustration of patients' experiences with PAH.
Results: The patients shared their experiences with PAH, which are collated into 6 themes below: (1) Symptoms: Shortness of breath, fatigue, and lack of energy are primary physical complaints. This inhibits their ability to execute basic activities of daily living. (2) Diagnosis: Patients report varied experiences with diagnoses, with some being diagnosed shortly after experiencing symptoms, while others' diagnoses were delayed for years. Female participants reported that their symptoms were attributed to other common causes, like obesity or asthma. (3) Effect on Life: Mental and emotional health are the biggest challenges participants face, and this is exacerbated by the isolation they feel from family and friends. Participants noted that their disease is invisible yet has an overt effect, particularly economic. (4) Health Wishlist: Ideal outcomes from treatment would enable patients to have more energy to participate in normal everyday activities. Patients want to remain active for as long as possible. (5) Desired Treatments: Some approved treatment options can be cumbersome and place limitations on patients' mobility and agility. Patients shared that oral medications could help them live with more freedom. (6) Seeking Care: Patients are highly interested in clinical trials but are concerned about inclusion criteria. Other challenges cited are need for time off work, being placed on placebo, and drug reactions. On approved medications, patients said they can experience stability; however, disease progression can be unpredictable and rapid (Figure 1).
Conclusion: This exchange revealed a need for patient-friendly resources for the newly diagnosed, psychosocial support, improved diagnostics, and patient input into clinical trial designs to help speed the development of new treatment options.

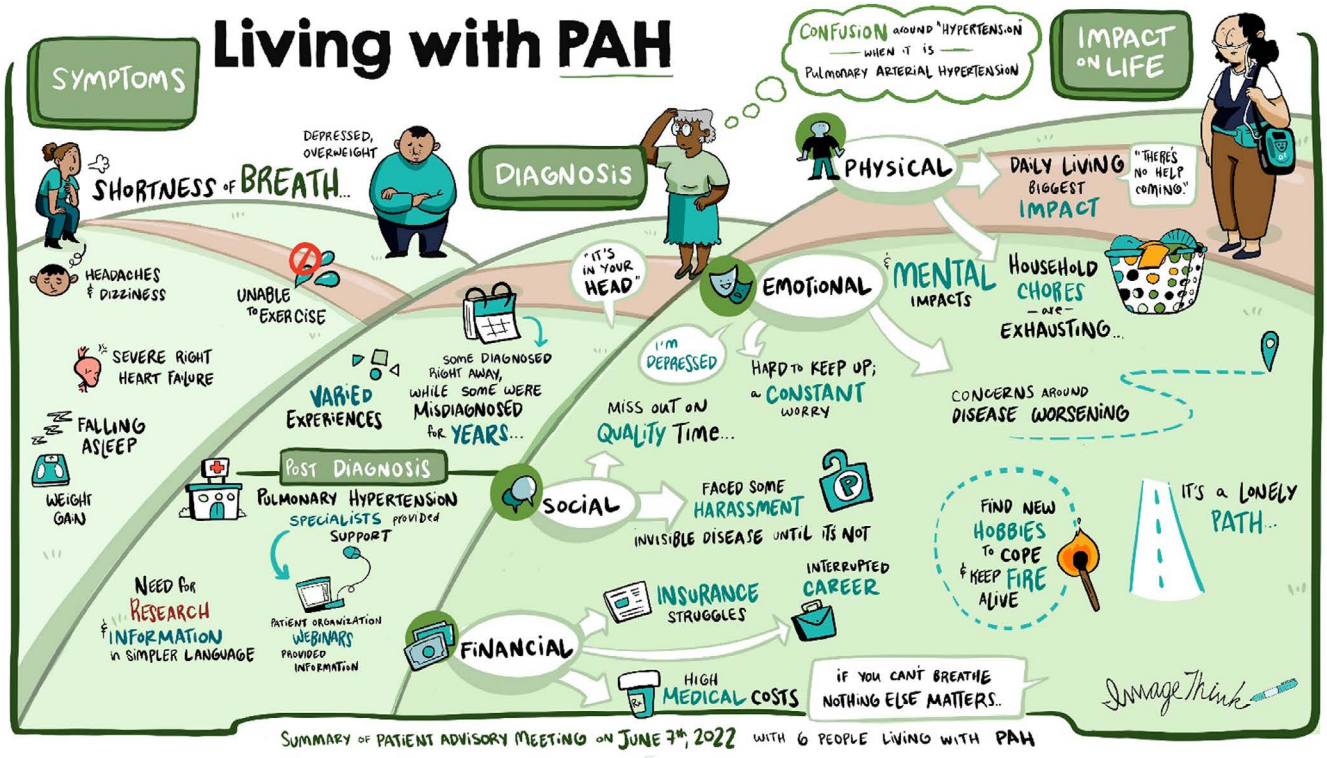


Figure 1: Illustration of PAH patient journey from patient advisory board meeting.

CASE REPORT: CANNABIDIOL (CBD) FOR TREATMENT OF REMODULIN® SITE PAIN

J. Brewer
Corewell Health, Sterling Heights, MI

A. K. Kimber
United Therapeutics Corporation, Research Triangle Park, NC

Category: Case Report
Subcategory: Therapeutic Strategies

Background: Cannabidiol (CBD) has been used for pain management in other disease states and other indications but has not been studied for pain relief from subcutaneous (SC) site pain related to SC treprostinil use. CBD is known to interact with some pathways through which the body initiates inflammation. Transdermal administration efficiently delivers medication directly to the local area where it is applied, thereby possibly reducing the dosage needed, decreasing side effects, and removing the need for systemic treatment.

Methods: We conducted case reports by following/evaluating 2 patients from the Pulmonary Hypertension Center who experienced site pain while on SC treprostinil and used topical CBD for pain management. These patients had previously tried various other suggested methods to mitigate the site pain but were unsuccessful. Therefore, topical CBD was tried as an alternative.
Results: The 2 patients that were followed/evaluated in the Pulmonary Hypertension Center while using topical CBD for site pain relief reported favorable results regarding mitigating their site pain.
Conclusion: CBD, which is nonpsychoactive and nonaddictive, may be considered a viable option for site pain mitigation with the use of SC treprostinil.

CLINICIAN'S GUIDE TO MANAGE PULMONARY HYPERTENSION USING CARDIOPULMONARY EXERCISE TESTING

C. Altherr
Indiana University School of Medicine, IN

Z. Fulkerson
Indiana University School of Medicine, IN

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Traditional methods of diagnosing pulmonary hypertension (PH) include invasive measures of cardiopulmonary hemodynamics acquired from right and left heart catheterization, which are typically performed at rest. However, since most patients are asymptomatic at rest, diagnostic tests in this state may underappreciate the patient's condition where dyspnea and abnormal physiologic processes only manifest during higher levels of exertion. Cardiopulmonary exercise testing (CPET) is a noninvasive means to quantify patient effort, aerobic capacity, and ventilation to perfusion (V/Q) matching during exercise. Variables from CPET have been related with pulmonary vascular pressure and aid in the diagnosis of PH, accurately reflect disease severity, predict adverse events, and reflect the response to therapeutic interventions.
Methods: Patients with PH tend to be exercise limited due to the inimical remodeling of the pulmonary vasculature, which leads to increases in vascular resistance and alveolar hypoperfusion. As a result, patients require increased ventilation pertaining to a certain degree of V/Q mismatch with increased dead space ventilation. Moreover, right ventricular wall thickness and chamber size increase in patients with established PH, which reduces left ventricular chamber size and causes decreased filling, compliance, and stroke volume. Failure of oxygen to be appropriately delivered to working skeletal muscle because of reduced oxygen diffusion and diminished left-sided cardiac output is reflected by lowered peak oxygen consumption during CPET.
Results: Excessive increases in ventilation relative to the demands of the work rate are described as ventilatory inefficiency and usually caused by V/Q mismatch, elevated chemoreceptor and muscle-receptor sensitivity, early lactate accumulation, and/or elevated pulmonary pressures. The ventilation to carbon dioxide output slope is associated with the degree of ventilatory inefficiency, and PH patients display higher ratios in accordance with the increase in pulmonary artery pressures (PAPs). Additionally, end-tidal CO_2 has been shown to have an inverse relationship at rest and at anerobic threshold with elevated PAP (Figure 1).
Conclusion: CPET provides the unique ability to noninvasively assess PH in patients primarily through aerobic capacity and V/Q coupling within the pulmonary system. This is of particular importance when attempting to identify PH early, as V/Q mismatching progressively worsens as pulmonary pressures continue to rise. Increased clinical acceptance of CPET in the assessment of pulmonary hemodynamics may decrease undiagnosed patients, allowing clinicians to implement early treatment plans and therapeutic options.

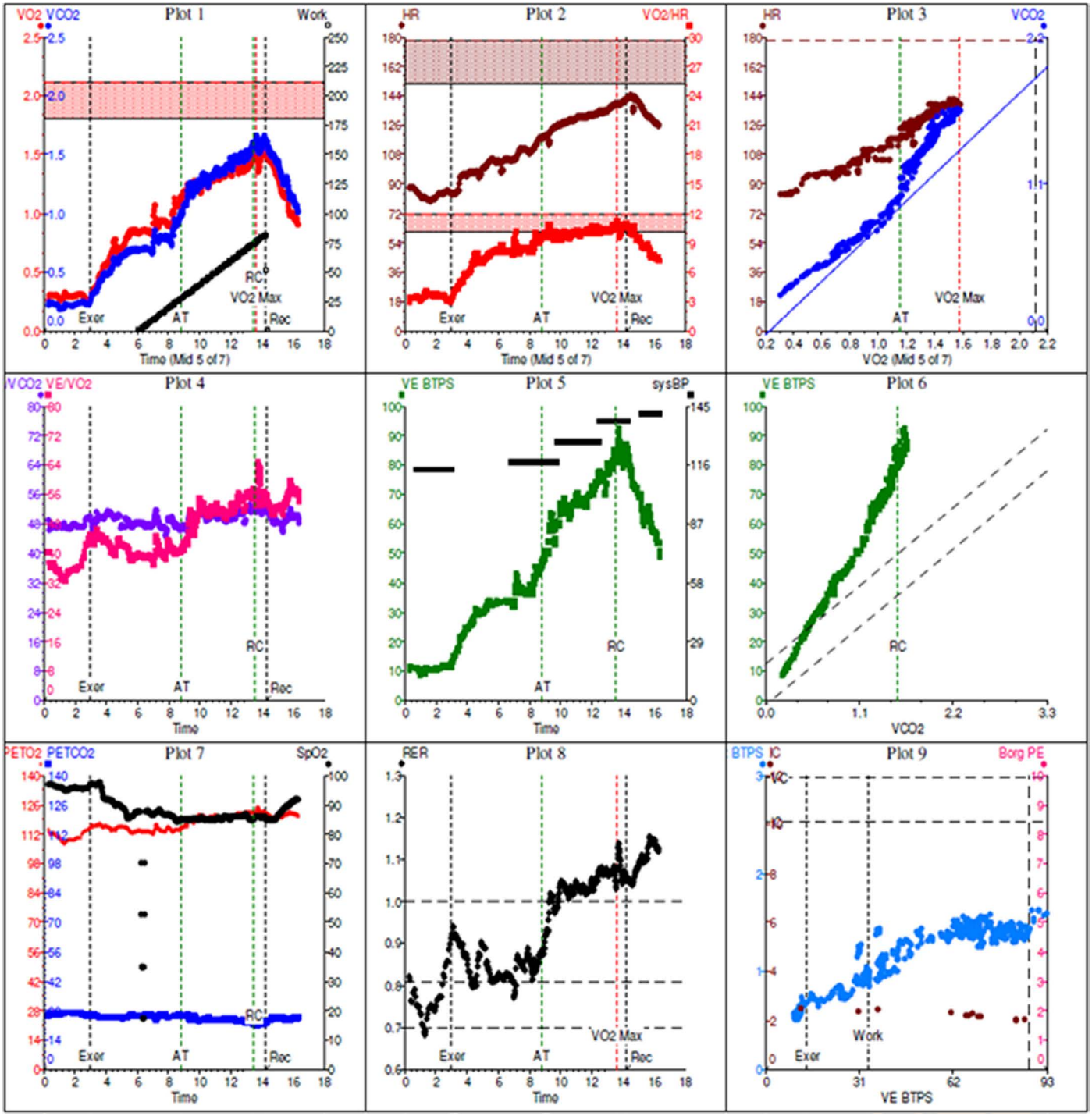


Figure 1: Nine-panel plot of a patient with known pulmonary hypertension.

PULMONARY HYPERTENSION ASSOCIATION REGISTRY (PHAR): A STATUS UPDATE AND RESOURCE FOR RESEARCH

C. D. Burger
Mayo Clinic Florida, Jacksonville, FL

K. Blank
Mayo Clinic Florida, Jacksonville, FL

K. Williams
Mayo Clinic Florida, Jacksonville, FL

Z. Drager
Mayo Clinic Florida, Jacksonville, FL

E. Joseloff
Pulmonary Hypertension Association (PHA), Silver Spring, MD

M. Granato
Pulmonary Hypertension Association (PHA), Silver Spring, MD

Category: Clinical Science
Subcategory: Databases and Registries

Background: The Pulmonary Hypertension Association Registry (PHAR) is the largest active longitudinal registry of patients diagnosed with World Health Organization diagnostic Group 1 pulmonary arterial hypertension or Group 4 chronic thromboembolic pulmonary hypertension. The principal purpose of the PHAR was to measure and improve adherence to published guidelines and quality of care for patients with pulmonary hypertension (PH) and subsequently improve outcomes. To facilitate that aim, the data repository has been leveraged for ongoing research by PHAR investigators.
Methods: Demographic and clinical data were collected from the PHAR data repository as of October 2022. Research proposals were reviewed and assessed by committee. Both abstracts and manuscripts were quantitated with focused areas highlighted.
Results: Of 82 accredited PH Care Centers (PHCCs), 67 (83%) participated in PHAR, and 65 (79%) centers have enrolled at least 1 patient, with over 2200 patients total (Table 1). Most were White women in their mid-50s. Less than 2% were age <18. The majority were Group 1 pulmonary arterial hypertension, somewhat evenly split between idiopathic and associated (Figure 1). Most were modified New York Heart Association Functional Class III with average 6-minute walk distance nearly 340 m (Table 2). Mean pulmonary artery pressure was moderately elevated, and pulmonary vascular resistance was just under 10 Wood units (Table 3). Most of the PHAR participants were on combination therapy with the most common agents being phosphodiesterase-5 inhibitors and endothelin receptor blockers (Table 4). The average emPHasis-10 score was 25.1 ± 12.3. As of January 2023, 41 proposals for research were submitted and reviewed, resulting in 35 (85%) approvals and 14 manuscripts published to date. There were also 24 abstracts, 4 of which were for 2023 national society meetings. The primary focus of the published

Table 1. Demographics of PHAR Participants

Description	All (N = 2247)
Sex	
Male	623 (27.7%)
Female	1594 (70.9%)
Missing	30 (1.3%)
Age	
Mean ± SD	54.86 ± 17.04
Median (IQR)	54.9 (43.2, 67.8)
Missing	12 (0.5%)
Race	
Chinese	12 (0.5%)
Filipino	31 (1.4%)
Japanese	2 (0.1%)
Korean	3 (0.1%)
Vietnamese	7 (0.3%)
Other Asian	13 (0.6%)
Black or African American	301 (13.4%)
Native Hawaiian/Pacific Islander	8 (0.4%)
White	1639 (72.9%)
American Indian	21 (0.9%)
Asian Indian	20 (0.9%)
More than one race	42 (1.9%)
Unknown/not reported	137 (6.1%)
Missing	11 (0.5%)
Ethnicity	
Hispanic or Latino	14 (4.4%)
Not Hispanic or Latino	288 (90.3%)
Unknown/not reported	17 (5.3%)
Missing	0 (0%)
Health insurance	
Private health insurance	1124 (50%)
Medicare	927 (41.3%)
Medicaid	351 (15.6%)
Medi-Gap	46 (2%)
SCHIP	3 (0.1%)
Military health care (TRICARE/VA, Champ-VA)	81 (3.6%)
Indian Health Service	7 (0.3%)
State-sponsored health plan	169 (7.5%)
Other government program	69 (3.1%)
Single service plan (eg, dental, vision, prescription)	38 (1.7%)
No coverage	43 (1.9%)
Education	
Under 18 years old	42 (1.9%)
Did not graduate high school	146 (6.5%)
High school/GED/vocational education graduate	675 (30%)
Some college or university	373 (16.6%)
Graduated from college or university	574 (25.5%)
Professional training beyond 4-year college or university	229 (10.2%)
Missing/do not know	15 (0.7%)

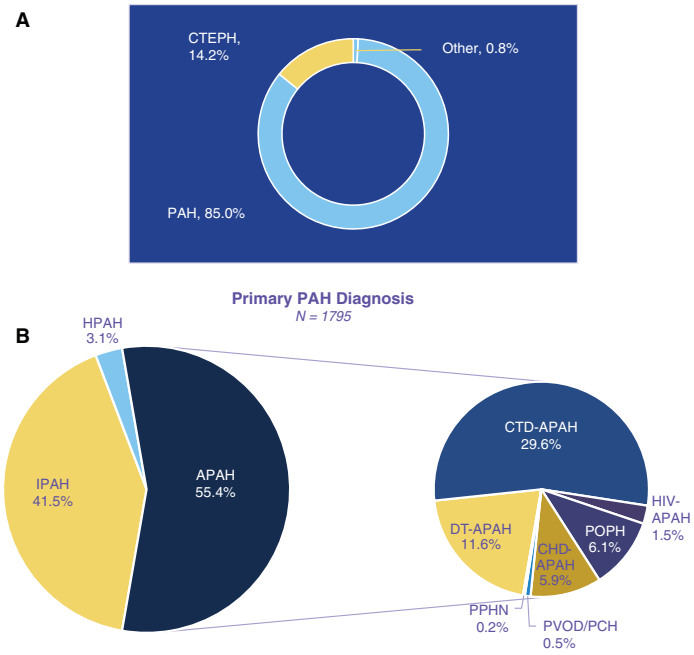


Figure 1: Diagnostic group classification of Pulmonary Hypertension Association Registry participants.

Table 2. Baseline Clinical Characteristics of PHAR Participants

Baseline characteristic	All (N = 2247)
6-minute walk distance, m	
Mean ± SD	335.41 ± 125.23
Median (25%ile, 75%ile)	340 (247, 420)
Missing	418 (18.6%)
NYHA/WHO Functional Class	
I	181 (8.1%)
II	778 (34.6%)
III	1005 (44.7%)
IV	135 (6%)
Missing	148 (6.6%)

Abbreviations: NYHA, New York Heart Association; WHO, World Health Organization.

manuscripts was distributed as follows: cause-related outcome 3, health care disparities 3, demographics 2, quality of life 2, treatment 2, and hospitalization/mortality 2. There have been 4 ancillary studies: 1 completed, 3 in progress potentially including those PHAR participants (79%) who agreed to additional research. Pharmaceutical companies have used PHAR data in support of drug delivery and development.

Conclusion: The PHAR represented a collaborative effort of the majority of PHCCs that enrolled a significant number of patients diagnosed with either Group 1 or Group 4 PH. The data collected represented demographic and clinical characteristics of those patients along with prospectively collected outcomes. Investigators at PHAR sites submitted multiple proposals for data queries with a broad range of research aims that resulted in several published manuscripts over the last 3 years. Ancillary and industry-related studies offer ongoing opportunities.

Table 3. Baseline Clinical Characteristics of PHAR Participants

Hemodynamics	All (N = 2247)
Right atrial pressure, mmHg	
Mean ± SD	9.85 ± 6.12
Median (IQR)	9 (5, 13)
Missing, No.(%)	146 (6.5%)
Pressure (mPAP), mmHg	
Mean ± SD	48.29 ± 13.66
Median (IQR)	48 (39, 57)
Missing	96 (4.3%)
Pulmonary artery wedge pressure (PAWP), mmHg	
Mean ± SD	11.09 ± 5.63
Median (IQR)	10 (7, 14)
Missing	188 (8.4%)
Left ventricular end-diastolic pressure (LVEDP), mmHg	
Mean ± SD	11.8 ± 4.98
Median (IQR)	11.5 (8, 14.25)
Missing	1827 (81.3%)
Pulmonary vascular resistance (PVR), Wood units	
Mean ± SD	9.72 ± 5.42
Median (IQR)	8.81 (5.76, 12.36)
Missing	325 (14.5%)
Cardiac output (CO), L/min	
Mean ± SD	4.35 ± 1.51
Median (IQR)	4.1 (3.3, 5.15)
Missing	217 (9.7%)
Cardiac index (CI), L/min/m^2	
Mean ± SD	2.31 ± 0.79
Median (IQR)	2.17 (1.79, 2.7)
Missing	260 (11.6%)

Table 4. Medication Patterns for PHAR Participants

PH-targeted treatment baseline, PAH patients	N = 2247
PH medications now	
None	404 (18.0%)
1	677 (30.1%)
2	848 (37.7%)
3	308 (13.7%)
≥4	10 (0.4%)
Medications at enrollment (w/in 6 months)	
Endothelin receptor antagonists (ERA)	1128 (50.2%)
Phosphodiesterase-5 (PDE-5) inhibitors	1549 (68.9%)
Soluble guanylate cyclase (sGC) stimulators	246 (10.9%)
Prostanoid (inhaled)	133 (5.9%)
Prostanoid (oral)	193 (8.6)
Prostanoid (parenteral)	493 (21.9%)
Prostanoid (any)	722 (32.1%)

NOVEL USE OF A PDE-5I DURING COVID-19

V.J. Lee
UCLA Health System, Los Angeles, CA

V. Alvadzhyan
UCLA Health System, Los Angeles, CA

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary hypertension (PH), specifically pulmonary arterial hypertension (PAH), is a rare and chronic disease, requiring life-long management with expensive medications that are typically difficult to tolerate from a side-effect standpoint. The peak of the COVID-19 pandemic was especially challenging when adding PH-targeted therapies and medications needed to manage patients' side-effect profiles. A phosphodiesterase-5 inhibitor (PDE-5i) is usually first-line therapy for management of newly diagnosed PAH, whether prescribed as monotherapy or upfront with an endothelin receptor antagonist (ERA). Adcirca, now commercially available in generic formulation, is particularly preferred because of its once-daily dosing and lack of pill burden as compared with generic Revatio, which may require up to 80 mg (4 tablets) 3 times daily (ie, 12 tablets per day). To circumvent or delay adding PH-targeted therapies, for those on monotherapy with a Food and Drug Administration-approved dose of tadalafil 40 mg daily or for those maximally treated on triple therapy, patients were supplemented an afternoon dose of tadalafil 20 mg as follows: 40 mg in the morning and 20 mg in the late afternoon.
Methods: This is a retrospective quality improvement study on patients' responses to an additional dose of a PDE-5i. Data were reviewed from October 2021 to January 2023 on patients' demographics, subjective tolerance, hospital admission, Crt, 6-minute walking test, brain natriuretic peptide, initiation of prostacyclin therapy, and cost analysis of obtaining additional dose of the PDE-5i.
Results: Current analysis of the data is in progress and will be updated once it is completed. A total of 50 patients' charts was reviewed.
Conclusion: Current analysis of the data is in progress, and the conclusion will be updated once it is completed.

ANXIETY AND DEPRESSION SCREENING TO IDENTIFY AT-RISK YOUTH: A QUALITY IMPROVEMENT PROJECT IN AN OUTPATIENT PULMONARY HYPERTENSION CLINIC

E. Whalen
Texas Children's Hospital, Houston, TX

Category: Clinical Science
Subcategory: Pediatrics

Background: Pulmonary hypertension (PH) is a disease associated with significant morbidity and mortality. It can negatively affect a child's ability to grow, develop, and perform normal tasks of daily living. Children with chronic diseases are thought to have higher rates of anxiety and depression (AD) than their healthy peers. However, there is a gap in evidence for the prevalence of AD and screening practices in children diagnosed with PH.
Methods: All eligible patients were identified in the preclinic huddle. A process map was created and reviewed with the PH team (nurses, providers, and social workers). Patients were given the questionnaires before the provider began the visit. The W.K. Kellogg Foundation logic model was adapted to understand planned work and objectives. The Centers for Disease Control and Prevention Framework for Program Evaluation aided the evaluation of the project.
Results: Thirty patients out of 47 eligible were screened, reaching 64% of the eligible population. Screening identified AD in 14 of the 30 patients, prompting further social work assessment and intervention, resulting in mental health service referrals and follow-up. The average total GAD-7 score was 4.9 (range, 0–16), and the average total PHQ-9 score was 4.8 (range, 0–20). Eighteen females were screened with an average age of 15.4 years, and 12 males were screened with an average age of 14.4 years. Females were found to have higher PHQ-9 scores of 5.6 ± 5.1 ($P = 0.001$) and GAD-7 scores of 5.7 ± 4.6 ($P = 0.002$) than males (3.2 and 3.5, respectively). A total of 4 patients required an additional suicide assessment due to findings from the screens (Figures 1 and 2).

Key Process Measure Data Summary

	June – August	September - December	Project Total
Screened	22	8	30
Eligible	37	47	47
Females screened	13	5	18
Average age (years)	*15.9*	*14*	*15.4*
Males screened	9	3	12
Average age (years)	*15*	*13.3*	*14.4*

Figure 1: Key process measure data summary.

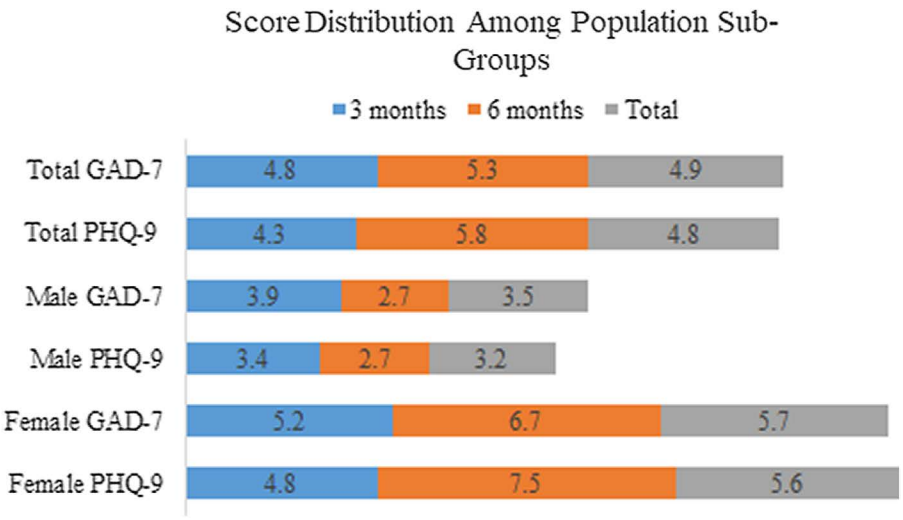


Figure 2: PHQ-9/GAD-7 score distribution.

Conclusion: In this targeted population, there was a high prevalence of unrecognized AD, necessitating the activation of institution-specific assessment and intervention protocols. Given these results, this project supports continued AD screening and response to fill a population need for improved mental health support.

INTEGRATED GENETIC COUNSELING IN A MULTIDISCIPLINARY PEDIATRIC PULMONARY HYPERTENSION CLINIC ENABLES HIGH-YIELD GENETIC TESTING AND FAMILY-BASED CARE

K. Schmit
Indiana University School of Medicine, Indianapolis, IN

B. M. Helm
Indiana University School of Medicine, Indianapolis, IN

S. M. Fitzgerald-Butt
Indiana University School of Medicine, Indianapolis, IN

T. D. Kivett
Indiana University School of Medicine, Indianapolis, IN

W. L. Bannon
Indiana University School of Medicine, Indianapolis, IN

R. M. Serrano
Indiana University School of Medicine, Indianapolis, IN

M. J. Johansen
Indiana University School of Medicine, Indianapolis, IN

G. S. Montgomery
Indiana University School of Medicine, Indianapolis, IN

Category: Clinical Science
Subcategory: Pediatrics

Background: Incorporation of a genetic counselor (GC) in a multidisciplinary pediatric pulmonary hypertension (PPH) clinic enables family-based care and high-yield genetic testing. GCs can triage patients to determine those most likely to benefit from both genetic counseling and genetic testing and

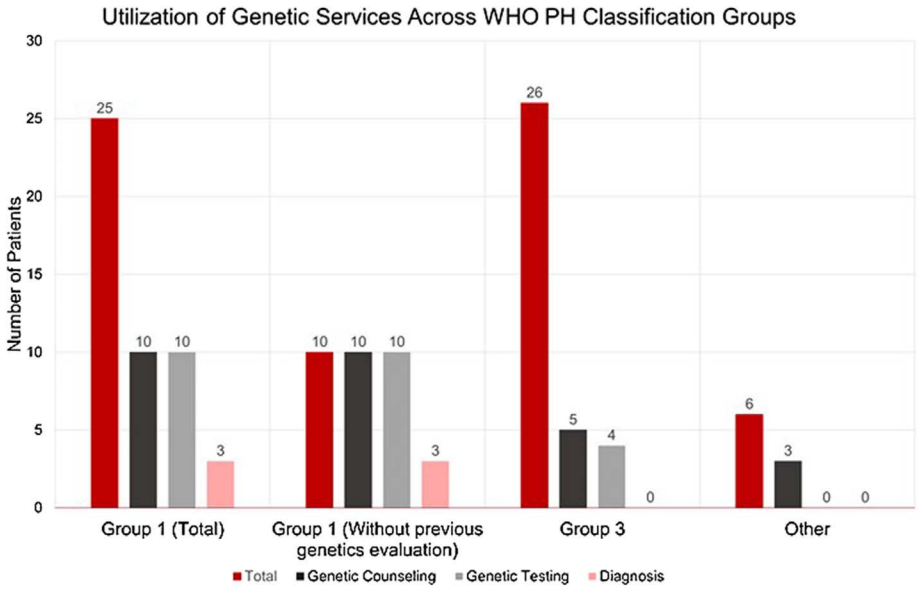


Figure 1: Number of patients who received genetic counseling, genetic testing, and a genetic diagnosis between clinical pulmonary hypertension classification groups as defined by the World Symposium on Pulmonary Hypertension (WSPH).

enable family-based care by providing family testing and screening recommendations.

Methods: For a 12-month period, from July 2021 to July 2022, all unique patients in the PPH clinic at Riley Hospital for Children were analyzed to determine if they had formal genetic counseling, had genetic testing, and/or received a genetic diagnosis. Patients were analyzed according to their clinical pulmonary hypertension classification, as defined by the World Symposium on Pulmonary Hypertension (WSPH).

Results: Sixty-three unique patients were analyzed. Of those, 23 (36.5%) saw a GC, 18 had genetic testing (28.6%), 15 (23.8%) had a comprehensive pedigree completed, and 5 received a genetic diagnosis (7.9%). Family screening and/or cascade genetic testing recommendations were provided to 7 patients (11.1%). For the 25 patients clinically classified as Group 1 (pulmonary arterial hypertension [PAH]), 15 had previous genetic diagnoses and were evaluated outside of the PPH clinic. The remaining 10 all received formal genetic counseling and had genetic testing (100%), with a formal molecular diagnosis in 3 (33%) of the 10 patients (Figure 1). Comparatively, for 26 patients clinically classified as Group 3 (pulmonary hypertension due to lung diseases and/or hypoxia), 5 (19.2%) had formal genetic counseling, 4 (15.4%) had genetic testing, and 0 (0%) received a molecular diagnosis (Figure 1).

Conclusion: GC integration in the PPH clinic facilitates genetic testing in appropriate patients, yielding to a high level of genetic diagnosis (30%) in Group 1 (PAH) patients. GC integration allowed for family-based care by providing family screening and genetic testing recommendations for 11.1% of patients seen.

UTILITY OF INTEGRATED GENETICS TO CREATE A GENETIC TESTING PRACTICE MODEL FOR A PEDIATRIC PULMONARY HYPERTENSION CLINIC

K. Schmit
Indiana University School of Medicine, Indianapolis, IN

B. M. Helm
Indiana University School of Medicine, Indianapolis, IN

S. M. Fitzgerald-Butt
Indiana University School of Medicine, Indianapolis, IN

T. D. Kivett
Indiana University School of Medicine, Indianapolis, IN

W. L. Bannon
Indiana University School of Medicine, Indianapolis, IN

R. M. Serrano
Indiana University School of Medicine, Indianapolis, IN

M. J. Johansen
Indiana University School of Medicine, Indianapolis, IN

G. S. Montgomery
Indiana University School of Medicine, Indianapolis, IN

Category: Clinical Science
Subcategory: Pediatrics

Background: Genetic counseling and, if indicated, genetic testing are recommended by most professional societies for patients with idiopathic and heritable pulmonary arterial hypertension (IPAH and HPAH, respectively) and their first-degree relatives (FDRs). Genetic counselors (GCs) provide support in pretest counseling, posttest counseling, and determination of test use management. Continued evaluation and inclusion of genes newly associated with pulmonary arterial hypertension (PAH) on genetic testing panels can increase genetic testing yield. Ongoing evaluation of genetic testing recommendations, evaluation of literature supporting new PAH-associated genes, and evaluation of available genetic testing panels are advantages of an integrated GC within a pediatric pulmonary hypertension (PPH) clinic. Currently, there is no evidence on how to best integrate a GC and a genetic testing model within a multidisciplinary PPH clinic.

Methods: Relevant PAH consensus guidelines were reviewed to determine recommendations for genetic counseling, genetic testing, and to determine important candidate genes. This along with clinical experience informed the creation of a genetic counseling/testing clinic model.

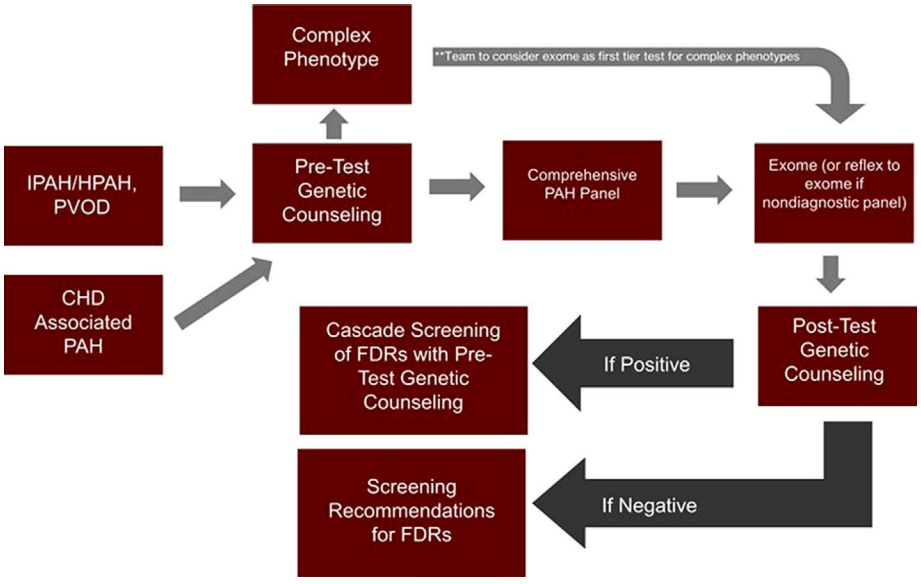


Figure 1:

Results: All major professional guidelines recommend pretest and posttest genetic counseling for individuals with HPAH and IPAH as well as FDRs for whom familial variant testing is available. Additionally, individuals with both PAH associated with congenital heart disease and pulmonary venoocclusive disease benefit from genetic testing. Comprehensive PAH genetic testing panels are recommended as a first-line test, and individuals with a nondiagnostic PAH panel may benefit from exome sequencing to identify novel and possible de novo causes of PAH.
Conclusion: Our evidence-based genetic testing model (Figure 1) ensures equitable and high-quality care for all patients. A GC embedded in clinic allows for regular evaluation of this model by reviewing published recommendations, investigating new candidate genes, and providing insight into the nuanced differences between the varied genetic testing panels.

TRANSITION OF INTRAVENOUS EPOPROSTENOL TO ORAL TREPROSTINIL IN A PATIENT WITH PULMONARY ARTERIAL HYPERTENSION: A PATIENT CASE REPORT

T. Saeed
Corewell Health Beaumont Troy Hospital, Troy, MI

H. M. Klotz
Corewell Health Beaumont Troy Hospital, Troy, MI

K. Noskey
Corewell Health Beaumont Troy Hospital, Troy, MI

J. M. Brewer
Corewell Health Beaumont Troy Hospital, Troy, MI

S. A. Allen
Corewell Health Beaumont Troy Hospital, Troy, MI

R. E. Baker
Corewell Health Beaumont Troy Hospital, Troy, MI

Category: Case Report
Subcategory: Therapeutic Strategies

Background: Prostacyclin therapy is commonly used for management of pulmonary arterial hypertension (PAH). Historically, prostacyclin therapies have only been available in parenteral or inhaled formulations; however, new oral formulations have emerged. Patients' clinical course and preferences may require transition from one formulation to another, but limited guidance exists regarding how to successfully transition from one formulation to another. We present our experience in transitioning a patient with Group 1 PAH from intravenous (IV) epoprostenol to oral (PO) treprostinil.
Methods: A 43-year-old female with a history of PAH associated with drugs and toxins, congestive heart failure, atrial fibrillation, coronary artery disease, acute lymphoblastic leukemia, and obesity presented to the hospital for a planned transition from IV epoprostenol to PO treprostinil. The patient has been on IV epoprostenol since May 2016. At the time of admission, she was stable at a dose of 60 ng/kg/min with a dosing weight of 100 kg. Epoprostenol was infused via CADD-Legacy® ambulatory infusion pump through a tunneled central catheter. The transition from IV epoprostenol to PO treprostinil was pursued for patient satisfaction and ease of medication administration. Patient was directly converted from IV epoprostenol to PO treprostinil with a target PO treprostinil dose of 14 mg 3 times a day (TID).
Results: The patient was able to undergo a direct transition from IV epoprostenol to PO treprostinil over the course of 72 hours while being monitored in the Cardiac Intensive Care Unit. The target dose of PO treprostinil was established by considering manufacturing conversion guidance for IV epoprostenol to IV treprostinil and IV treprostinil to PO treprostinil, as well as the patient's recent 10% weight loss. After switching the patient from her home CADD-Legacy ambulatory infusion pump to the hospital's IV infusion pump, the IV epoprostenol was titrated down twice daily by 9 ng/kg/min while simultaneously the PO treprostinil dose was increased by 2 mg with each infusion adjustment. The patient was able to tolerate the transition well and was discharged home after a 5-day hospital admission with the new PO treprostinil regimen following successful discontinuation of IV epoprostenol.
Conclusion: Despite limited guidance regarding how to successfully transition from IV epoprostenol to PO treprostinil, we report a successful direct conversion from IV epoprostenol to PO treprostinil with no resulting adverse effects at our institution.

EXERCISE-INDUCED PULMONARY ARTERIAL HYPERTENSION IN SELECT PATIENTS WITH KNOWN ATRIAL SEPTAL DEFECT/PATENT FORAMEN OVALE: SINGLE CENTER EXPERIENCE

K. Kavanaugh
Banner Medical Group, Greeley, CO

Category: Case Report
Subcategory: Diseases and Conditions Associated with PH

Background: A small subset of patients with unexplained dyspnea was identified in a select at-risk population for exercised-induced pulmonary arterial hypertension (PAH) with suspected or previously identified atrial septal defect/patent foramen ovale. Early detection of PAH, meeting Group I criteria using 2022 European Society of Cardiology/European Respiratory Society clinical guidelines is critical to

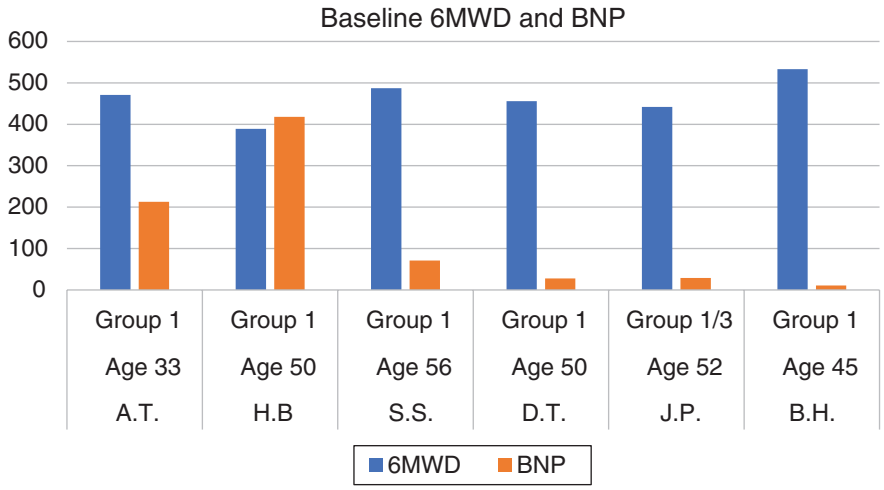


Figure 1: Charted changes noted after right heart catheterization (RHC) with exercise protocol.

implement targeted PAH therapy when appropriate to delay PAH disease progression.

Methods: Data collection was obtained and reviewed from medical records using system electronic medical record. Measurements were charted based on values obtained from studies (echocardiogram/right heart catheterization). Evaluated relationships and variables between cases.
Results: Although a small sample size, we can potentially identify similar patients from our select community who could benefit from thorough review and comprehensive screening for PAH to avoid delays in initiation of appropriate PAH targeted therapies.
Conclusion: We are using a multidisciplinary practice group to develop and implement protocols to comprehensively study and subsequently identify appropriate subset of patients/Group I PAH that may potentially benefit from PAH targeted therapies.

HANK THE HEART AND PULMONARY HYPERTENSION (PH) MEDICATION MANAGEMENT: CHARACTER STORYTELLING ANIMATIONS DIGITAL MEDIA TOOL TO FURTHER EDUCATE AND ENGAGE PATIENTS AND FAMILIES WITH PH

M. Cash
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

M. Magness
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

K. Luebbe
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Category: Case Report
Subcategory: Pediatrics

Background: Pulmonary hypertension (PH) is a rare, complex disease affecting both children and adults. Efforts to provide health education are imperative as patients/caregivers can feel overwhelmed or confused by the complexity of the disease and treatment options. Health literacy affects a patient's/caregiver's capacity to acquire, process, and understand health information and make informed health decisions. Enhancing health literacy improves the patient/caregiver knowledge about illness, can alleviate anxiety about the disease, and plays a significant role in determining the degree of overall adherence to recommended therapies. An abundance of adult-centric patient educational materials, formatted as handouts and online readable materials are available, but there is a scarcity of pediatric specific material. YouTube™ videos accommodate visual and auditory learners, which increases engagement from both children and their caregivers. It is also free, which allows ease of access for anyone with internet capabilities. Our first video about PH in a series of planned educational videos received over 20000 views. Given this, we established the goal of developing content to include more educational topics for our patient population.
Methods: Cincinnati Children's Media Lab is an established animation team and multimedia lab which partners with institutional specialties to create brief, informative, and visually engaging animated educational videos. The PH team partnered with the Media Lab to create a series of character-based animations specific to PH. The animations were designed to be educational and engaging for the child and adult learner with content vetted and set at the sixth-grade fluency level by the organizational health literacy team. From idea to final product, the PH team collaborated with the Media Lab to assemble topic specific educational content, followed by development of a main character

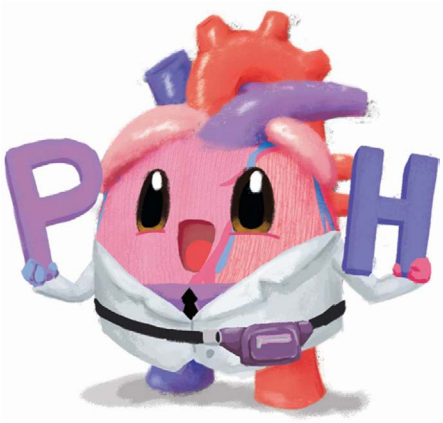


Figure 1: Prespecified subgroup analysis demonstrated consistent benefit of seralutinib on pulmonary vascular resistance (PVR) across subgoups.

(ie, Hank the Heart) and supporting scenes. A rough draft storyboard was assimilated where content, both audio and visual, could be edited. The final visual product was rendered with background music and voiceover added by sound engineers and a voice actor. Once complete, content can be uploaded and electronically shared.
Results: See Conclusion.
Conclusion: The advent and availability of consumer technologies offers access to online educational materials as an alternative teaching tool for clinicians while educating both pediatric patients and their caregivers. This is a unique opportunity for our institution to partner with the Media Lab and develop such content. We expect that offering this unique education at an acceptable health literacy fluency level will motivate the patient and family to understand and adhere to recommended therapies. In addition, we anticipate it will alleviate anxiety about the disease and treatment while empowering patients and their caregivers to make informed health decisions.

TONGUE TWISTER OR PULMONARY HYPERTENSION SUBSPECIALTY COORDINATION SPECIALIST

W. Mowbray
Seattle Children's Hospital, Seattle, WA

Category: Case Report
Subcategory: Pediatrics

Background: Patients with pulmonary hypertension (PH) and their families have complex medical needs and are challenged with ongoing issues in access to care, decreased personalization of care, and individual health disparities. Our pediatric PH Care Center team serves patients over a 4-state region Washington, Alaska, Montana, and Idaho. We recognized our pediatric patients and families were struggling with issues related to ability to access care, decreased personalization of care, inability to coordinate complex diagnostic testing across multiple departments (cardiopulmonary exercise testing [CPET], cardiac magnetic resonance imaging [cMRI], pulmonary function testing [PFT], echocardiograms, sleep studies, swallow studies, genetics clinic, pulmonary clinic, etc), distance from our center, financial concerns, and social stressors. We wanted to address these patient disparities and yet improve the work for our team members. We identified a need to support our patients and our PH program with a coordinator role that did not require provider or registered nurse (RN) involvement and allow the MA the ability to work to the fullest extent of licensure and expand job parameters beyond rooming and obtaining diagnostic studies.
Methods: We used multiple quality improvement (QI) processes and direct observation to examine the needs of our patients and needs in our PH program. The outcome of these processes and assessment of current staffing allowed for identification and need for the creation of this role. We initially started by selecting 1 area which we could monitor with a QI using the plan-do-check-act process: creation and maintenance of a PH patient database by use of a clinic MA. We saw immediate improved patient tracking and outpatient follow-ups. We were able to track inpatient consults and new outpatient referrals efficiently. With the success of the database trial, we approached the Heart Center Administration with the request for a dedicated MA and designated time to work with our PH team and provide basic clinical support. With the support of administration, we continued to expand the MA role to increase MA involvement within our program and added responsibilities within the licensure of our MA but beyond the standard scope of practice of an MA. Over time, the position evolved into a nonnursing coordinator role.
Results: The development of this role has benefited our patients across all aspects of care. Some of the identified areas supported by this role include complex appointment coordination with diagnostic testing (cMRI, computed tomography angiography, CPET, PFT, sleep studies, and videofluoroscopic swallowing studies), coordination of specialty clinics (pulmonary, genetics, nutrition, etc), working with cardiac surgery coordinators for cardiac catheterizations and cardiac surgery, knowledge of hospital and ambulatory processes (admission and discharge), ability to track and enter monthly labs, enter REMs reporting and counseling, and participate in RedCap data entry. Orders are pended and verified in a timely manner to perform testing such as electrocardiograms, 6-minute walking distance, cardiac monitor placement, clinical intake, and discharge. Patients have benefited from increased face-to-face interaction and involvement with our team. RNs are freed from lower-level clinical work and able to focus on higher-acuity patient needs and education. Providers can delegate minor clinical administrative tasks including the tracking of patients and are notified of patient needs and discrepancies. This role has improved interpersonal contact with patients and families before they come to clinic and when they are in clinic, assisting in identifying and escalating social determinants of health needs. Patients experience improved access and follow-up. The position has allowed us to work with the families who live outside a 3-hour drive to our facility to streamline their clinic visits. Our coordinator has initiated a process with our team where we work with local providers and cardiologists to bring PH care to the families in their local communities when possible. We are better able to identify and addressing cultural disparities for families who live 2000 miles away in remote villages in Alaska and assisting them to make a clinical visit to Seattle smoother and less stressful when possible. We have improved the disconnect between the inpatient wards and the ambulatory side with the discharge of at-risk infants and patients and coordination of follow-up appointments with complex scheduling across departments. We have used and integrated the knowledge of an MA who was experienced with the complexities of caring for cardiac patients with PH and created a position to address gaps in our program.

Conclusion: The successful integration of this role within the subspecialty PH program has led the single ventricle/Fontan and electrophysiology subspecialties to replicate this position for their programs in the Heart Center at Seattle Children's Hospital. Other PH programs may benefit from exploring this position and building a similar role for their programs. Using the knowledge and clinical skills of a nonnursing coordinator with direct face-to-face interactions with families could help to bridge gaps between the needs of the patients, RNs, providers and clinic and assist in tasks that are often overlooked and not in the scope of existing roles. This role can help to improve access to care for patients and families, personalizing and individualizing care by identifying needs or issues patients and families encounter.

SELEXIPAG USE IN PEDIATRIC PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

M. Grossman
Children's Hospital of Philadelphia, PA

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Selexipag, a prostacyclin receptor agonist, is approved for use in adult patients with pulmonary arterial hypertension (PAH). There is an ongoing clinical trial to determine optimal dosing for pediatric patients. Currently available published literature describing dosing practices in pediatric patients is limited, with the largest study including 15 patients.
Methods: This is a retrospective chart review of patients <18 years old with diagnosed PAH who were prescribed selexipag between September 20, 2020, and October 21, 2022. Patients were identified using a database maintained by the institution's PAH team. The primary objectives were to describe selexipag dosing strategies used by the PAH team and any changes in concomitant PAH therapies (phosphodiesterase-5 inhibitors, endothelin receptor agonists, and prostacyclin derivatives) during the selexipag titration period. Secondary objectives were to describe the efficacy (changes in catheterization, echocardiogram, and/or 6-minute walk test [6MWT] results) and safety (reason for dose reductions or discontinuations) of selexipag. All results are descriptive in nature.
Results: Twenty-seven patients aged 1–17 years, weighing 10–63 kg, started a median dose of oral selexipag 100 mcg twice daily. Therapy was increased by a median of 100 mcg twice daily every 6 days to a maximally tolerated median dose of 800 mcg twice daily. All 24 patients on another prostacyclin derivative were able to discontinue therapy at their maximum tolerated selexipag dose; other concomitant PAH therapies did not change. No patient had catheterization data collected before and after selexipag initiation. Changes in echocardiogram data and 6MWT results were variable. No patient discontinued selexipag; 4 patients received decreased doses due to flushing (n = 1), drug interactions (n = 2), or increased frequency of nose bleeds (n = 1).
Conclusion: Selexipag use in pediatric patients appears to be safe and well tolerated. The titration regimen used at the institution resulted in patients being able to discontinue another prostacyclin derivative. No other PAH medication changes were made with selexipag therapy.

MAKING A SPLASH… IN SEARCH OF A SAFE WAY TO SUBMERGE ON SUBCUTANEOUS TREPROSTINIL THERAPY

D. Kittel
Ohio State Wexner Medical Center, Columbus, OH

Category: Clinical Science
Subcategory: Quality of Life

Background: Subcutaneous (SQ) site maintenance is burdensome for patients on continuous treprostinil therapy. Patients self-administer a small catheter via a needle injection device under the skin. Setting each new site often results in 5–7 days of debilitating pain and erythema, often referred to as "hell week." Promoting longevity of sites up to 3 months is therefore of utmost importance. Although the Remunity pump itself may be submerged for a short time under water, it is the site that is most difficult to maintain. Patients frequently report that the supplies allotted from the specialty pharmacies to protect sites from water during showering/bathing are often ineffective. To achieve a more normal lifestyle, some patients have been noted to interrupt their continuous infusions to shower or swim. With a half-life of 4 hours, patients have a false sense of security that they are safe to disconnect from their treprostinil pumps without complications. Our patient herein admits to having previously disconnected the pump to swim after reading on social media sites that other patients disconnect to submerge. This is not only against medical advice but also dangerous. Unfortunately, not enough research has been performed on best practices to waterproof SQ sites. Our patient took it upon herself to find a better solution and found that the Allevyn Life dressing afforded reliable waterproofing.
Methods: The existing SQR site is covered by an IV3000 dressing. The site, tubing, and pump are secured with tape for extra support. A test strip which detects the presence of moisture is placed beside the SQR site. The Allevyn Life dressing (8.25 × 8.25 in) is applied, smoothed out completely with no wrinkles or buckles, and the patient will submerge in water for 20 minutes. Upon exiting the pool, the Allevyn Life dressing is removed. The IV3000 dressing over the existing SQR site is

shown to be completely dry. The test strip shows no evidence of moisture, thereby demonstrating the waterproof capability of the Allevyn Life dressing.
Results: The Allevyn Life dressing by Smith & Nephew was successfully used by 1 patient to reliably waterproof her pump and site while submerging in water.
Conclusion: Pending institutional review board approval, we intend to further investigate the reliability of this dressing by having other patients on SQ therapy use it to submerge in water in a controlled setting. Moisture strips will be used to ensure that the dressing is occlusive. Surveys of trial patients will be conducted before and after using the dressing to assess satisfaction with the Allevyn dressing compared with current dressings. The surveys will also gauge the effect on quality of life as patients may now submerge in water.

A MULTI-INSTITUTIONAL RESPONSE TO PROMOTING CAREGIVER EDUCATION IN PEDIATRIC PULMONARY HYPERTENSION: DEVELOPMENT OF 3 EDUCATIONAL BROCHURES

M. Magness
Cincinnati Children's Hospital Medical Center, Cincinnati, OH

E. Colglazier
UCSF Benioff Children's Hospital, San Francisco, CA

C. Parker
UCSF Benioff Children's Hospital, San Francisco, CA

V. Brown
Vanderbilt University Medical Center, Nashville, TN

E. Ely
Texas Children's Hospital, Houston, TX

E. Whalen
Texas Children's Hospital, Houston, TX

V. Grenolds
Children's Hospital Colorado, Aurora, CO

E. Jackson
Seattle Children's Hospital, Seattle, WA

K. Tillman
Children's Wisconsin, Milwaukee, Wisconsin

Category: Case Report
Subcategory: Pediatrics

Background: As part of the PPHNet, the Advanced Practice Provider and Nursing (APPN) Committee identified 2 main areas of focus for educational brochures to develop: subcutaneous (SQ) treprostinil management and World Health Organization (WHO) Group 3 associated pulmonary hypertension (PH). For children diagnosed with severe PH, the use of continuous prostacyclin therapy is often used for aggressive pulmonary vasodilation. This therapy may be associated with changes to quality of life related to SQ site pain and management. A SQ treprostinil guide was created with experienced parent/patient input as a resource for new SQ parents/patients including pain and site management troubleshooting, practical advice from patients and parents, and basic medication information. Patients with WHO Group 3 associated PH make up a large portion of pediatric PH patients. In the setting of this diagnosis, there is limited patient and caregiver educational materials, both printed and electronic. The APPN committee identified 2 types of lung diseases that are often associated with PH to focus on: bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH). Representatives from 6 PPHNet centers (6 total APPNs) volunteered to develop a caregiver educational flyer specific to BPD and CDH-associated PH describing the definition, prevalence, risk factors, assessment/testing, treatment, and long-term follow-up to be used to help support caregiver education.
Methods: A review of the published literature available for all 3 topics, SQ treprostinil management, PH in BPD, and PH in CDH, was completed by members of the APPN Committee in the project. During monthly meetings, the educational brochures were outlined and edited to meet user readability, both in reading level (average ninth grade) and graphic layout. The content was derived from the published literature and expert practice.
Results: The APPN Committee produced 3 brochures that enable patients and families to have access to concise written educational documents. These documents have also been translated into Spanish and Arabic and will be reviewed at 2-year intervals.
Conclusion: Using available literature and professional expertise from multiple institutions, centers can produce well-written and visually pleasing educational brochures. These brochures fill a gap in written literature available to pediatric PH patients and caregivers. Future plans include posting the brochures to the PPHNet Website for wider availability.

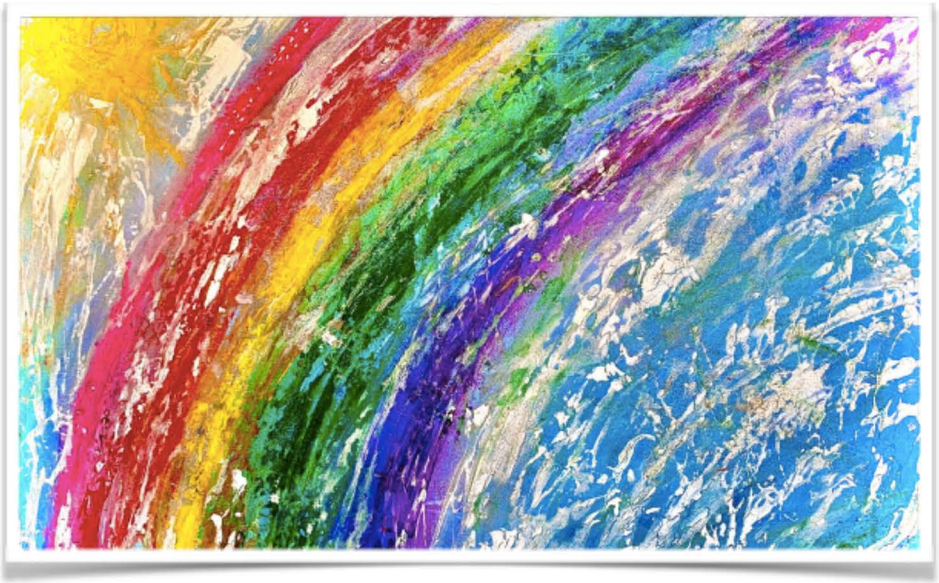
"SQ" Prostacyclin Therapy A guide for new medication starts

Bronchopulmonary Dysplasia & Pulmonary Hypertension: A Guide for Patients & Families.

"SQ" Prostacyclin Therapy

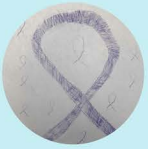
A guide for new medication starts

BY: ELISE WHALEN, NP, CLAIRE PARKER NP, ERIN ELY, RN, MELISSA MAGNESS, NP, & KATY TILLMAN, NP ON BEHALF OF PPHNET NURSING COMMITTEE



Pulmonary Hypertension
An overview of the disease, symptoms, & testing

Treatment options



Pain Management Strategies

Frequently Asked Questions: Things I Wish I knew

Pulmonary Hypertension: What is it?

An overview

Pulmonary hypertension (PH) is another name for high blood pressure in the lungs. It is a big word, but let's break it down. "Pulmonary" means lungs, and hypertension means "high blood pressure." The high blood pressure in the lungs occurs because the arteries narrow down causing higher blood pressures. This higher pressure in the lungs makes the right side of the heart work harder to push blood through the lungs. This extra work causes the heart to become less flexible and even get bigger over time.

SYMPTOMS

Symptoms may include being unable to perform exercise or do activities that are normal for age. Increased tiredness, shortness of breath, dizziness, upset stomach, decreased appetite, and swelling of the face hands, and feet are commonly seen.

TESTING

Your doctor may order an echocardiogram (ultrasound of the heart), chest x-ray, or MRI (pictures of the heart by a magnetic field and radio waves). They could order a cardiac catheterization. This procedure directly measures the pressures and flow in the heart.

Figure 1:

Bronchopulmonary Dysplasia & Pulmonary Hypertension: A Guide for Patients & Families

By: Melissa Magness, NP, Anna Brown, NP, Elizabeth Colglazier, NP, Alicia Grenolds, NP, Emma Jackson, NP, & Elise Whalen, NP on behalf of the PPHNet APP and Nursing Committee

Did you know?

- Between 10-60% of children with BPD develop PH.
- Echocardiography screening for PH is recommended for all infants with moderate to severe BPD at 36 weeks

What is bronchopulmonary dysplasia (BPD)?

Bronchopulmonary dysplasia (BPD) is a condition of halted lung development that is primarily seen in children born prematurely (typically born < 30 weeks gestation and birthweight < 2 pounds). BPD can range from mild to severe and can improve as the child grows. Some patients with BPD may need long-term oxygen therapy and breathing help from machines like ventilators, even after they go home.

What is pulmonary hypertension (PH)?

Some children with moderate to severe BPD may be diagnosed with PH which is high blood pressure in the lungs. In BPD, PH is caused by small or abnormal development of blood vessels in the lungs. High blood pressure in the lungs can put extra stress on the right side of the heart, which can affect its ability to pump blood well.

RISK FACTORS DURING PREGNANCY

- Preeclampsia
- Fetal Growth Restriction
- Infection
- Oligohydramnios (low/absent amniotic fluid)
- Genetic Conditions

RISK FACTORS AFTER BIRTH

- Prolonged mechanical ventilation
- Infection
- Hypoxemia
- Presence of cardiac shunts (abnormal connections in the heart)
- Aspiration (accidental breathing in of fluid into lungs)

Figure 2:

IMPROVING NURSING KNOWLEDGE AND SELF-EFFICACY WITH INTRAVENOUS PROSTACYCLIN ADMINISTRATION

L. Reyes
Johns Hopkins School of Nursing, Baltimore, MD

J. McDermott
Johns Hopkins School of Nursing, Baltimore, MD

V. Davidson
The Mount Sinai Hospital, New York, NY

V. Travis
The College of Mount Saint Vincent, Bronx, NY

V. Cimino
Rogue Scholar Consulting, Baltimore, MD

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Management of intravenous (IV) prostacyclin administration in the inpatient setting introduces significant challenges. IV prostacyclins are high-risk, low-frequency medications that pose a significant risk to patient safety if used in error. A lack of standardized procedures and education related to the nursing administration of IV prostacyclins has led to a knowledge gap among nurses responsible for its infusion.
Methods: A convenience sample of registered nurses (N = 21) from a medical intensive care unit of a teaching hospital was used. The project used a 1-group presurvey and postsurvey design that compared nursing knowledge of IV prostacyclins and self-efficacy with IV administration. Satisfaction with the intervention was also assessed. The intervention was a 30-minute online module incorporating didactic and audiovisual modes of instruction. Optional teach-back sessions were also provided.
Results: The effectiveness of the educational intervention was statistically significant for improved nursing knowledge of IV prostacyclins ($P < 0.01$) and cognitive ($P < .001$) and psychomotor self-efficacy of IV prostacyclin administration ($P < 0.05$). Affective self-efficacy was not statistically significant. There were no significant differences in knowledge or all self-efficacy domains for participants who attended the optional teach-back session. Participants overwhelmingly reported satisfaction with its accessibility, appropriateness for level of experience, and improved knowledge from training.
Conclusion: The findings suggest that the implementation of an online educational module is an effective training strategy to improve nursing knowledge and self-efficacy with IV prostacyclin administration. Online didactic and audiovisual methods of instruction are an effective way to affect nursing knowledge and self-efficacy with IV medication management.

TRANSITION FROM TD300 INHALATION DEVICE TO DRY-POWDER INHALER FOR TREPROSTINIL ADMINISTRATION: COMPARING DOSING, TOLERABILITY, AND REASON FOR CONVERSION

V. Portik
Accredo Health Group, Warrendale, PA

L. Ortman
Accredo Health Group, Warrendale, PA

J. Johnson
Accredo Health Group, Warrendale, PA

K. Chasse
Accredo Health Group, Warrendale, PA

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: The objective was to evaluate tolerability, patient-reported adverse events, and reason for conversion in patients who used a TD300 inhalation device and then transitioned to a dry-powder inhaler (DPI) to administer inhaled treprostinil. The design is a retrospective, crossover comparison of patients on inhaled treprostinil who used the TD300 device for at least 12 months before converting to a DPI and used the inhaler for at least 6 months.
Methods: A review of the electronic medical records was conducted to evaluate patient maintenance dose postconversion, reported reason for conversion, and patient-reported adverse events related to patients using inhaled treprostinil for pulmonary arterial hypertension (PAH) treatment. Inclusion criteria included patients aged 18–89 and carried a diagnosis of either World Health Organization (WHO) Group 1 PAH or WHO Group 3 pulmonary hypertension (PH) associated with interstitial lung disease (ILD). Patients were included if they completed 12 months of therapy using a TD300 device followed by 6 months using a DPI. Patients started with inhaled treprostinil via TD300 inhalation after March 2, 2020, and the DPI after July 20, 2022. Exclusion criteria included any patient who displayed a gap in therapy at any point during the review period or who transitioned >1 time from a TD300 device to DPI or from a DPI to the TD300 device. Records were reviewed to interpret the reason for transition, dose equivalence on conversion to DPI, and patient-reported adverse events experienced on either inhalation device.
Results: The sample size of 32 patients reviewed showed that 91% (29/32) of patients initiated a conversion to DPI due to ease of use (78% [25/32] for convenience and 13 [4/32] due to desire for less complex regimen). Three patients (9% [3/32])

resulted in an unknown reason for transition. Twenty-one patients (66% [21/32]) were able to convert to an equivalent treprostinil dose and frequency using the DPI. Six patients (19% [6/32]) were able to achieve a higher dose upon transition, and 5 patients (15% [5/32]) achieved a lower maintenance dose. Side-effect data were collected for both inhalation devices for the first 6 months the patient was on service with each device. While on the TD300 device, the most common side effects (>10%) included cough, headache, increased shortness of breath, diarrhea, congestion, dizziness, hypotension, nausea, muscle/joint pain, upset stomach, and edema. Administration with a DPI resulted in side effects (>10%) aligning with those in the package insert, including cough, increased shortness of breath, congestion, and edema.

Conclusion: Conversion from a TD300 inhalation device to a DPI was well tolerated wmosty of patients achieving an equivalent dose of inhaled treprostinil. This coupled with the reported ease-of-use advantage of the DPI makes transitioning a viable option for patients treating PAH and PH-ILD with inhaled treprostinil.

TOLERABILITY OF TREPROSTINIL DRY-POWDERED INHALER IN PATIENTS WITH PULMONARY HYPERTENSION RELATED TO FIBROSING INTERSTITIAL LUNG DISEASE AT A LARGE RESPIRATORY REFERRAL CENTER

J. Rice
National Jewish Health, Denver, CO

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Inhaled treprostinil is approved for pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD). A dry-powdered inhaler formulation (treprostinil DPI) was Food and Drug Administration approved in March 2022 for

Table 1: Patient Demographics

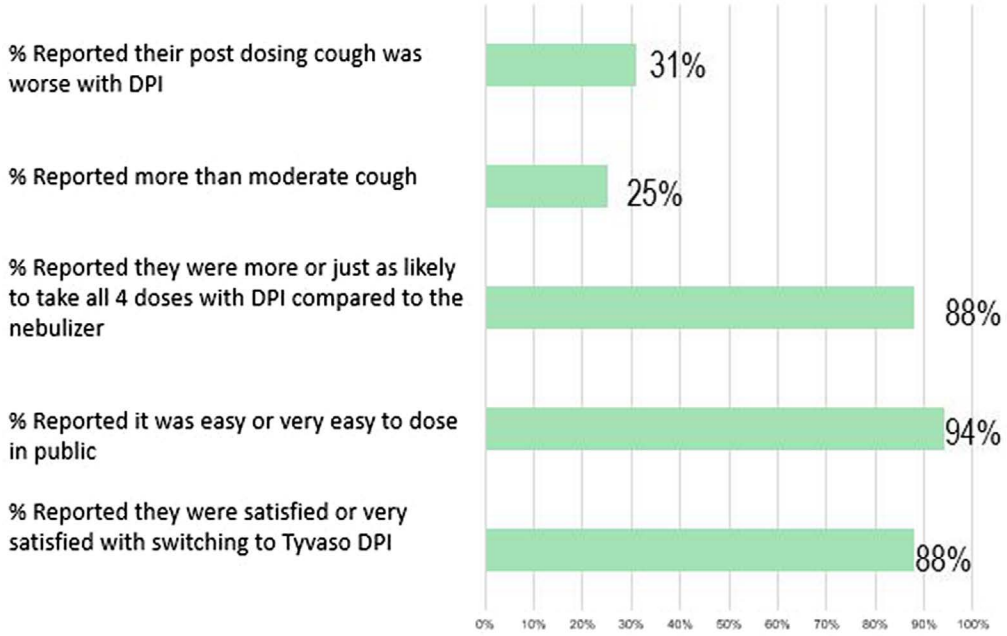
Number of patients	23
Age (years), median (range)	76 (49-82)
Sex	
Male	13
Female	10
ILD type	
CTD-ILD	12
IPF	4
CPFE	3
Chronic organizing pneumonia	1
Chronic HP	1
Granulomatous lymphatic ILD	1
LIP	1
Treprostinil neb dose (breaths), median (range)	12 (9-18)
Starting Tyvaso DPI dose (mcg), median (range)	64 (48-80)
Functional Class	
II	13
III	10
Pre-treprostinil PVR (WU), mean (SD)	5.29 (± 1.9)
FVC (% predicted), mean (SD)	73 (± 23)
DLCO (% predicted), mean (SD)	37 (± 16)
BNP (pg/mL), median (SD)	67.5 (155.9)
6 MWD (m), mean (SD)	299.81 (± 113.9)
Distance saturation product (DSP) – 6MWD x SpO2 nadir (m%), mean (SD)	255.5 (± 98.4)

Table 2: Pretransition and Posttransition Data

	Pre-Transition	Post-Transition
FVC (% predicted), mean (SD)	73 (± 23)	71 (± 23) 14
DLCO (% predicted), mean (SD), n*	37 (± 16)	42 (± 16) 13
BNP (pg/mL), median (CI)	67.5 (33.2-151.8)	84.4 (43.2-110.9) 14
6MWD (m), mean (SD)	299.8 (±113.9)	293.2 (± 113.2) 16
RVSP (mmHg), mean (SD)	47.91 (± 17.8) 21	54.57 (± 18.7) 14
TAPSE (cm), mean (SD)	2.17 (± 0.43)	2.16 (± 0.43) 13
DSP (m%)	255.5 (±98.4)	240.8 (± 96.9) 16
Change in 6MWD (m)		51.36 (±67) 16
Change in DSP (m%)		5.43 (± 58.3) 16

* n listed if < 23 (data collection ongoing)
Note: All pre-transition data were reported when patients were on nebulized treprostinil

Table 3: Patient Survey Data (n = 16)



patients with PAH or PH-ILD based on a recent clinical trial (BREEZE); however, the safety and tolerability of the DPI formulation was only evaluated in patients with PAH. Patients with PH-ILD were excluded in this study and only studied on inhaled nebulizer during the INCREASE trial. Tolerability of Tyvaso DPI has not been formally studied in patients with PH-ILD who possess altered breathing mechanics.

Methods: Upon commercial availability of treprostinil DPI, patients on nebulized treprostinil were given the option to switch during regular follow-up. Data on pretransition and posttransition 6-minute walking distance, brain natriuretic peptide, echocardiogram, hemodynamics, and spirometry were collected within 3–6 months of first use of the DPI. A patient-experience questionnaire was designed and administered to patients posttransition.

Results: Between July 2022 and April 2023, 23 patients with fibrosing ILD were transitioned from the nebulized form of inhaled treprostinil to DPI, with 4 patients planned for transition in the coming weeks. At baseline, patients were on a mean dose of 12 breaths 4 times daily and transitioned successfully to 64 mcg 4 times daily. No change in baseline PH-related therapy occurred during this transition. Table 1 summarizes the baseline characteristics of the patients that completed the transition. A survey answered by 7 patients at the time of submission indicated they were all *very satisfied* with the transition and that treprostinil DPI was well tolerated and was *very easy* to use. All patients reported a cough with treprostinil DPI that, when compared with treprostinil nebulizer, was better in 38% of patients, the same in 31%, and worse in 31%. Patients reported they were more (44%) or as likely (44%) to take all 4 doses of treprostinil DPI compared with the nebulized formulation. Only 12% of patients reported they were less likely to take a dose compared with the nebulizer. Five patients (21.7%) who were transitioned to the DPI discontinued taking it. Three of the 5 discontinued due to side effects and transitioned back to

Table 4: Patient Satisfaction and Symptom Survey

	Very dissatisfied, I regret the change 1	Dissatisfied 2	Neutral, neither satisfied nor dissatisfied 3	Satisfied 4	Very Satisfied, I am glad I made the change 5
1. How satisfied are you with making the change from nebulizer to DPI? Please choose on a scale of 1 - 5.	○	○	○	○	○
	Very Difficult - so difficult that I don't use it outside of my home 1	Difficult - hard to use it when I leave home 2	Moderately challenging - I have to plan around taking the medication when outside my home 3	Easy - it is not a problem 4	Very Easy - I can take it outside of the home without concerns. 5
How easy is it to use Tyvaso DPI in public? Please choose on a scale of 0 - 5.	○	○	○	○	○
Are you more likely to take all 4 doses per day with Tyvaso DPI than with Tyvaso nebulizer?	○ Yes, more likely to take all 4 doses with DPI than with nebulizer ○ Same, just as likely to take all 4 doses with DPI as with nebulizer ○ No, less likely to take all 4 doses with DPI than with nebulizer				
	I always missed a dose 1	I almost always missed a dose 2	50% of the days I took 4 doses 3	I almost never missed a dose 4	I never missed a dose 5
On a scale of 1-5, how often were you taking all 4 doses with Tyvaso nebulizer each day (before switching to DPI)?	○	○	○	○	○
	No cough 1	Almost no cough 2	Some cough 3	A lot of cough 4	Severe cough 5
Are you coughing after taking DPI?	○	○	○	○	○
Is your post-treatment cough changed since the change from Tyvaso nebulizer to DPI?	○ It's better ○ It's the same ○ It's worse				

the nebulizer. Two discontinued completely, 1 due to lung transplant and the other due to hypotension (Tables 2–4). **Conclusion:** In this analysis of patients with PH-ILD, transition from nebulized treprostinil to DPI was well tolerated. Most patients preferred the DPI formulation. More data need to become available regarding long-term safety and tolerability in a larger cohort. Data collection is ongoing.

STUDY DESIGN OF THE DECENTRALIZED, PATIENT-CENTRIC EVOLVE STUDY EVALUATING REAL-WORLD USE OF NEXT GENERATION INFUSION PUMPS TO DELIVER PARENTERAL TREPROSTINIL IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

M. R. Sketch
United Therapeutics Corporation, Durham, NC

M. Broderick
United Therapeutics Corporation, Durham, NC

V. Wang
United Therapeutics Corporation, Durham, NC

Category: Clinical Science
Subcategory: Databases and Registries

Background: With recent Food and Drug Administration guidance and advocacy groups encouraging more patient-focused drug development and incorporation of the patient voice, there has been a shift from traditional clinical trials to those collecting direct patient feedback, or patient-centric trials. This is especially important in rare diseases, such as pulmonary arterial hypertension (PAH). In combination with advancing digital health technologies, therein lies an opportunity for a virtual trial directly engaging with patients and reducing patient burden for participation. Parenteral treprostinil is indicated for the treatment of PAH and available via continuous intravenous or subcutaneous (SC) infusion delivered by an external infusion pump. For almost 20 years, 1 pump has been available to patients in the US for the delivery of SC treprostinil, highlighting a need for newer, next-generation infusion pumps to improve patient experience. One such pump, the Remunity® Pump for Remodulin (treprostinil) injection, has been specifically developed to be used by patients with PAH; however, there is a need for data on its real-world use.
Methods: The EVOLVE (NCT05060315) study is a virtual, observational, patient-centric study to evaluate the real-world use of Remunity, following approximately 60 patients for up to 8 weeks after beginning use of their next-generation infusion pump and consists of remote and electronic assessments completed by patients via a mobile application. Two cohorts of patients will be enrolled: 1 cohort new to parenteral prostacyclin-class therapy and 1 cohort currently receiving SC treprostinil via another infusion pump (ie, previous generation infusion pump) and transitioning to a next-generation infusion pump. The primary objective is to observe and assess drug administration activities, time spent on drug administration activities, and patient-reported outcomes, including quality of life, treatment satisfaction, and patient perception of devices. The secondary objectives are to assess infusion site pain/reaction relief strategies/medications in patients receiving SC treprostinil and collect information related to the dosing of SC treprostinil. Specifically, in those transitioning from a previous-generation infusion pump, secondary objectives are to observe transition mechanics from previous-generation to next-generation infusion pumps and to compare patient perception, treatment satisfaction, and time spent on drug administration activities with next-generation to previous-generation pumps to administer SC treprostinil, where available.
Results: This study is currently open to enrollment. Results forthcoming.
Conclusion: Conclusions forthcoming.

INTEGRATION OF REVEAL LITE 2 RISK CALCULATOR INTO EPIC

J. Sager
Santa Barbara Cottage Hospital Pulmonary Hypertension Center, Santa Barbara, CA

K. Unzueta
Santa Barbara Cottage Hospital Pulmonary Hypertension Center, Santa Barbara, CA

Category: Basic Science
Subcategory: Therapeutic Strategies

Background: Current best-practice guidelines for pulmonary hypertension (PH) treatment recommends patients receive an objective risk assessment at time of diagnosis and at routine intervals to evaluate disease progression. PH risk calculator tools have been proven useful in enabling clinicians to predict clinical outcomes and escalate treatment as needed. We recognized the need to integrate a formal PH risk assessment tool into the electronic health record at our institution.
Methods: We chose to integrate the REVEAL Lite 2 Risk Calculator based on ease of use, streamlined noninvasive scoring criteria, and proven ability to predict long-term outcomes and detect response to treatment. We collaborated with our EPIC analyst to design a REVEAL Lite 2 Calculator prototype which we applied to our EPIC system. Aspects of the calculator were modified and revised as needed until we achieved a working embedded calculator. A smart phrase was then created to allow for efficient addition of the risk calculator to medical doctor progress note.
Results: We successfully integrated a fully operational REVEAL Lite 2 Risk Calculator into our EPIC system. The addition of this formal risk assessment tool has proven to be an invaluable enhancement to our clinical workflow. We now have a validated PH risk stratification tool allowing rapid performance of a PH risk assessment.

Conclusion: The integration of a formal PH risk assessment tool into the electronic record allows for initial and longitudinal risk assessment for PH patients. Embedding PH risk assessment tools into EPIC has a positive effect on clinical workflow by allowing for enhanced data-driven clinical decision making in a rapid fashion and ultimately optimizing patient care. The PH risk assessment tool has become an additional vital sign.

SUCCESSFUL TRANSITIONS FROM ORAL TREPROSTINIL TO SELEXIPAG IN 2 PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION IN A RURAL CARE SETTING: CASE SERIES

J. Germani
West Virginia University, Morgantown, WV

B. Jalil
West Virginia University, Morgantown, WV

Category: Case Report
Subcategory: Therapeutic Strategies

Background: Oral prostacyclin agents have been the standard therapy for pulmonary arterial hypertension (PAH) in addition to nitric oxide pathway agents and endothelin receptor antagonists. Currently, oral treprostinil and selexipag are available as oral synthetic prostanoid agents. However, oral treprostinil may cause severe uncontrolled headaches and diarrhea, and transitions to selexipag are considered to mitigate these adverse effects. However, limited evidence exists regarding how to down-titrate oral treprostinil and up-titrate selexipag without rebound effects.
Methods: We present 2 PAH patients who successfully transitioned from oral treprostinil to selexipag. Due to the limited literature for this transition, the transition schedule was made based on the estimated dose equivalence between parenteral and oral treprostinil products and the approximate conversion ratio between parenteral treprostinil and selexipag.
Results: Patient 1 is a 58-year-old female with a history of idiopathic pulmonary hypertension (PH) who was electively admitted to the hospital for the transition from oral treprostinil to selexipag due to abdominal pain and intolerance to higher doses of oral treprostinil. The patient had World Health Organization (WHO) Functional Class 2 symptoms, and the baseline 6-minute walk distance (6MWD) was 273 m. Her PAH medication regimen included riociguat 0.5 mg 3 times daily, ambrisentan 10 mg once daily, and oral treprostinil 8.5 mg twice daily. The patient was successfully transitioned to selexipag 1000 mcg twice daily over 8 days during the hospitalization and discharged. At outpatient, selexipag was further titrated up to 1600 mcg twice daily over 2 months after discharge. Her symptoms and 6MWD were stable at 274 m, and there was no evidence of clinical decline. Her adverse effects were also significantly improved after the transition to selexipag. She remained a WHO Functional Class 2. Patient 2 is a 48-year-old female with a history of PAH who experienced severe migraine headaches and diarrhea due to oral treprostinil. Her PAH medication regimen was sildenafil 20 mg 3 times daily and oral treprostinil 3.5 mg 3 times daily. The patient developed severe lower extremity edema due to macitentan. Her baseline 6MWD was 285 m and WHO Functional Class 3. Due to her significant adverse effects of the previous regimen and relatively current stable course, her oral treprostinil was transitioned to selexipag at an outpatient setting over 2 months without clinically significant deterioration. She experienced minor headaches, nausea, and diarrhea during the transition, but her migraine and diarrhea significantly improved.
Conclusion: Two patients with PAH were successfully transitioned from oral treprostinil to selexipag without clinically significant deterioration. Our 2 patient cases demonstrated practical titration examples in both inpatient and outpatient settings. Further details in the transition schedule and clinical course will be discussed in the poster presentation.

THE PITFALLS OF SPECIFIC THERAPY IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DEFECTS

S. Gratsianskaya
Federal State Budgetary Institution, National Medical Research Centre of Cardiology, Moscow, Russia

T. Martynyuk
Federal State Budgetary Institution, National Medical Research Centre of Cardiology, Moscow, Russia

Z. Valieva
Federal State Budgetary Institution, National Medical Research Centre of Cardiology, Moscow, Russia

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) in patients with Eisenmenger syndrome (ES) and PAH after defect closure is included in the clinical classification of PAH associated with congenital heart defects (PAH-CHD).
Methods: There were 42 patients: 25 patients with PAH-CHD and ES and 17 patients with PAH after defect closure evaluated in our pulmonary hypertension center according to the data of Russian National Registry of Patients With Pulmonary Arterial Hypertension (NCT03707561). Patients were followed for 24 months.
Results: The duration of PAH therapy in patients with PAH-CHD is estimated at 3.0 (2.0, 5.0) years. There were no

differences in groups in the duration of therapy. In assessing the duration of specific therapy with various drugs by 24 months, it was found that the duration of sildenafil therapy was 3.5 (2.0, 5.0) years in the group with ES and 3.0 (2.0, 5.0) years in patients with PAH after defect closure. The duration of bosentan therapy was 4.0 (2.0, 5.0) years and 3.0 (2.0, 7.0) years, respectively. The duration of macitentan therapy was 1.0 (1.0, 1.0) years and 1.0 (1.0, 1.0) years, respectively. The duration of riociguat therapy was 1.0 (1.0, 1.5) years and 2.0 (2.0, 2.0) years, respectively. Duration of therapy with iloprost was 1.5 (1.0, 2.0) years and 2.5 (1.0, 5.0) years, respectively. During analyzing the changes in PAH therapy for 2 years, it was found that, in the group with ES (n = 25), by the 24th month, 52% of patients received combined specific therapy. In patients with PAH after defect closure (n = 17), by the second year of follow-up, combination therapy occurred in 67% of patients, which indicates the illness severity in this group.
Conclusion: Our data suggest that adults with PAH after defect closure have a more severe course of the disease that requires combination therapy.

STREAMLINING CLINICAL TRIAL RECRUITMENT WITH AUTOMATED PRESCREENING WORKFLOWS: A SOLUTION TO OVERCOMING RESOURCE CONSTRAINTS

D. Yang
UC Davis Medical Center, Sacramento, CA

P. Pajouhesh
UC Davis Medical Center, Sacramento, CA

S. Wuu
UC Davis Medical Center, Sacramento, CA

N. Sood
UC Davis Medical Center, Sacramento, CA

Category: Clinical Science
Subcategory: Diagnosis/Screening and Physiologic Studies

Background: Clinical trial recruitment significantly affects the success of clinical trials, with prescreening constituting a crucial step in identifying potentially eligible patients. However, constraints such as inadequate staffing and insufficient time for comprehensive prescreening due to personnel stretched thin across multiple responsibilities often pose substantial barriers to patient recruitment.
Methods: To address this, we designed an automated screening workflow using widely accessible Microsoft Office tools. Our strategy employs electronic surveys which feed data into datasheets that automatically prescreen patients and indicate their general eligibility for specific studies based on their requirements.
Results: Applying these automated workflows showed promising results by significantly reducing the staff time spent in the prescreening process. It eliminated the need to repeatedly review patient records to assess eligibility criteria for multiple studies, allowing for a more efficient approach to patient recruitment.
Conclusion: Automated prescreening workflows can expedite the patient referral process, potentially accelerating recruitment into clinical trials. This approach offers a feasible solution to mitigate the challenges presented by resource constraints in the prescreening phase of clinical trial recruitment. Additionally, it allows an easy method for physicians to refer patients to a study site for potential participation in active trials as well as for a wider pool of potential patients to be screened in the same timeframe. Our experience with automation of prescreening underscores the potential of digital tools to improve the efficiency and effectiveness of recruitment in clinical trials, thus further diversifying our participant pool.

SERALUTINIB FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION: RESULTS FROM THE PHASE 2 TORREY TRIAL

R. P. Frantz
Mayo Clinic, Rochester, MN

V. V. McLaughlin
University of Michigan, Ann Arbor, MI

S. Sahay
Houston Methodist Hospital/Weill Cornell Medicine, Houston, TX

P. Escribano Subías
University Hospital 12 de Octubre, Complutense University, Madrid, Spain

R. L. Zolty
University of Nebraska Medical Center, Omaha, NE

R. L. Benza
Ohio State University, Columbus, OH

R. N. Channick
UCLA Medical Center, Los Angeles, CA

K. M. Chin
UT Southwestern Medical Center, Dallas, TX

V. R. Hemnes
Vanderbilt University, Nashville, TN

L. S. Howard
Imperial College Healthcare NHS Trust, London, UK

O. Sitbon
Université Paris-Saclay, Le Kremlin-Bicêtre, France

J.-L. Vachiéry
HUB—Hôpital Erasme, Brussels, Belgium

R. T. Zamanian
Stanford University, Stanford, CA

M. Cravets
Gossamer Bio, Inc., San Diego, CA

R. F. Roscigno
Gossamer Bio, Inc., San Diego, CA

D. Mottola
Gossamer Bio, Inc., San Diego, CA

E. Elman
Gossamer Bio, Inc., San Diego, CA

E. Parsley
Gossamer Bio, Inc., San Diego, CA

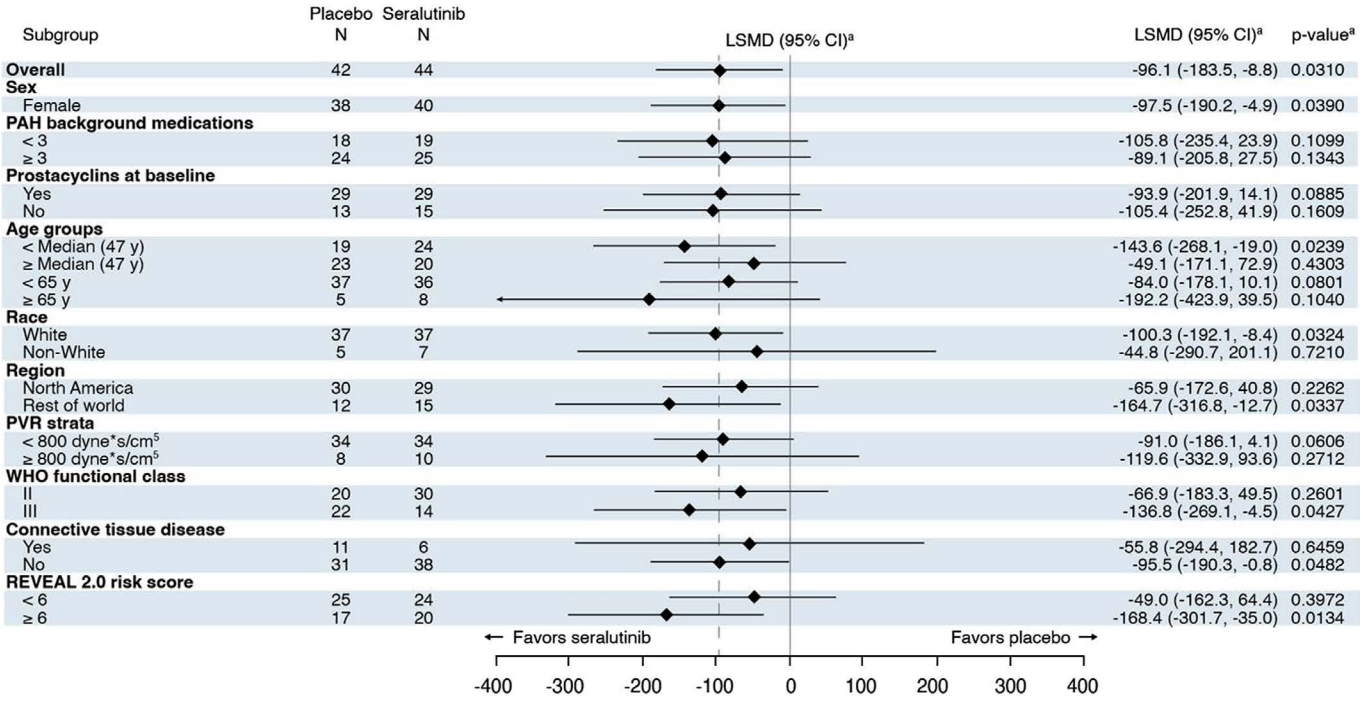
R. Aranda
Gossamer Bio, Inc., San Diego, CA

L. S. Zisman
Gossamer Bio, Inc., San Diego, CA

H.-A. Ghofrani
Justus Liebig University Giessen, Giessen, Germany
on behalf of the TORREY Study Investigators

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: PDGFR, CSF1R, and c-KIT kinase pathways play key roles in the inflammation, proliferation, and fibrosis that drive pulmonary arterial vascular remodeling in pulmonary arterial hypertension (PAH). Seralutinib is a novel, potent kinase inhibitor designed for dry powder inhalation to reach the deep lung and target these dysfunctional pathways.
Methods: TORREY, a Phase 2, randomized, double-blind, placebo-controlled, multicenter study, evaluated the efficacy and safety of inhaled seralutinib in PAH over 24 weeks. Eligible subjects (World Health Organization [WHO] Group 1 pulmonary hypertension [PH], Functional Class [FC] II or III) on standard background therapy were randomized 1:1 to seralutinib 90 mg or placebo by dry powder inhaler twice daily. The primary endpoint was change from baseline to Week 24 in pulmonary vascular resistance (PVR) by right heart catheterization. Secondary and exploratory endpoints included change in 6-minute walk distance (6MWD) and NT-proBNP. Safety was assessed during scheduled visits.
Results: Eighty-six subjects were randomized to treatment (seralutinib, n = 44; placebo, n = 42) at 40 sites worldwide; 80 subjects completed the study. Seralutinib and placebo groups were balanced except for WHO FC: seralutinib, 68%/32% FC II/III; placebo, 48%/52% FC II/III. At baseline, most subjects (96.5%) received ≥2 PAH medications; 44.2% were receiving parenteral prostacyclin. At Week 24, PVR was significantly decreased by seralutinib, with a placebo-corrected reduction of 14.3% (95% CI = –183.5, –8.8; $P = 0.0310$). Among FC



[a] Based on an ANCOVA model with multiple imputation. ANCOVA, analysis of covariance; LSMD, least squares mean difference; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; WHO, World Health Organization.

Figure 1: Prespecified subgroup analysis demonstrated consistent benefit of seralutinib on pulmonary vascular resistance (PVR) across subgoups.

III subjects, the effect on PVR was more pronounced, with a placebo-corrected reduction of 20.8% (95% CI = –269.1, –4.5; $P = 0.0427$). Prespecified subgroup analyses demonstrated a strong concordance of benefit across seralutinib-treated subgroups (Figure 1). Reductions in NT-proBNP were significant at Weeks 12 (LSMD[SE]: –309.6[119.76]; $P = 0.0116$) and 24 (LSMD[SE]: –408.3[120.86]; $P = 0.0012$). 6MWD improved directionally overall (+6.5 m, P = NS) and significantly in FC III subjects (+37.3 m, $P = 0.0476$). At Week 24, worsening to FC IV was observed in 3 placebo-treated subjects and no seralutinib-treated subjects. The most common adverse event in the seralutinib group was mild-moderate cough (43.2% versus 38.1% for placebo).

Conclusion: The TORREY study met its primary endpoint by demonstrating a significant reduction in PVR in the seralutinib group. This is the first clinical trial to show a reduction in PVR by a novel inhaled PDGFR, CSF1R, and c-KIT kinase inhibitor in PAH. Prespecified subgroup analyses showed strong concordance of seralutinib benefit. The reduction in PVR is meaningful in the context of the associated reduction in NT-proBNP. Inhaled seralutinib was well tolerated in this study population. Based on these results, a Phase 3 study is planned. RPF, VVM contributed equally to this work. This abstract was previously presented at the ATS 2023 International Conference (Frantz RP et al. Am J Respir Crit Care Med. 2023;207:A6726).

EFFECTS OF INHALED SERALUTINIB ON RIGHT VENTRICULAR-PULMONARY ARTERIAL COUPLING AND RIGHT HEART FUNCTION IN PULMONARY ARTERIAL HYPERTENSION

R. P. Frantz
Mayo Clinic, Rochester, MN

K. Tello
Justus Liebig University Giessen, Giessen, Germany

V. M. Moles
University of Michigan, Ann Arbor, MI

S. Solomon
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

M. Cravets
Gossamer Bio, Inc., San Diego, CA

R. Osterhout
Gossamer Bio, Inc., San Diego, CA

J.-M. Bruey
Gossamer Bio, Inc., San Diego, CA

R. F. Roscigno
Gossamer Bio, Inc., San Diego, CA

R. Aranda
Gossamer Bio, Inc., San Diego, CA

J.-L. Vachiery
HUB—Hôpital Erasme, Brussels, Belgium

R. Badagliacca
Sapienza University of Rome, Rome, Italy

R. L. Benza
Ohio State University, Columbus, OH

V. V. McLaughlin
University of Michigan, Ann Arbor, MI

L. S. Zisman
Gossamer Bio, Inc., San Diego, CA

H.-A. Ghofrani
Justus Liebig University Giessen, Giessen, Germany

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Impaired right ventricular-pulmonary arterial (RV-PA) coupling portends a poor prognosis in pulmonary arterial hypertension (PAH), and right ventricular free wall strain/systolic pulmonary artery pressure (RVFWS/sPAP) has been reported as a measure of RV-PA coupling. Furthermore, increased RVFWS and right atrial area (RAA) as well as decreased pulmonary artery compliance (PAC) are associated with increased mortality risk in PAH. Seralutinib is a novel, small-molecule kinase inhibitor that targets PDGFR, CSF1R, and c-KIT administered via dry powder inhaler. TORREY, a Phase 2, double-blind, randomized, placebo-controlled study of inhaled seralutinib in patients with PAH (NCT04456998) met its primary endpoint, demonstrating a significant reduction in pulmonary vascular resistance (PVR) from baseline (BL) to Week 24 compared with placebo. In addition, seralutinib significantly decreased NT-proBNP.
Methods: Eighty-six patients with World Health Organization (WHO) Group 1 pulmonary hypertension (PH; Functional Class II, III), ages ≥ 18 years, PVR ≥ 400 dyne·s/cm^5, and on stable PAH standard-of-care therapy (the majority of whom were on double and triple therapy with approved PAH medications) were enrolled. Right heart catheterization (RHC) and full echocardiography were performed at BL and Week 24 and at BL, Week 12, and Week 24, respectively; both were analyzed in a blinded central laboratory. To calculate RVFWS/sPAP, the sPAP from RHC was used. PAC was calculated from RHC data with the formula (SV/[PAS – PAD]). Statistical analysis was performed using analysis of covariance (ANCOVA).
Results: At Week 24, the change in RVFWS/sPAP was lower in the seralutinib group than placebo (Table 1). The changes in RVFWS and RAA were lower in the seralutinib group versus placebo at Weeks 12 and 24 (Table 1). Change

Table 1: Echocardiography Changes From Baseline at Weeks 12 and 24

Week 12

Parameter	Placebo		Seralutinib			
	n	LS Mean Change ± SE	n	LS Mean Change ± SE	LS Mean Difference (SE)	p-value
RAA (cm^2)	40	3.36 ± 0.808	38	1.24 ± 0.831	-2.12 (1.037)	0.0442
RVFWS (%)	39	3.39 ± 0.965	40	0.09 ± 0.938	-3.3 (1.201)	0.0076

Week 24

Parameter	Placebo		Seralutinib			
	n	LS Mean Change ± SE	n	LS Mean Change ± SE	LS Mean Difference (SE)	p-value
RAA (cm^2)	41	3.36 ± 0.693	36	1.36 ± 0.725	-1.99 (0.897)	0.0293
RVFWS (%)	41	3.74 ± 0.985	37	1.11 ± 1.005	-2.62 (1.240)	0.0377
RVFWS/sPAP	41	0.054 ± 0.016	35	0.002 ± 0.017	-0.051 (0.020)	0.0123

LS, least squares; RAA, right atrial area; RVFWS, right ventricular free wall strain; sPAP, systolic pulmonary arterial pressure; all p values are nominal.

in NT-proBNP correlated with change in RAA ($r = 0.43$). At Week 24, change in PAC was greater in the seralutinib group (–0.02 ± 0.085 placebo, 0.19 ± 0.089 seralutinib; LSMD: 0.22 [0.104]; $P = 0.04$). There was no effect of seralutinib on left ventricular ejection fraction.

Conclusion: Treatment with seralutinib was associated with a significant reduction of RVFWS/sPAP. In addition, significant differences in RVFWS itself, RAA, and PAC were observed. These treatment effects support improved RV-PA coupling and right heart function. In conjunction with concordant reductions in PVR and NT-proBNP, these data suggest potential favorable effects of seralutinib in PAH. Seralutinib is in clinical development as a potential new treatment option for patients with PAH.

This abstract was previously presented at the ESC Congress 2023 (Frantz RP et al. Eur Heart J. 2023;44(suppl).

SERALUTINIB IMPROVES PULMONARY ARTERIAL BLOOD VESSEL VOLUME DISTRIBUTION IN PULMONARY ARTERIAL HYPERTENSION: RESULTS OF THE TORREY PHASE 2 IMAGING SUBSTUDY

R. P. Frantz
Mayo Clinic, Rochester, MN

F. N. Rahaghi
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

M. Delcroix
University Hospitals of Leuven, Leuven, Belgium

S. Sahay
Houston Methodist Hospital/Weill Cornell Medicine, Houston, TX

N. Sood
UC Davis Medical Center, Sacramento, CA

R. L. Zolty
University of Nebraska Medical Center, Omaha, NE

M. M. Chakinala
Washington University School of Medicine, St Louis, MO

V. Franco
The Ohio State University Wexner Medical Center, Columbus, OH

P. Jansa
General University Hospital, Prague, Czech Republic

S. M. Shapiro
Greater Los Angeles VA Healthcare System and David Geffen UCLA School of Medicine, Los Angeles, CA

L. A. Spikes
University of Kansas Medical Center, Kansas City, KS

W. Stevens
The University of Melbourne at St. Vincent's Hospital, Fitzroy VIC, Australia

R. J. White
University of Rochester Medical Center, Rochester, NY

P. Muchmore
FLUIDDA, Inc. New York, NY

B. Lavon
FLUIDDA, Inc. New York, NY

J. de Backer
FLUIDDA, Inc. New York, NY

T. Duong-Verle
Gossamer Bio, Inc., San Diego, CA

R. F. Roscigno
Gossamer Bio, Inc., San Diego, CA

D. Mottola
Gossamer Bio, Inc., San Diego, CA

R. Aranda
Gossamer Bio, Inc., San Diego, CA

M. Cravets
Gossamer Bio, Inc., San Diego, CA

R. Osterhout
Gossamer Bio, Inc., San Diego, CA

J.-M. Bruey
Gossamer Bio, Inc., San Diego, CA

E. Parsley
Gossamer Bio, Inc., San Diego, CA

V. V. McLaughlin
University of Michigan, Ann Arbor, MI

R. P. Frantz
Mayo Clinic, Rochester, MN

H.-A. Ghofrani
Justus Liebig University Giessen, Giessen, Germany

L. S. Zisman
Gossamer Bio, Inc., San Diego, CA

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Seralutinib, a novel, inhaled kinase inhibitor with anti-inflammatory and antiproliferative effects, met the primary endpoint of reduction in pulmonary vascular resistance in the Phase 2 TORREY trial in pulmonary arterial hypertension (PAH; NCT04456998) and has the potential to treat pulmonary vascular remodeling. This abnormal remodeling includes distal pruning and proximal pulmonary arterial dilation. Quantitative analysis of these features is possible with computed tomography (CT) imaging.
Methods: The TORREY CT substudy used thin-section, volumetric noncontrast chest CTs followed by automated pulmonary vascular segmentation to evaluate the reverse remodeling potential of seralutinib. Baseline and Week 24 blood vessel volumes (BVVs) were determined at distinct levels defined by vessel cross-sectional area (CSA) in 19 subjects on a background of 2–3 approved PAH therapies. BVVs of pulmonary arteries with a CSA < 5 mm^2 (BV5A) and > 10 mm^2 (BV10A) were calculated. The BV5A to BV10A ratio (BV510ARATIO) was used to express relative redistribution of pulmonary arterial BVV. Linear regression was used to model the treatment effect.
Results: The BV510ARATIO increased from baseline to Week 24 in the seralutinib group (n = 7) versus placebo (n = 12; $P = 0.028$), and BV510ARATIO changes correlated with changes in stroke volume ($R = 0.65$, $P = 0.0033$) and pulmonary artery compliance ($R = 0.56$, $P = 0.016$).
Conclusion: In heavily treated PAH subjects, adding seralutinib for 24 weeks led to a significant redistribution of pulmonary arterial BVV to smaller vessels. These data visualize and quantify seralutinib's treatment effect on the pulmonary arterial vasculature in PAH.

CASE SERIES—PARTIAL ANOMALOUS PULMONARY VENOUS CONNECTIONS

V. Raval
AnMed Health, Anderson, SC

Category: Case Report
Subcategory: Pediatrics

Background: Partial anomalous pulmonary venous connections (PAPVCs) are rare congenital anomalies in which some of the pulmonary veins are erroneously connected to the right atrium rather than the left. Scimitar syndrome (SS) is a specific type of PAPVC in which the anomalous connection is typically to the inferior vena cava and is additionally associated with atrial septal defects and hypoplasia of the right lung and pulmonary artery. There are 2 forms: a more severe infantile form and a milder adult form, which will be discussed in this case study. The adult form is often asymptomatic and is rarely severe enough to require surgical correction. Here, we present a case of adult SS and PAPVC severe enough to lead to pulmonary hypertension and right-sided congestive heart failure.
Methods: The patient is a 41-year-old female who presented for evaluation for shortness of breath along with some swelling in lower extremities. Patient had prior history of smoking and methamphetamine usage. She had elevated d-dimer at 687 so had computed tomography scan of chest with contrast to rule out pulmonary embolism (PE), which was negative for PE but showed abnormal pulmonary venous return with enlarged right ventricle. Patient underwent right heart catheterization (RHC), which revealed severe precapillary pulmonary hypertension secondary to anomalous pulmonary venous return. Her echocardiogram revealed a right ventricular systolic pressure of 90 mmHg, severely dilated right atrium, and ventricle with systolic flattening of interventricular septum and severe tricuspid regurgitation. The patient was started on oral dual combination therapy and was set to be evaluated at a tertiary care center for

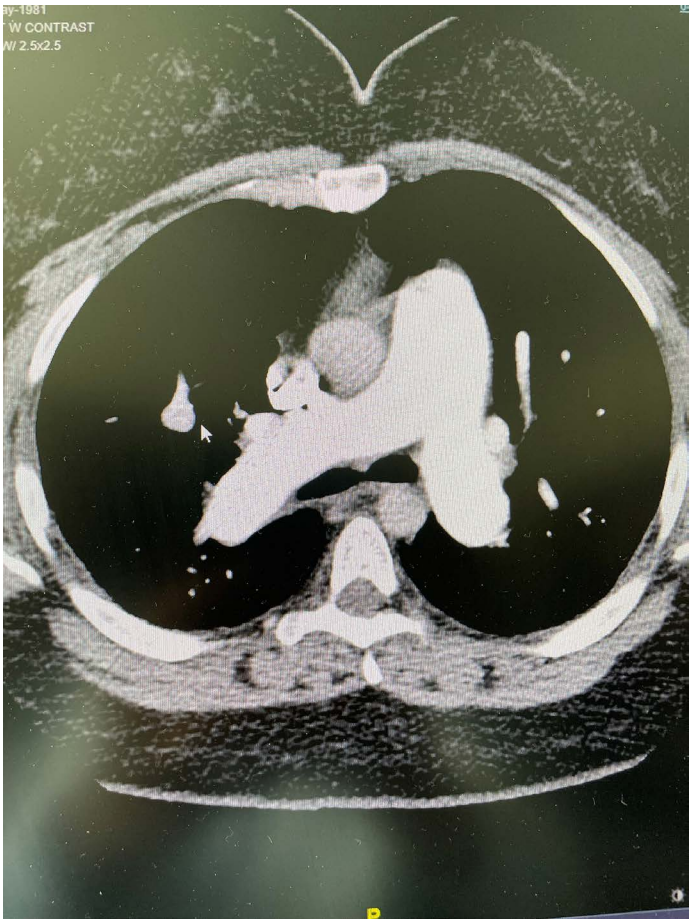


Figure 1: Partial anomalous pulmonary venous return (PAPVR) computed tomography (CT) chest.

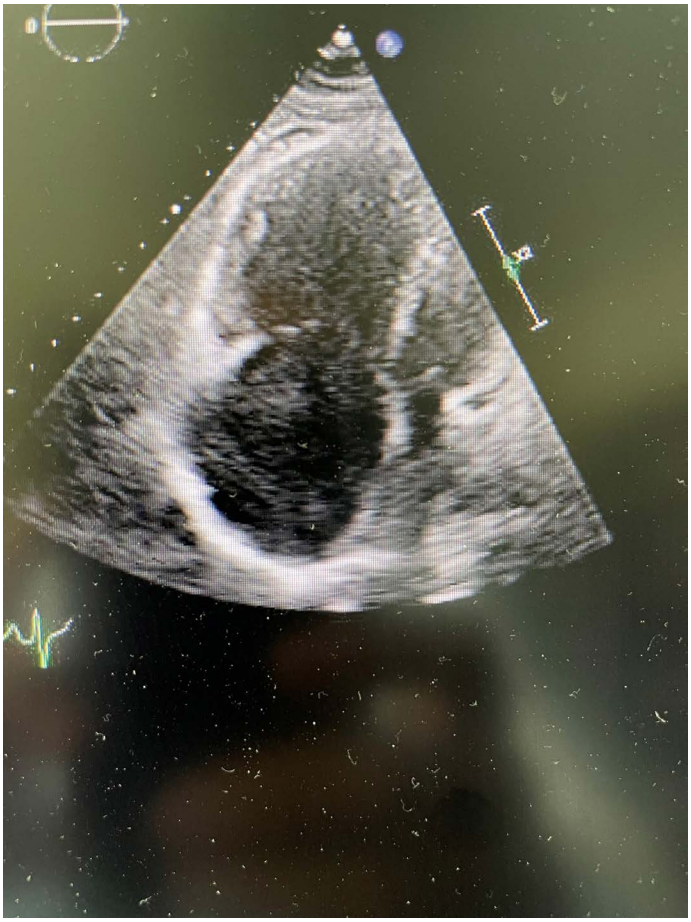


Figure 2: Partial anomalous pulmonary venous return (PAPVR) echocardiogram (ECHO).

evaluation of the shunt. Due to poor compliance, she failed to follow up and represented with much worsening symptoms in 14 months also including skin rash. She was additionally evaluated by dermatology for a chronic history of livedo vasculopathy with poorly healing ulcerations. On arrival, she was noted to have diffuse livedo reticularis and multiple areas of ulcers with necrosis across the extremities, worse in the lower limbs. Autoimmune and oncologic workups were negative, and ulcers were thought to be due to a combination of poor perfusion leading to necrosis and chronic methamphetamine use with associated skin changes. Biopsies demonstrated erosion of the skin with underlying superficial vascular ectasia and fat necrosis. The patient due to worsening hemodynamics was started on parenteral prostacyclin therapy. She was transferred to the Medical University of South Carolina for management and surgical evaluation. She underwent another RHC which demonstrated precapillary pulmonary hypertension with mean pulmonary artery pressures of 46 mmHg, transpulmonary gradient 27 mmHg, diastolic pressure gradient 14 mmHg, and pulmonary vascular resistance of 3.47 Wood units. It also

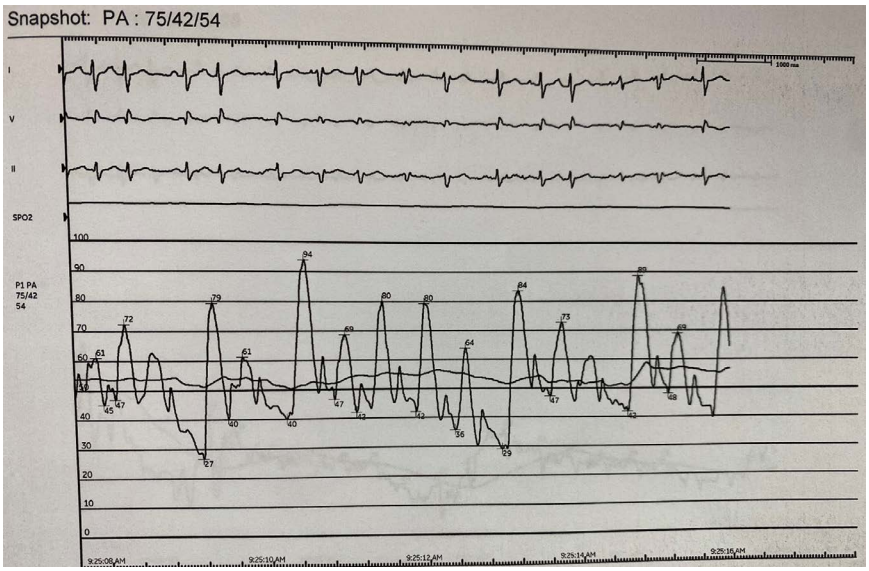


Figure 3: Partial anomalous pulmonary venous return (PAPVR) right heart catheterization (RHC).

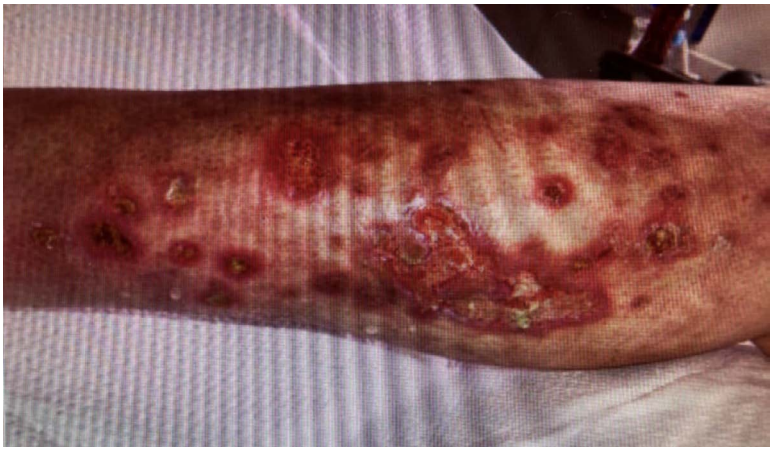


Figure 4: Partial anomalous pulmonary venous return (PAPVR) skin.

revealed a low pulmonary artery pulsatility index of 1.44, indicating poor right ventricular function. Due to her chronic and severe pulmonary hypertension, she is currently a poor candidate for surgical correction because of the increased likelihood of poor outcomes postoperatively and is maintained on triple pulmonary vasodilator therapy.

Results: SS is an extremely rare congenital anomaly, estimated to only occur in 2 in every 100000 births. The condition has been described in autopsies since 1836 and was not found in a live patient until 1949. Though the exact mechanisms are not yet fully understood, it is thought that the syndrome occurs from a persistence of embryologic vasculature and a failure of right pulmonary artery development. There are 2 main anomalies seen in SS: 1 in which both the right upper and lower pulmonary veins drain into the inferior vena cava (IVC) and 1 in which there is partial or complete right lower pulmonary vein draining to the IVC. The latter form was seen in this patient along with symptoms typical of a more severe presentation: fatigue, exertional dyspnea, and pulmonary hypertension. These symptoms are more often seen in the more severe infantile form but can be found in adults with SS, especially if other congenital cardiorespiratory anomalies are present. In this patient though, there were no other anomalies; the extensive history of smoking methamphetamine and tobacco likely exacerbated her condition and led to her decline. In adults, medical intervention is preferred, and surgery is generally reserved for severely symptomatic patients or patients with a Q_P/Q_S ratio >1.5, which would indicate significant shunting. The patient's ratio was 1.7. There are 2 main pathways for surgical SS correction: either resecting the part of the lung connected to the anomalous vein or rerouting flow of the anomalous vein to the left atrium; any other defects would need to be repaired as well. Several procedures can be used depending on the extent of aberrant circulation and lung hypoplasia. However, all procedures carry a high risk of thrombosis due to the low-velocity flow in venous circulation. The skin findings in this patient could be a unique manifestation of chronic cardiopulmonary disease. Plexiform lesions can be seen in patients with severe pulmonary hypertension but are typically found in lung tissue when samples are available. However, the pathology demonstrated is remarkably like that seen in this patient's biopsies, especially the vessel dilation and thickening. Additionally, the necrosis and poor healing could indicate decreased perfusion and even thrombi from the lungs due to the widespread and chronic pulmonary endothelial inflammation (Figures 1–4).

Conclusion: Though rare, it may be useful to consider the diagnosis of partial anomalous pulmonary venous return and SS in patients with pulmonary hypertension of unknown etiology, especially if severe and with cyanosis at presentation. Surgical correction is possible, and patients should be evaluated rapidly in addition to receiving appropriate medical treatment. While the adult form is rare, finding this underlying condition and altering the patient's care as needed could help prevent future health deterioration and heart failure.

PRACTICES AFFECTING MACITENTAN AND SELEXIPAG PATIENT PERSISTENCE RATES USING PULMONARY ARTERIAL HYPERTENSION CLINICAL SITE AND PATIENT PERSPECTIVES: A US QUALITATIVE RESEARCH ANALYSIS (PERSIST)

C. McEvoy
Washington University School of Medicine, St Louis, MO

F. Rogers
Temple University Hospital, Heart and Vascular Institute, Philadelphia, PA

M. Kigman
University of Texas Southwestern Medical Center, Dallas, TX

S. Studer
Actelion Pharmaceuticals US, Inc., Titusville, NJ

T. Tobore
Actelion Pharmaceuticals US, Inc., Titusville, NJ

G. Gomez Rendond
Actelion Pharmaceuticals US, Inc., Titusville, NJ

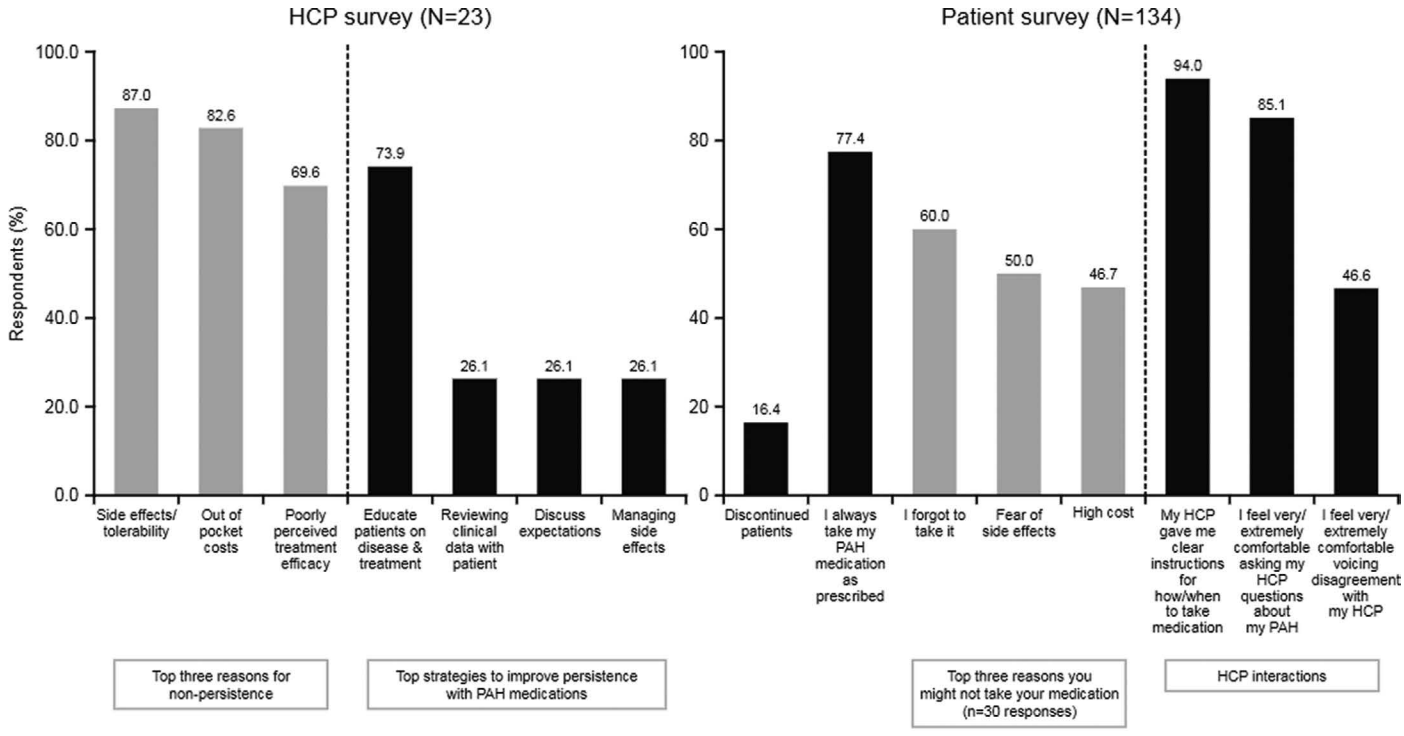
M. Rahman
Actelion Pharmaceuticals US, Inc., Titusville, NJ

O. A. Shoblin
Inova Fairfax Hospital, Falls Church, VA

Category: Clinical Science
Subcategory: Diseases and Conditions Associated with PH

Background: Macitentan and selexipag reduce the risks of disease progression and hospitalization for patients with pulmonary arterial hypertension (PAH). Medication

persistence is important for optimizing patient outcomes but may be suboptimal in PAH. PERSIST (Protocol AC-055-513), a cross-sectional US real-world study, aimed to explore factors affecting macitentan and selexipag persistence.
Methods: PERSIST captured health care professional (HCP) and patient perspectives (November 2019 to August 2022) using a 1-time interview (HCPs) or survey (patients). HCPs were recruited from sites with high and low specialty pharmacy shipment rates during a recent 12-month period and ≥8 selexipag or ≥10 macitentan patient exposures. PAH patients self-reporting macitentan and/or selexipag use over the last 12 months were eligible. Persistent users had received macitentan for ≥3 months or stable selexipag dose for ≥1 month (without interruption >30 days), and discontinued users had stopped medication for >30 consecutive days during the last 12 months.
Results: HCPs surveyed (N = 23) perceived the most common reasons for nonpersistence to be side effects/tolerability (87% responses), treatment cost (83%), and perceived insufficient efficacy (70%). Strategies to improve persistence included educating patients about PAH and its treatment (74%), reviewing objective data (assessments, tests) with patients (26%), discussing expectations at first visit (26%), and managing side effects (26%). At low medication shipment rate sites, there was disconnect between HCP perception of persistence (86%) versus ≤40% medication shipment. Patients (N = 134) included 78 macitentan users (71 persistent; 7 discontinued) and 56 selexipag users (41 persistent; 15 discontinued). Based on patient responses, the most common reason for not taking medication as prescribed was forgetfulness in persistent patients (15/18 [83%]) and fear of side effects in discontinued patients (8/12 [67%]). Patient-cited barriers to persistence included perceived insufficient treatment efficacy and insurance coverage/out-of-pocket costs. Most frequently cited reasons for taking PAH medication were symptom improvement in persistent patients (79/111 [71%]) and HCP instruction in discontinued patients (12/22 [55%]). Most patients discussed treatment choices with their HCP (112/134 [84%]). Some were uncomfortable asking questions, and only half (62/133 [47%]) felt very/extremely comfortable disagreeing with HCP recommendations (Figure 1).
Conclusion: Results indicate that HCPs perceive persistence to be higher than indicated by medication shipment data and highlight the importance of continuous patient engagement, improvement of patient/HCP communication, disease and treatment education, and early management of side effects. Barriers such as patients' discomfort communicating with HCPs should be addressed to facilitate persistence.



HCP, healthcare professional; PAH, pulmonary arterial hypertension.

Figure 1: Key findings from health care professional (HCP) and pulmonary arterial hypertension (PAH) patient surveys in the PERSIST study.

PRELIMINARY COMPARISON OF EFFECTIVENESS OF PULMONARY VASODILATORS BETWEEN PRECAPILLARY AND COMBINED PRECAPILLARY AND POSTCAPILLARY PULMONARY HYPERTENSION PATIENTS

M. Doshi
University of Michigan, Ann Arbor, MI

S. McDevitt
University of Michigan, Ann Arbor, MI

E. Kline-Rogers
University of Michigan, Ann Arbor, MI

V. McLaughlin
University of Michigan, Ann Arbor, MI

V. M. Moles
University of Michigan, Ann Arbor, MI

Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Authors of previous studies expressed improved functional capacity in precapillary pulmonary hypertension (PH) patients—such as pulmonary arterial hypertension-prescribed PH-specific medications and in patients with combined precapillary and postcapillary PH (Cpc-PH)—managed with pulmonary vasodilators. PH medical therapy leads to pulmonary vasodilation and a decrease in pulmonary vascular resistance, which may contribute to better functional capacity. We aim to understand the clinical effect of pulmonary vasodilators in Cpc-PH compared with precapillary PH patients.
Methods: Demographic, clinical, and exercise capacity data derived from the University of Michigan Pulmonary Hypertension Patient Registry was obtained at the time of diagnosis and at 1-year follow-up for patients undergoing an evaluation for PH. Information including that of right heart catheterization, 6-minute walk (6MW), functional class, and brain natriuretic peptide (BNP) levels were assessed between groups. Patients with information on baseline and 1-year follow-up data who had documented prescriptions of PH medication were included in the study. The medications given consisted of phosphodiesterase-5 (PDE-5) inhibitors (Pre: 94.2%, Cpc: 96.2%), endothelin receptor antagonists (Pre: 52.9%, Cpc: 38.5%), and prostacyclin analogs (Pre: 37.9%, Cpc: 34.6%).
Results: Of 474 PH patients in the database, 82 precapillary, and 21 Cpc-PH patients were included. Precapillary patients were defined as those with pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg and classified as Group I, while the Cpc-PH patients had a PCWP > 15 mmHg and were classified as Group II. In terms of baseline hemodynamics for precapillary and Cpc patients, respectively, median RA was 10 mmHg versus 14 mmHg, median pulmonary artery (PA) 46 mmHg versus 52.5 mmHg, median PCWP 12 mmHg versus 19mmHg, and pulmonary vascular resistance (PVR) 7.1 WU versus 7.8 WU. Precapillary PH patients showed improvement in World Health Organization (WHO) Functional Class, with 31.7% of patients in groups I and II at baseline versus 47.6% at follow-up ($P = 0.005$). Cpc-PH patients changed from 38.1% to 57.1% groups I and II, although this did not reach statistical significance ($P = 0.102$). The difference in change to WHO groups I and II between precapillary and Cpc-PH patients from baseline to 1 year was 3.2% ($P = 0.792$, effect size = 0.084). BNP levels in the precapillary group were reduced at 1 year but not in patients with Cpc-PH. Additionally, Cpc-PH patients demonstrated significantly increased 6MW distance ($P = 0.01$). The difference in improvement

Table 1: Baseline Versus FU Difference in Precapillary Group Versus Difference in CpcPH Group

	Pre-Capillary PH, n = 82			Cpc-PH, n = 21		
	Baseline	Follow-Up	*p-value	Baseline	Follow-Up	*p-value
WHO Class, I/II, %	31.7	47.6	0.005	38.1	57.1	0.102
WHO Class, III/IV, %	68.3	52.4	0.005	61.9	42.9	0.102
BNP Level	483.0	213.2	0.001	182.5	210.8	1.000
6MW Distance, m	342.8	364.4	0.075	300.3	364.9	0.01

between Cpc-PH and precapillary PH patients was 43.1 m in favor of the Cpc-PH group ($P = 0.091$, effect size = 0.444). **Conclusion:** Although PH-targeted therapy in Cpc-PH patients is associated with a trend toward functional capacity improvement at 1-year follow-up, this change was blunted compared with patients with precapillary PH. Moreover, there was not a significant difference in BNP levels in patients with Cpc-PH. However, the Cpc-PH group demonstrated improvement in 6MW distance. This small sample size of highly selected Cpc-PH patients indicates further study of the safety and efficacy of pulmonary vasodilators in this cohort is warranted.

ROLE OF GENETIC TESTING IN PULMONARY ARTERIAL HYPERTENSION EVALUATION: A PATIENT AND CLINICIAN SURVEY RESULTS

J. Rice
National Jewish Health, Denver, CO

Category: Clinical Science
Subcategory: Diagnosis/Screening and Physiologic Studies

Background: A well-known association exists between genetic mutations and the development of pulmonary arterial hypertension (PAH). The BMPR2 gene is a well-documented culprit mutation in the disease. Patients with genetic mutations tend to be diagnosed earlier but have worse outcomes than other forms of PAH. Despite guidelines recommending genetic testing, it remains underused. We conducted a survey of patients with PAH and PAH experts from expert care centers to understand their respective views toward genetic testing.
Methods: From May 2022 to October 2022, 2 separate institutional review board-approved surveys were sent to patients with PAH and clinicians who treat PAH. The patient survey included 22 questions targeted to assess their experience, knowledge, and expectations about genetic testing. The clinician survey consisted of 25 separate questions to understand their views of and barriers to obtaining genetic testing. Both

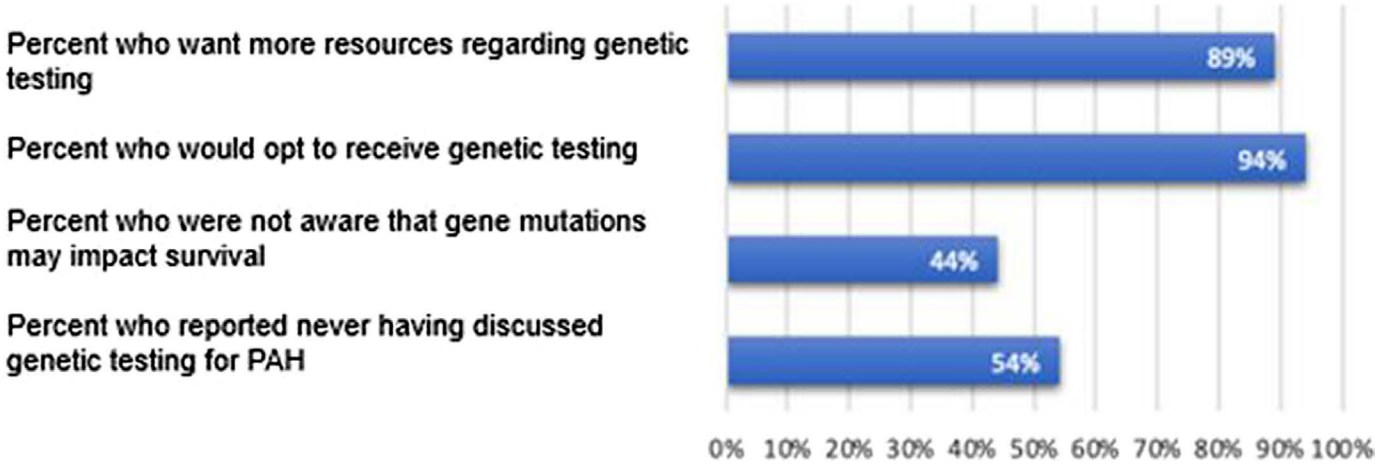


Figure 1: Patient survey results (n = 233).

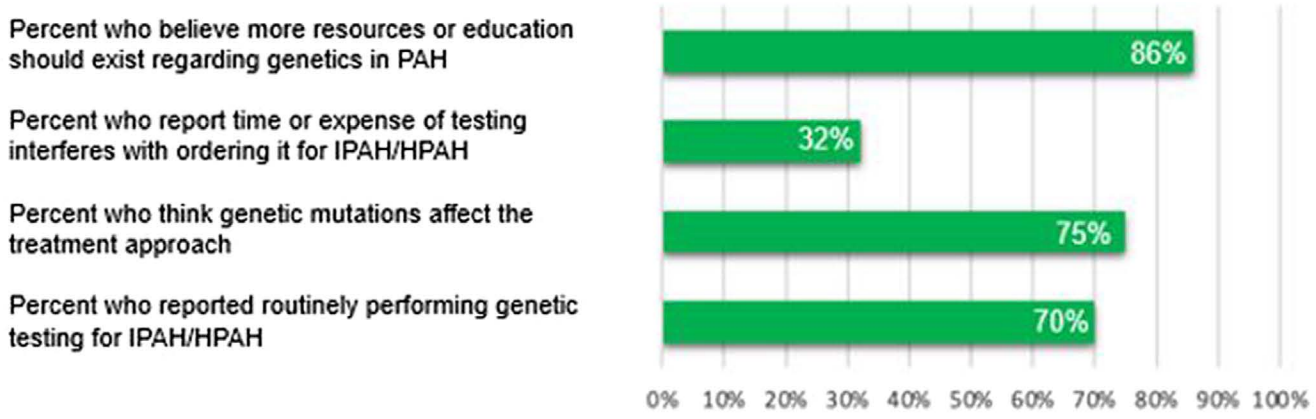


Figure 2: Clinician survey results (n = 38).

surveys were disseminated via pulmonary hypertension (PH) support groups, social media, and through the Pulmonary Hypertension Association (PHA), which provided PH clinician and researcher emails.
Results: A total of 235 patients completed the survey, 91% of whom were women. Eighty percent had self-reported World Health Organization (WHO) Group 1 disease; 12% were confirmed heritable PAH (HPAH), and 48% were confirmed idiopathic PAH (IPAH). Forty-eight percent of respondents did not know that PAH can be caused by genetic variation. While 81% responded that they would consider undergoing genetic testing, only 28% reported they were offered genetic testing (Figure 1). Fifty-two clinicians completed the survey. About two-thirds of clinicians reported awareness of current guidelines for genetic testing (Figure 2). Seventy-five percent indicated that identification of genetic mutations affected treatment approaches, but only 70% of providers reported performing genetic testing routinely during IPAH or HPAP evaluations. Eighty-five percent of clinicians cited cost of the test as a barrier to testing, while 49% cited time taken to navigate genetic testing referral as barriers to testing. However, despite the potential out-of-pocket costs, 34% of patients reported a desire to obtain genetic testing. Overall, 89% of patients and 86% of clinicians agreed that additional information and resources regarding genetic education were needed.
Conclusion: Common barriers to testing included cost as reported by both patients and clinicians and time to refer as reported by clinicians. Patients and clinicians indicated a desire for more education and access to additional information regarding genetic testing.

Advances in
Pulmonary Hypertension
Pulmonary Hypertension Association
801 Roeder Road, Suite 1000
Silver Spring, MD 20910-4496