ISSN 1933-088X

Advances in Pulmonary Hypertension

Vol 20, No 3; 2021

Official Journal of the Pulmonary Hypertension Association

PAH as a Systemic Disease

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
Kara Kopchinski,
Managing Editor
Allen Press, Inc.

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 Hypertensio*n 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.

The Medical Encyclopedia defines a systemic disease as an entity affecting the entire body, rather than a single organ or body part. So, is PAH, the disease of "high blood pressure in the lungs", as the lay people call it, a systemic disease? I would argue, yes! First of all, PAH is part of several systemic disorders and what happens in the lungs happens also in other parts of the body. This argument is easily won when we think of systemic sclerosis, but not only. Second, PAH is a systemic disease, much like systemic hypertension. Even in its purest form, the idiopathic or hereditary PAH, the rest of the body is affected when various organs begin suffering from inadequate perfusion, initially with exertion, then even at rest. Third, as we begin to end the COVID-19 pandemic, let's not forget about the other, more persistent, duplicitous pandemic, obesity, a systemic disease that also exerts its toxic effects on the pulmonary vasculature.

In this issue of *Advances* we address exactly these aspects of pulmonary vascular disease. Drs. Rahul Argula and Samuel Friedman from the Medical University of South Carolina provide a thorough, nonetheless very practical, overview of the various forms of SSc associated PH and the challenges caused by overlapping forms. They highlight advances in the screening, therapeutic management and risk stratification strategies for the various forms of PH. Lastly, they touch upon the more novel approaches, involving immunomodulatory treatments that are being currently investigated.

I teamed up with my young PH star from Tufts Medical Center, Dr. Divya Menon, to discuss a topic that is often forgotten, both to diagnose and to treat: PH in hematologic disorders. We focused on two main entities: myelodysplastic syndromes and hemolytic anemias.

The impact of obesity on PH (and vice versa) was examined by Drs. Anna Hemnes from Vanderbilt University and Debbie Levine from University of Texas Health Science Center who, very elegantly, explained the complex connections between the metabolic derangements driven by obesity and its effects on the lung vasculature. But what can we do when there is no "magic pill" to make you lose weight? The PHPN corner, led by Claire Parker from Vanderbilt University and authors Ai Jin Lee, Rebecca Alonzo, Charlotte Lipsky, Yessenia I. Ortega, Shannon A. Salveson, and Kathy McCloy, offers practical approaches to wiser and healthier nutrition and exercise for our PH patients, utilizing activity devices and friendly encouragements.

Lastly, I joined forces with Karen Fagan from University of South Alabama, Rod Oudiz from UCLA Medical Center, Panagis Galiatsatos from Johns Hopkins University, and my colleague from Tufts Medical Center, Hap Farber, to talk in a round table about our experiences during the pandemic. All experienced clinicians and PH specialists that worked assiduously in the front line for the past year and a half to battle our common enemy, SARS-CoV19, we shared thoughts on how COVID-19 affected our PH patients and what the measures were to ensure a safe environment and clinical practice from a distance, utilizing virtual visits. We conveyed our surprise that very few PH patients developed severe infection and praised our patients for their sensible approach to a potentially devastating disease.

I thank all the authors for their willingness to contribute to this issue and the *Advances* staff for their hard work, dedication, and enthusiasm. I hope you will enjoy reading it and that it will make you think more globally about PH, as part of the body and the environment.

Dr. Ioana R. Preston
Associate Professor of Medicine
Tufts University School of Medicine
Director, PH Center
Tufts Medical Center
Boston, MA

 DOI:10.21693/1933-088X-20.3.70

REGULAR ARTICLE

Pulmonary Hypertension in Collagen Vascular Disorders: Systemic Sclerosis: An Overview of Systemic Sclerosis-Associated Pulmonary Hypertension

Samuel H. Friedman, MD
Department of Pulmonary, Critical Care, Allergy, & Sleep Medicine
Medical University of South Carolina

Rahul G. Argula, MBBS, MPH
Pulmonary Vascular Disease Program
Adult and Pediatric Respiratory Therapy Services
Medical University of South Carolina

Systemic sclerosis (SSc) is a disease state characterized by a significant lifetime risk for the development of pulmonary hypertension (PH). SSc-associated PH is comprised of a heterogenous array of phenotypes. SSc patients are at risk for both precapillary and postcapillary PH conditions. These include pulmonary arterial hypertension (PAH), PH secondary to interstitial lung disease (ILD-PH), and left heart disease associated PH. SSc-PAH is a vasculopathy that is distinct from idiopathic PAH and probably PAH associated with other connective tissue diseases. This concise review provides an overview of the various forms of SSc-PH, as well as advances in the screening, therapeutic management, and risk stratification strategies for the various types of SSc-PH. As the same SSc patient often displays multiple overlapping PH groups, treatment decisions are complex and often need to be individualized. This review also attempts to provide a rational framework for the management of SSc-PH patients with overlapping disease phenotypes.

INTRODUCTION

Systemic sclerosis (SSc) is a rare multisystemic connective tissue disease characterized by autoimmune dysregulation, chronic inflammation, and collagen deposition resulting in end-organ fibrosis.[1] There are 2 main phenotypes of SSc: diffuse cutaneous SSc (dc SSc) and limited cutaneous SSc (lc SSc), distinguished by the pattern and the extent of cutaneous involvement.[1] Diagnosis of SSc depends on the fulfillment of the 2013 American College of Rheumatology and European League Against Rheumatism classification criteria.[2] Morbidity and mortality in SSc are largely driven by end-organ dysfunction resulting from fibrosis and microvascular obliteration in the lungs, heart, and kidneys. Lung disease is the most common cause of death in the SSc population with interstitial lung disease (ILD) and pulmonary hypertension (PH) being the first and second leading causes of mortality, respectively.[1,3]

According to the Sixth World Symposium on Pulmonary Hypertension (WSPH), PH is classified into groups 1–5 based on the primary etiopathogenesis of the PH (Table 1).[4] SSc patients are at risk for multiple forms of PH.[5] While individual SSc patients can exhibit any one of the following phenotypes of PH, namely: groups 1, 1.6, 2, or 3; in clinical practice, there can be a considerable overlap in the expression of disease phenotypes. SSc-related pulmonary arterial hypertension (SSc-PAH) is the most common form of collagen vascular disorder-associated PAH in North America and Europe.[6,7] A rare subgroup of WSPH group 1 disease, or group 1.6, known as pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (PVOD/PCH) has also been described in SSc patients.[5] SSc-related ILD is a leading cause of morbidity and mortality and WSPH group 3 PH has been reported in SSc-ILD patients (SSc-ILD-PH).[8] Finally, cardiac involvement in the form of myocardial fibrosis and myocardial dysfunction and associated WSPH group 2 PH (SSc-LVD-PH) have also previously been described in SSc patients.[9,10] This concise review aims to provide a brief overview of the epidemiology, screening, and description of the different phenotypes of SSc-PH, their pathophysiology and management.

Diagnosis and Epidemiology

In an SSc patient, the diagnosis of precapillary PH (WSPH groups 1, 1.6, and 3) is made using right heart catheterization (RHC) when the mean pulmonary artery pressure (mPAP) is >20 mmHg, pulmonary capillary wedge pressure (PCWP) is ≤15 mmHg, and the pulmonary vascular resistance (PVR) is ≥3 Woods Units, while a diagnosis of postcapillary PH (WSPH group 2) is made when PCWP is >15 mmHg in combination with similar criteria for mPAP.[11] Further characterization of the exact precapillary PH phenotype requires additional clinical data such as pulmonary function testing (PFT), chest imaging (high-resolution computed tomography [HRCT]), V/Q scan, and echocardiographic data.[4]

The prevalence of PH in individuals with SSc was noted to be around 7% from 1 European meta-analysis of 5 different studies. In this study, 83 out of 1165 individuals with SSc had PH with 77% (51% SSc-PAH, 26% SSc-ILD-PH) having precapillary PH, 21%

Correspondence: friedsam@musc.edu
Disclosure: The authors have no relevant personal financial relationships to disclose.

postcapillary disease, while 2% had PVOD.[7] In the DETECT study, which included 62 participating centers from North America, Europe, and Asia, using a strategy to enrich for SSc-PAH (SSc duration > 3 years and diffusion capacity of the lung for carbon monoxide [DLCO] < 60% predicted), 145/646 screened patients, or 31% were found to have PH. SSc-PAH (WSPH Group 1) was the commonest etiology (19%), while SSc-ILD-PH (WSPH Group 3) and the left ventricular (LV) dysfunction group (WSPH Group 2) had 6% each.[12]

Screening

Given the high prevalence and the lifetime risk for the development of PH in patients with SSc, screening is an important strategy for the early identification of all phenotypes of SSc-PH, especially SSc-PAH. While there have been various, clinical, autoimmune antibody, and lung function testing-based associations with the development of PH in the SSc population, none of these parameters have individually been useful from a PH screening standpoint.[13] The current guidelines recommend annual screening with echocardiograms for all patients with SSc.[14,15] The 2015 European Society of Cardiology (ESC)/ European Respiratory Society (ERS) criteria using echocardiographic parameters comprise an effective strategy to screen for SSc-PAH patients.[14] SSc is the only collagen vascular disorder for which such an echocardiogram-based strategy is currently recommended. Screening strategies using composite screening instruments such as the DETECT or ASIG tools can identify patients with SSc-PAH with a high sensitivity and negative predictive value (NPV).[12]

While these composite screening tools were designed primarily with a focus on SSc-PAH, they perform fairly well with regard to detection of groups 2 and 3 PH as well. In a study by Hao et al,[16] the 2015 ESC/ERS criteria, DETECT, and ASIG algorithms all were able to detect any form of SSc-PH with a sensitivity >95%. In that study, the ASIG algorithm had a sensitivity of 95.8%, NPV of 92.3%, and had the highest specificity and positive predictive values of all 3 algorithms. However, it is important to note that this population was enriched for SSc-PAH. In our practice, we have found the ASIG algorithm very easy to operationalize, as it only requires PFT data and a serum N-terminal pro B-type natriuretic peptide level to implement, and both of these clinical variables are easily available in most outpatient practices (Figure 1).

Table 1. Sixth World Symposium on Pulmonary Hypertension Classification[a]

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 Connective tissue disease[b]
1.4.2 HIV infection
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 (PVOD/PCH) involvement[b]
1.7 Persistent PH of the newborn syndrome
2. PH due to left heart disease[b]
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital or acquired cardiovascular conditions leading to postcapillary PH
3. PH due to lung diseases and/or hypoxia[b]
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4. PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5. PH with unclear and/or multifocal mechanisms
5.1 Hematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

[a]Pulmonary hypertension classifications according to the proceedings from the Sixth World Symposium on Pulmonary Hypertension (WSPH). PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction; HIV: human immunodeficiency virus.

[b]WSPH subgroups prevalent in SSc-PH.

With significant advances in awareness, screening, therapies, and risk stratification, the 1- and 3-year survival rates in incident SSc-PAH patients appear to be similar to those in idiopathic pulmonary arterial hypertension (IPAH) patients, but prospective data from the Pulmonary Hypertension As-

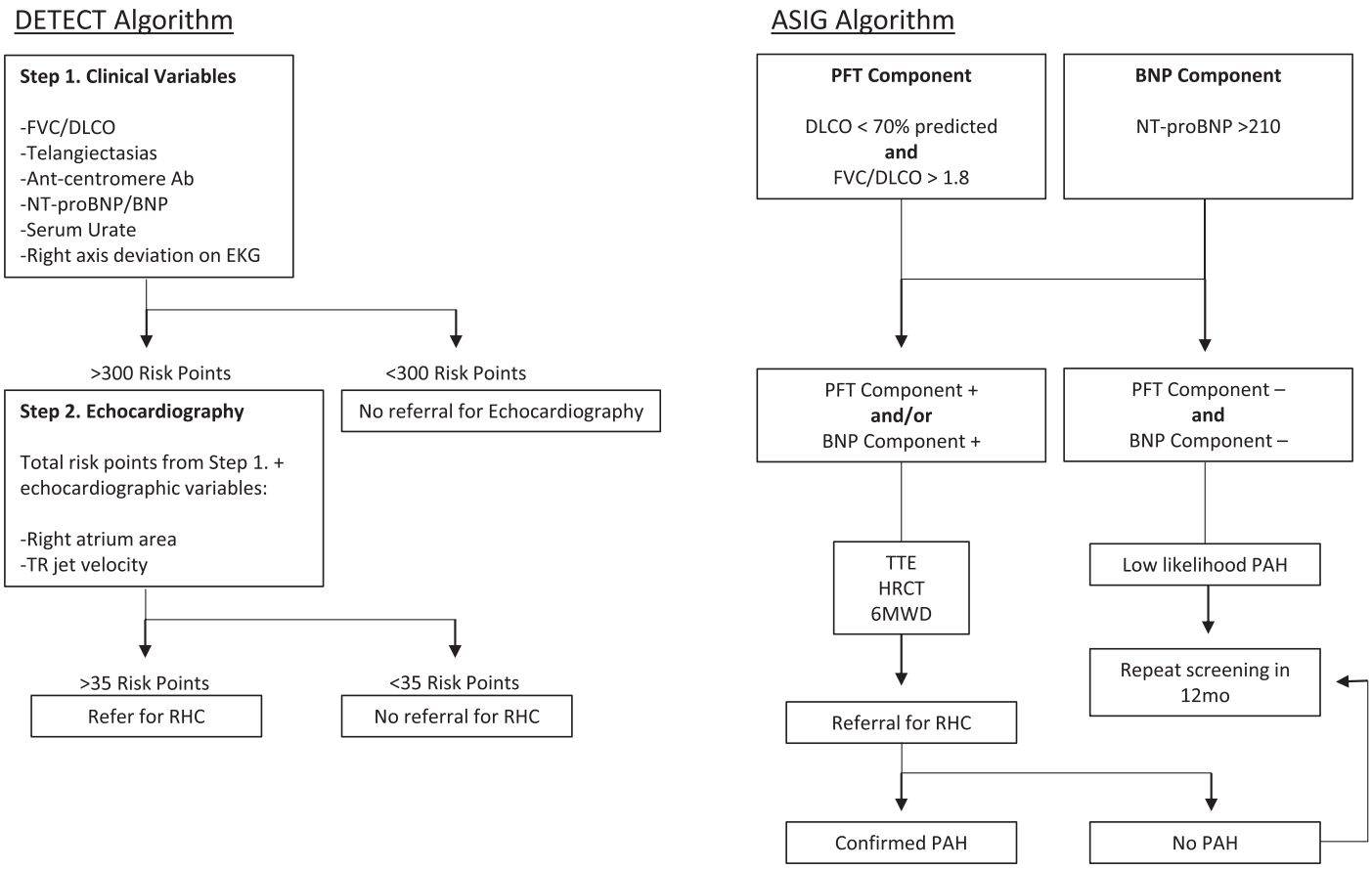

Figure 1: Comparison of systemic sclerosis-associated pulmonary hypertension (SSc-PH) screening algorithms. Side-by-side comparison of screening algorithms for SSc-PH. The DETECT algorithm assigns numerical scores to combined clinical variables using a customized Web-based calculator. This score is used to determine referral for echocardiogram and subsequently right heart catheterization. ASIG algorithm uses PFT and NT-proBNP data to determine patient candidacy for further workup, including RHC. ASIG: Australian Scleroderma Interest Group; NT-proBNP: N-terminal pro B-type natriuretic peptide; DLCO: diffusion capacity of the lung for carbon monoxide; FVC: forced vital capacity; PFT: pulmonary function test; RHC: right heart catheterization; TR: tricuspid regurgitation. Adapted from Hao Y et al.[16]

sessment and Recognition of Outcomes in Scleroderma (PHAROS) registry and other institutional cohorts show that the SSc-PAH population continues to have a long-term survival disadvantage.[17] While lead-time bias could explain some of the improvements in short-term survival rates in the SSc-PAH cohort, earlier intervention with vasodilator therapies and/or diuretics could have prevented or delayed right ventricle (RV) failure and improved survival prospectively.[18] Early detection seems to confer a survival advantage in SSc-PAH when compared with symptom-based evaluation for PAH.[19] Further, 22% of SSc-PAH patients in the PHAROS cohort were asymptomatic at the time of their PAH diagnosis.[20] For this reason, screening for PH and PAH is a valuable strategy in the SSc population.

SSC-PH PHENOTYPES

1. SSc-PAH

While both limited and diffuse SSc patients can develop PAH, the lc SSc phenotype appears to have a higher risk for the development of PAH.[1] PAH is a disease that directly affects the small- to medium-sized pulmonary arteries, leading to vascular remodeling. Initially thought to be analogous to the idiopathic form of PAH, histopathologic analyses more recently suggest that SSc-PAH is a distinct vasculopathy with unique histologic and prognostic characteristics.[21–23] SSc-PAH appears to be different than IPAH, as noted by a lack of plexiform lesions, presence of pulmonary arterial (PA) or arteriolar intimal fibrosis, and some fibrosis of veins or venules.[21] Histologic analyses of SSc-PAH lung tissue have further revealed that PVOD-like lesions and pulmonary vein fibrosis are relatively common in SSc-PAH.[24,25] This may help explain some of the adverse effects associated with the use of PA vasodilators in SSc-PAH patients.

Treatment of SSc-PAH

a. Pulmonary Artery Vasodilators: While there is emerging interest in using adjunctive immunomodulatory agents in the management of SSc-PAH, PA vasodilators are the mainstay of treatment in SSc-PAH. The current guidelines support the use of all PA vasodilators approved for other WSPH group 1 disease patients. These recommendations are based on efficacy and safety data from multiple randomized clinical trials using PA vasodilators that also included SSc-PAH patients.[13,14] There are 3 main pathways currently targeted by available drug therapies: nitric oxide, endothelin,

and prostacyclin pathways. A variety of oral, parenteral, and inhaled formulations are available for the management of SSc-PAH patients.[26]

Most patients now start combination therapy with a phosphodiesterase type V inhibitor (PDE5i) and an endothelin receptor antagonist (ERA). These medications are administered orally and are generally used as first-line agents for PAH owing to their milder side effect profile than prostanoids (prostacyclin pathway analogs). PDE5is were approved for PAH patients after the SUPER and PHIRST trials, both of which included a subset of connective tissue disease-associated PAH (CTD-PAH) (including SSc-PAH) patients.[27,28]

ERAs target endothelin receptors on vascular smooth muscle, thereby preventing the vasoconstrictive effect of circulating endothelin proteins. Ambrisentan, macitentan, and bosentan are the currently approved ERAs. ERA therapy has been shown to improve quality of life and exercise tolerance via 6-minute walk distance (6MWD) in CTD-PAH and SSc-PAH patients, although the beneficial effects in these patients may be attenuated when compared with patients with IPAH.[29–31]

Prostanoids act mainly via binding to the prostacyclin (IP) receptors, activating adenylate cyclase, resulting in the production of cAMP, reducing Ca^{+2} concentrations, and causing vasodilation. To this day, intravenous (IV) prostanoids remain the most potent therapy offered for SSc-PAH patients.[13] Epoprostenol, treprostinil and the IP receptor agonist selexipag are the prostanoids approved for PAH therapy. Epoprostenol is only available in an IV formulation, while treprostinil is available in oral, parenteral, and inhaled routes. Selexipag is administered via the oral route. All the prostanoid formulations have been shown to improve the functional capacity and exercise tolerance (6MWD) in PAH patients, including SSc-PAH patients.[32–36] It is also important to note that optimization of PH in SSc patients involves the use of diuretics, management of arrhythmias, conduction abnormalities, and treatment of coexisting comorbidities such as sleep apnea.[14,37]

b. Immunomodulator Therapy: As noted above, while SSc-PAH is a unique pulmonary vasculopathy, SSc has also been shown to impact the RV adaptation to this pulmonary arteriopathy, which contributes to a greater morbidity and mortality in SSc-PAH.[38] Further, since SSc is a multiorgan disease with an established etiopathogenic basis in immune dysregulation, strategies using immunomodulator therapies as adjuncts in the management of SSc-PAH have garnered some attention. Three categories of immunomodulators studied to date are (a) immunosuppressive, (b) anti-inflammatory, and (c) antiproliferative agents.

A single-institutional, retrospective cohort study exploring the use of immunosuppressive therapy (cyclophosphamide, glucocorticoids) previously showed no benefits in the SSc-PAH population.[39] B-cell depletion, on the other hand, seems to hold some promise. A multicenter, placebo-controlled trial showed that rituximab is safe and well tolerated in SSc-PAH and showed a significant improvement in 6MWD at 48 weeks. Although the study did not meet its a priori established primary outcome, it should be noted that the study was hampered by poor enrollment that forced an alteration of the study design midway through the study.[40]

The antiproliferative agent imatinib, a tyrosine kinase inhibitor was shown in the IMPRES trial to improve 6MWD and hemodynamics among PAH patients including SSc-PAH patients; however, its utility has been called into question due to serious adverse events (intracranial hemorrhage).[41] The CATALYST trial (NCT0265735) evaluating the use of bardoxolone, an NF-κB inhibitor and novel anti-inflammatory agent, in patients with CTD-PAH had to be ended prematurely during the COVID-19 pandemic, after preliminary analyses showed that the study was unlikely to meet its primary endpoint of 6MWD improvement.

Correction of the imbalance in transforming growth factor (TGF) β/BMP signaling appears to hold promise in all forms of PAH including SSc-PAH. While preliminary phase 2 data from FK-506 (tacrolimus) use in PAH showed favorable safety data, therapeutic efficacy was not significant.[42] More recently, the PULSAR trial, another phase 2 study, evaluated the efficacy for sotatercept, a novel TGFβ ligand trap, in PAH.[43] Sotatercept was shown to improve exercise capacity and improve pulmonary vascular hemodynamics in WSPH group 1 PAH patients that included a small number of SSc-PAH patients. Sotatercept is now being studied in multiple phase 3 studies (NCT04576988, NCT04896008, NCT04811092), and SSc-PAH patients are eligible. The new developments in the field of PAH therapeutics are paving a promising and imminent path forward for a more precise and targeted treatment of SSc-PAH.

Prognosis and Risk Stratification

Even though SSc-PAH patients are considered WSPH group 1 and their current management guidelines are similar to those of IPAH patients, the treatment response and prognostic trends of SSc-PAH patients are very different when compared to IPAH patients.[44] While SSc-PAH is a unique pulmonary vasculopathy when compared with IPAH, SSc patients have also been shown to have impaired RV function that is independent of the pulmonary vascular load.[45] In comparison with IPAH, SSc-PAH patients have also been shown to have a reduced RV contractile reserve.[46,47] Further, RV function in SSc-PAH patients does not appear to improve when compared with IPAH patients, despite the up-titration in PA vasodilator therapies over the course of the disease.[48] Therefore, RV maladaptation in SSc-PAH patients is another important contributor to the worsened morbidity and mortality when compared with IPAH patients. While all etiopathogenic mechanisms underlying this RV dysfunction have not been elucidated, 2 major mechanisms appear to be (1) abnormal increase in myocardial fibrosis and (2) diminished myofilament calcium sensing and contractile force.[38]

As previously noted, while there appear to be some short-term survival improvements, SSc-PAH patients continue to have a long-term survival disadvantage.[17] Clinical experience also suggests the presence of multiple SSc-PAH

phenotypes, with some "endo-phenotypes" exhibiting a particularly aggressive disease form and others demonstrating a more stable clinical course. Early and periodic risk assessment could potentially identify those patients at high risk for early decompensation.[49] The 2 widely used risk prediction algorithms are the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL 2.0) risk calculator and the 2015 ESC/ERS risk stratification guidelines.[14,50] The calculator is able to stratify PAH patients into low (<5% 1-year mortality), intermediate (5%–10% 1-year mortality), and high risk (>10% 1-year mortality) categories using a number of clinical variables.[50] The REVEAL 2.0 risk calculator was originally developed for all WSPH group 1 patients and has since been validated in an SSc-PAH cohort; however, it is limited in its ability to predict survival in some of the highest risk SSc-PAH patients.[49]

2. PVOD/PCH

PVOD and PCH are both expressions of the same pulmonary vascular disease which is a subset of WSPH group 1 PAH (1.6). Of all the CTDs, SSc appears to have the strongest association with PVOD/PCH. While the exact incidence and prevalence in SSc patients is unknown, the lc variant of SSc seems to have a predilection for PVOD. PVOD affects the small postcapillary venules, causing a directly postcapillary form of PH that can be difficult to diagnose.[24] The hemodynamic features noted during RHC are like that of an SSc-PAH patient, and so it is challenging to differentiate this disease from PAH. HRCT imaging often reveals signs of PVOD such as interlobular septal thickening, centrilobular ground glass opacities, mediastinal lymphadenopathy, and sometimes pleural effusions. PVOD patients also tend to exhibit more hypoxemia and a significantly lower DLCO.[51] Vasodilator therapy often is not tolerated, and patients can develop pulmonary edema from potent therapies such as ERAs and prostanoids. Disease course is progressive and fatal, and lung transplantation remains the only definitive treatment.

3. SSc-ILD-PH

ILD remains the most common cause of death in SSc patients.[52] Progressive parenchymal fibrosis leads to chronic alveolar hypoxia, hypoxic pulmonary vasoconstriction, and arteriolar remodeling in addition to a progressive loss of pulmonary vascular surface area. These adverse alterations in the pulmonary vasculature lead to elevated pulmonary artery pressures and PH. The dc SSc patients have a higher predilection for the development of ILD.[1] The prevalence of ILD in SSc is estimated to be 25%–50%. While the estimated prevalence of PH in idiopathic pulmonary fibrosis (IPF) is thought to be 30%–50%, the exact prevalence of SSc-ILD-PH is not known.[53] In the DETECT study, which included patients with forced vital capacity (FVC) > 40% predicted and DLCO < 60% predicted, the prevalence of SSc-ILD-PH was 6%.[12] Despite the high prevalence of SSc-ILD, WSPH group 3 PH is not as common as SSc-PAH.[54,55] However, the prognosis of SSc-PH with ILD is particularly poor and likely the worst of any form of SSc-PH, with an estimated 3-year survival rate of 35%.[56]

Parenchymal abnormalities and interstitial changes are widely prevalent in SSc patients. The Sixth WSPH guidelines on group 3 PH define significant parenchymal disease (from a PH standpoint) as FVC < 70% predicted and CT chest that shows extensive parenchymal involvement.[57] Clinical trials of oral or IV PA vasodilators have mostly resulted in no clinical benefits for patients with all forms of ILD-related PH, including SSc-ILD-PH patients. Inhaled prostacyclins seem to hold particular promise in SSc-ILD-PH.[58] The major advantage of inhaled therapy is direct drug delivery to the pulmonary vasculature and, more specifically, direct delivery through functional or ventilating lung tissue without disrupting VQ matching. The recently concluded INCREASE trial in patients with ILD-PH demonstrated that inhaled treprostinil improved exercise capacity when compared with placebo.[58] In that trial, 22% of the participants had underlying CTD, including SSc.

It is important to recognize that, before considering inhaled vasodilator therapies for the ILD-PH patient, the patient's lung disease or hypoxia (supplemental oxygen) and possible coexisting sleep apnea must be addressed first. Similarly, disease-modifying immunosuppression with mycophenolate mofetil or cyclophosphamide may be used to prevent further limit inflammation and progression of pulmonary fibrosis.[59,60] The SENSCIS study demonstrated the efficacy of nintedanib either in isolation or in combination with immunosuppressive therapies in decreasing the rate of progression of SSc-ILD.[61] There is now an emerging role of IL-6 inhibition (tocilizumab) in the management of SSc-ILD.[62,63] Prevention of progression of fibrosis directly slows down the rate of loss of pulmonary vascular surface area and may impact the progression of PH in this disease group. Once ILD management has been optimized, it is reasonable to evaluate and treat residual PH, as discussed below.

Given the high prevalence of some degree of ILD in almost all patients with SSc, differentiating group 1 from group 3 disease can be particularly challenging. Often, patients present with significant pulmonary vascular disease in the background of extensive ILD. These patients would benefit from being cared in pulmonary vascular disease programs with experience in managing SSc-PH patients. In Figure 2 and Table 2, we highlight our approach to the management of an SSc patient with suspected PH.

4. SSc-Associated LV Myocardial Dysfunction-Related PH (SSc-LVD-PH)

SSc can lead to myocardial fibrosis and LV dysfunction resulting in pulmonary venous congestion and subsequent WSPH group 2 PH.[10,37] These patients exhibit an elevated PCWP on RHC, in addition to an elevated mPAP. In addition to primary myocardial inflammation and fibrosis, microvascular coronary disease in SSc may also contribute to myocardial damage.[64] The prevalence of cardiac involvement is estimated to be 50%–80% on autopsy studies; however, clinical heart

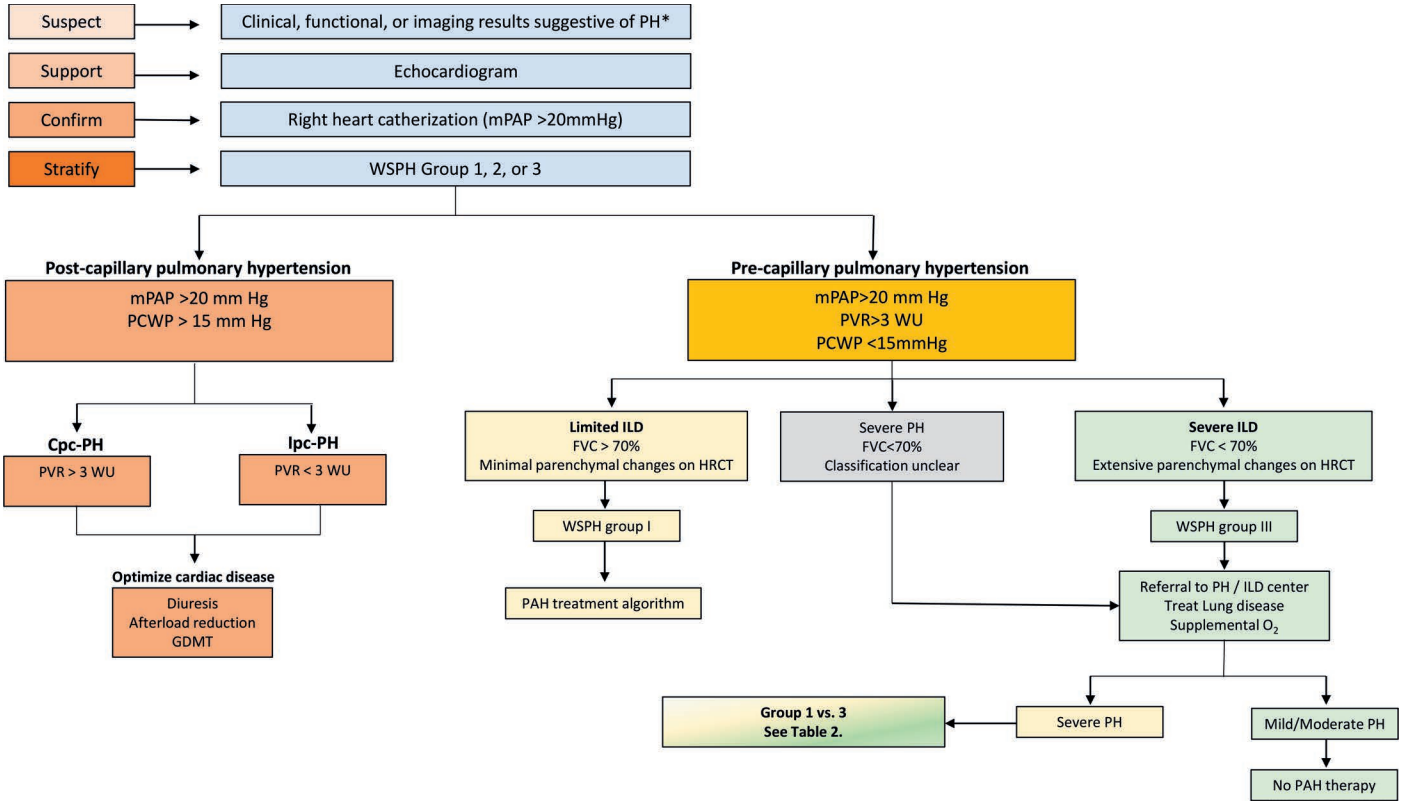

Figure 2: Systemic sclerosis-associated pulmonary hypertension (SSc-PH) algorithm. Proposed approach to screening, diagnosis, subgroup classification, and management of SSc-PH patients. *Clinical findings suggestive of PH may include progressive dyspnea, exercise intolerance, signs of right heart failure on exam, loud P2, electrocardiogram with right ventricle strain, elevated B-type natriuretic peptide, or reduced 6 minute walk distance. CI: cardiac index; Cp-PH: combined precapillary and postcapillary PH; DLCO: diffusion capacity of the lung for carbon monoxide; ERA: endothelin receptor antagonist; FVC: forced vital capacity; GDMT: guideline-directed medical therapy; HRCT: high-resolution computed tomography; Ipc-PH: isolated postcapillary PH; ILD: interstitial lung disease; mPAP: mean pulmonary artery pressure; PCA: prostacyclin agonist; PCWP: pulmonary capillary wedge pressure; PDE5i: phosphodiesterase type V inhibitor; PVR: pulmonary vascular resistance; WSPH: World Symposium on Pulmonary Hypertension; WU: Woods units. Adapted with permission of the © ERS 2021.[57]

failure symptoms are less common.[65] Diastolic dysfunction leading to heart failure with preserved ejection fraction (HFpEF) is the predominant presentation of cardiac involvement in SSc on echocardiography, estimated to affect 20%–45% of patients.[7,66] Occult LV dysfunction is also often unmasked during the management of precapillary PH in SSc patients, often when assessing response to PA vasodilator therapies.[66]

There are currently no SSc-LVD-PH-specific guidelines outside of volume management, diuretic therapy, and periodic monitoring for the development of superadded pulmonary vascular disease later in the disease course. The ongoing research in the field of HFpEF therapeutics could soon yield adjunctive therapies for the management of SSc-LVD-PH patients.

OVERVIEW OF THE MANAGEMENT OF THE SSC PATIENT WITH SUSPECTED PH

Treatment of PH in an SSc patient can be quite challenging given the coexistence of different and competing phenotypes of pulmonary vascular disease, heterogeneity of disease progression, and treatment response. In our experience, there are 3 essential principles for managing PH in the SSc population:

(1) Identifying the appropriate phenotype is important, and often utilizing an expert PH and ILD center with experience in the management of these patients is helpful (Figure 2). In our experience, one of the most challenging aspects of caring for SSc patients with PH is accurate phenotyping. As was highlighted earlier, identifying significant pulmonary vascular disease that is "layered" on top of the background ILD can be an incredibly challenging endeavor.[67,68] While there has been important work done in this area, we use an approach similar to that highlighted by Forfia et al[67] to differentiate the SSc-ILD/chronic obstructive pulmonary disease patient with significant pulmonary vascular disease from the SSc-ILD-PH patient (Table 2).

(2) Risk stratification at baseline and follow-up visits is important to monitor response to therapy and also for consideration of early referral for lung transplantation in nonresponders. It is important to note that the current risk stratification algorithms are validated for use in SSc-PAH patients and are not validated for use in other phenotypes of PH in the SSc population.

(3) Lack of improvement in the quality of life with therapy should prompt reconsideration of the phenotype of PH. Use of PA vasodilators currently is

Table 2. Differentiating World Symposium on Pulmonary Hypertension (WSPH) phenotypes in systemic sclerosis (SSc) patients with lung disease and pulmonary hypertension (PH)[a]

Clinical parameter	Favors WSPH Group 1	Favors WSPH Group 3
Clinical features	Signs of RV failure: Elevated JVP, +AJR	May or may not have signs of RV failure
EKG	RV strain Right-axis deviation RV hypertrophy	May or may not have evidence of RV strain
PFT	FVC < 70% predicted FVC/DLCO > 1.8	FVC < 70% predicted FVC/DLCO < 1.8
Chest imaging	No significant ILD Extent of disease <30%	Severe ILD Extent of disease >30%
Echocardiography	RV/LV ratio > 1.0 TAPSE < 20 mm Moderate-severe systolic IVS flattening Late or midsystolic notching of doppler FVE in RVOT	RV/LV ratio 0.6–1.0 TAPSE > 20 mm Mild systolic IVS flattening Late systolic or no notching of doppler FVE in RVOT
RHC	RAP > 15 mm Hg CI < 2.5 $^{l\text{-}min\text{-}1}$-m^2 PVR > 6 WU	RAP < 15 mm Hg CI ≥ 2.5 $^{l\text{-}min\text{-}1}$-m^2 PVR < 6 WU
CPET	Breathing reserve < 20% O_2 pulse reduced VE/VCO_2 slope significantly increased	Breathing reserve < 20% O_2 pulse normal VE/VCO_2 slope normal or slightly increased

[a]Evaluation of the complex SSc patient with PH and lung disease. Evaluation of different clinical parameters may help identify patients favoring a WSPH group 1 or a WSPH group 3 phenotype and which patients may have a positive response to pulmonary vasodilator therapy. AJR: abdomino-jugular reflux; CI: cardiac index; CPET: cardiopulmonary exercise testing; DLCO: diffusion capacity of the lung for carbon monoxide; EKG: electrocardiogram; FVC: forced vital capacity; FVE: flow velocity envelope; ILD: interstitial lung disease; IVS: interventricular septum; JVP: jugular venous pressure; LV: left ventricle; PFT: pulmonary function test; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RHC: right heart catheterization; RV: right ventricle; RVOT: right ventricular outflow tract; TAPSE: tricuspid annular plane systolic excursion; VCO_2: volume of exhaled carbon dioxide; VE: expired ventilation; WU: Woods units. Table adapted from Forfia et al. [67]

reserved for treatment in the SSc-PAH population, while inhaled vasodilators seem to hold promise for the management of SSc-ILD-PH. Use of PA vasodilators in the other phenotypes of PH in the SSc population is not encouraged outside of clinical trials at this time.

SUMMARY

SSc-PH comprises multiple phenotypes, and an accurate identification of the phenotype of pulmonary vascular disease is critical to the successful management of these patients. Screening is important to identify patients at an early stage to be able to effectively delay or prevent the progression to RV failure. SSc-associated pulmonary vascular disease is unique, and novel therapeutic targets could lead to a more tailored approach to treating this challenging group of patients.

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REGULAR ARTICLE

Hematologic Disorders and Pulmonary Hypertension

Divya Padmanabhan Menon, MBBS
Pulmonary, Critical Care, and Sleep Division
Tufts Medical Center
Boston, MA

Ioana R. Preston, MD
Pulmonary, Critical Care, and Sleep Division
Tufts Medical Center
Boston, MA

INTRODUCTION

Group 5 pulmonary hypertension (PH) has long remained an elusive entity. Data over the past decade have consistently shown links between hematologic disorders and pulmonary vascular disease. PH due to hematologic disorders exemplifies how pulmonary vascular disease is intertwined with vascular abnormalities at the systemic level.

At the last (6th) World Symposium on PH in 2018, Group 5 PH was defined as "PH with unclear and/or multifactorial mechanisms," and PH secondary to hematologic disorders forms Subgroup 5.1 (Table 1).[1] This subgroup includes 2 primary and very important etiologic entities, namely chronic hemolytic anemias and myeloproliferative disorders, both of which will be discussed in detail. Postsplenectomy PH was previously considered a unique subgroup in this category. However, at the 6th World Symposium, it was deemed a risk factor, rather than a unique clinicopathologic entity, given its role in the development of PH in other hematologic conditions, such as β-thalassaemia,[2] or in chronic thromboembolic PH (CTEPH, Group 4 PH).[3]

MYELOPROLIFERATIVE DISORDERS

The 2008 World Health Organization classification of chronic myeloproliferative disorders include multiple entities as listed in Table 2.[4] Of these, patients with chronic myelogenous leukemia, polycythemia vera (PV), primary myelofibrosis, and essential thrombocythemia (ET) are at particularly high risk of PH.

Prevalence of PH in myeloproliferative disorders (MPDs)

Several small studies have evaluated PH via echocardiography (defined as a right ventricular systolic pressure >35 mm Hg) in myeloproliferative disorders (MPDs) with a widely variable estimated prevalence. Two studies in cohorts of under 50 patients each reported echocardiographic PH prevalence rates of over 40% in ET.[5,6] More recently, larger studies have reported lower prevalence rates, although higher when compared to the general population. For instance, in a 2020 study by Lopez-Mattei et al,[7] out of 143 patients with myelofibrosis, 14% had echocardiographic PH, and these patients had significantly elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Similarly in a study screening 183 MPD patients with transesophageal echocardiograms (TTEs), 7.7% were found to have echocardiographic signs of PH.[8] However, in a recent meta-analysis examining 17 studies evaluating PH in MPDs, it was found that studies using TTE estimated a prevalence of 5-fold higher than those using right heart catheterization for the PH diagnosis.[9]

Etiopathogenesis of PH in MPDs

PH in MPDs develops via multiple pathologic mechanisms resulting in unique phenotypes.

CTEPH is one of the most prominent phenotypes in MPD patients. MPDs induce a state of hypercoagulability, historically widely reported in PV and ET and more recently even in myelofibrosis. In a seminal study that followed over 1200 PV patients over a 20-year period, arterial and venous thrombotic events were reported in 41% patients, with nearly 64% of these occurring at or prior to diagnosis of PV.[10] Studies in ET have reported thrombotic rates of nearly 30% and myelofibrosis around 11%.[11]

Table 1. Group 5: PH With Unclear and/or Multifactorial Mechanisms[a]

5.1 Hematological disorders • chronic hemolytic anemias • myeloproliferative disorders (MPDs)
5.2 Systemic and metabolic disorders (eg, Gaucher disease)
5.3 Other disorders including fibrosing mediastinitis
5.4 Complex congenital heart disease

[a]Adapted after Simonneau et al.[1]

Table 2. WHO Classification of Myeloproliferative Neoplasms[a]

Chronic myelogenous leukemia, *BCR-ABL1*–positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
Myeloproliferative neoplasms, unclassifiable

[a]Adapted after Vardiman et al.[4]

Key Words—hemolytic anemias, myeloproliferative disorders, pulmonary hypertension group 5, sickle cell disease
Correspondence: ipreston@tuftsmedicalcenter.org

 DOI:10.21693/1933-088X-20.3.80

In addition to high platelet count or red blood cell counts directly induced thrombosis, hyperviscosity is a major independent risk factor. Differential peripheral displacement of platelets in high red blood cell load states causes shear-induced platelet activation and consequent thrombosis.[12] Altered red blood cell and leukocyte membrane structure also promote clot formation in MPDs as does polymorphonuclear leukocyte activation due to Janus Kinase-2 mutations. In addition to large clot burden, microscopic tumor emboli also form within the pulmonary vasculature. Age, prior thrombotic events, cardiovascular risk factors[13] and the presence of inherited thrombophilia such as the Factor V Leiden mutation, all further increase the risk of thrombotic events in these patients. As mentioned previously, splenectomy, often used in the therapy of certain hematologic disorders, can induce a hypercoagulable state. In a study evaluating postsplenectomy portal venous thrombosis, a 2% rate was reported, with this number rising up to 10% in patients with underlying hematologic diseases.[14]

Drug-induced PH in MPDs is also an important entity. Tyrosine-kinase inhibitors, which are frequently used in MPD therapy, have been implicated by several studies and have been associated with precapillary forms of PH, resembling Group 1 pulmonary arterial hypertension (PAH). In the French PH registry, a PH incidence rate of 0.45% was reported in chronic myelogenous leukemia patients treated with dasatinib. Clinical or hemodynamic improvements were reported with drug discontinuation in the majority of these patients.[15] Several other drugs in the tyrosine-kinase inhibitor class have been associated with PH in smaller studies. In addition, chemotherapy-induced pulmonary veno-occlusive disease is now an increasingly recognized cause of pulmonary vascular disease. A 2016 study evaluating patients with pulmonary veno-occlusive disease in the French registry revealed that 83.8% of these patients had been exposed to alkylating agents, with 43.2% having received cyclophosphamide.[16] Bone marrow transplantation can also amplify the risk of pulmonary veno-occlusive disease in the MPD population.[17]

Portopulmonary hypertension is one other potential cause of pulmonary vascular disease in MPDs. Portal hypertension was reported in 13.8% of serial patients with PV, ET, and myelofibrosis seen at a hematology clinic.[18] In a meta-analysis of studies reporting hepatic vascular thrombosis in hematologic neoplasms, the mean prevalence of MPDs and Janus Kinase-2 mutations was 31.5% and 27.7% in patients with portal venous thrombosis.[19] While not all portal venous thromboses result in portopulmonary hypertension, it does increase the risk of its occurrence in these patients. In addition to thrombotic complications, direct extramedullary hematopoiesis in the portal vasculature has been postulated as a mechanism of portal thrombosis.[20]

Pulmonary extramedullary hematopoiesis and myeloid metaplasia has also been described within pulmonary vasculature of MPD patients, leading not only to an obstructive physiology, but also an inflammatory vascular remodeling simulating PAH arteriopathy.[21]

Management of MPD-PH

To date, there are no data or clinical trials evaluating PAH-specific therapy in MPD-PH. The focus of therapy remains the treatment of the underlying hematologic pathology. There are no specific data or society recommendations on additional anticoagulation or antiplatelet therapy in this population either. For instance, in PV, antiplatelet prophylaxis is standard of care, but its impact on pulmonary venous thromboembolism and PH remain unclear as does the role of additional anticoagulation. While cytoreductive therapy such as hydroxyurea can be used in high-risk patients to prevent thrombotic events, data on its effect on pulmonary vascular pathology remain limited to isolated case reports.[22] Similarly, mitigation of PAH postallogenic bone marrow transplant in myelofibrosis has been reported, but robust studies remain lacking.

In a case series by Guilpain et al[23] in 2008 reporting the clinical features and management of 10 patients with MPD PH, 6 were found to have CTEPH and 4 with other forms of MPD PH. All 4 patients with proximal CTEPH had an underlying diagnosis of PV. Three of these successfully underwent thromboendarterectomy and 1 with end-stage right heart failure was treated with a combination of surgery and inhaled iloprost but eventually died of right heart failure. Two patients with distal CTEPH were medically managed with bosentan, 1 of whom died of right heart failure. All patients were treated with cytoreductive therapy +/- phlebotomy. Among the 4 patients with non-CTEPH MTD PH, all received cytoreductive therapy and only 1 received PAH-specific therapy with epoprostenol. All 4 died, 2 of whom from right heart failure. While riociguat is currently the only approved therapy of nonoperative CTEPH (Group 4 PH), there are no specific studies or recommendations for the treatment of CTEPH in the setting of MPDs.

In the recent past, there has been interest in the use of Janus Kinase-2 inhibitors in MPD PH. In 15 patients with myelofibrosis and echocardiographic parameters of PH, improvements were seen in NT-proBNP and right ventricle (RV) function post therapy with ruxulotinib, but not with other conventional agents.[24] In addition, recent preclinical data in PH animal models have shown that ruxolitinib attenuates pulmonary artery smooth muscle cell proliferation and improves pulmonary hemodynamics and RV remodeling. These data taken together are indicative that the Janus Kinase-2 pathway may be of special interest in the niche subset of MPD PH as a novel therapeutic target.

CHRONIC HEMOLYTIC ANEMIAS

Of the chronic hemolytic anemias (CHAs), several entities have been associated with PH, such as paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis, sickle cell disease (SCD) and thalassemia, the latter 2 being associated with a much heavier pulmonary disease burden.

Prevalence of PH in CHAs

Several studies have reported mortality correlations with tricuspid regurgi-

tant jet velocity (TRV) and estimated pulmonary artery systolic pressure on TTE in SCD.[25] A study that screened 398 patients with SCD with TTE and then proceeded with right heart catheterization if the TRV was at least 2.5 m/s, reported a 27% prevalence of PH based on TTE and 6% (24 patients) when confirmed by right heart catheterization.[26] Among the 24 patients with PH, 11 had normal pulmonary capillary wedge pressures, indicating a precapillary arteriopathy. Similarly, in a study that screened echocardiographically 529 SCD patients with subsequent right heart catheterization in 84, precapillary PH was confirmed in 10.4% of patients. Of note, mean pulmonary artery pressure, diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance all independently correlated with mortality.[27] Median survival was 6.8 years in those diagnosed with precapillary PH. The ATS guideline statement for PH in SCD proposes an increased risk for mortality defined as a TRV ≥ 2.5 m/s, an NT-proBNP ≥ 160 pg/mL, or PH confirmed by right heart catheterization.[28] Echocardiographic screening per their recommendations should be performed every 1 to 3 years in adults. In patients with TRV ≥ 2.5 m/s, prior venous thromboembolism, more severe hemolysis or frequent pain crises, a shorter duration interval for repeat TTEs should be used. Guidelines from other bodies including the American Society of Hematology and the National Lung, Heart and Blood Institute vary and screening remains an area of controversy at this time.

Studies in thalassemia similarly report variable prevalence rates based on TTE vs right heart catheterization screening. However, a recent large multicenter study of over 1000 patients with β-thalassemia reported a PH prevalence of 2.1% based on invasive hemodynamics.[2]

Etiopathogenesis of CHA PH

PH in CHAs is multifactorial, involving a combination of factors ranging from direct effects of hemolysis and hypercoagulability to pulmonary vascular complications of CHA therapy.

Group 2 PH is common in this cohort because of restrictive cardiomyopathy and other risk factors for diastolic dysfunction[29] including hypertension, end stage renal disease, high output failure from anemia, etc. Hypercoagulability from the activation of prothrombotic factors in SCD and from asplenia increases the risk of CTEPH. Proposed pathogenic mechanisms of PH include depletion of nitric oxide by hemolysis-induced release of arginase-1, circulating free hemoglobin, endothelin-1 upregulation, and proliferative arteriopathy from vascular endothelial growth factor upregulation, all contributing to the dysfunction of the pulmonary vasculature.[30]

Management of CHA PH

Screening: As previously mentioned, the ATS guideline for SCD PH recommends echocardiographic screening every 1 to 3 years in adults. In high-risk patients (eg, high hemolytic burden), more frequent screening intervals are recommended. Based on several studies correlating TRV to SCD PH outcomes, the ATS proposes the following:

- In those with TRV ≤ 2.5 m/s: routine screening continued
- TRV 2.5 to 2.9 m/s: consider increased frequency of screening and escalate SCD therapies. If patients are symptomatic, have a decreased 6-minute walk distance or increase in NT-proBNP, then right heart catheterization is recommended.
- TRV ≥ 3: right heart catheterization for definitive diagnosis.

Therapy: Aggressive management of the underlying hematologic dyscrasia is recommended. Hydroxyurea is well described in SCD literature to reduce the incidence of thoracic complications including acute chest syndrome and should be initiated in patients with PH or evidence suggestive of pulmonary vascular disease such as an elevated NT-proBNP. Chronic transfusion therapy to maintain low levels of sickled red cells can be used in this population if hydroxyurea is contraindicated.[28] Supportive therapy such as supplemental oxygen and cautious diuresis (to prevent acute sickling) should be considered. Patients with SCD and PH are reported to have a higher risk of venous thromboembolism than SCD patients without PH.[31] However, SCD also carries an inherent risk of cerebral and other hemorrhagic events. Hence, as the guidelines stand, in patients with SCD PH without an elevated risk of bleeding, lifelong anticoagulation is recommended if diagnosed with current or prior thromboembolic events.[28]

Regarding PAH-specific agents, there have been very few directed clinical trials examining their use in SCD PH. The ASSET 1 and 2 trials, which evaluated bosentan in patients with SCD PAH and SCD pulmonary venous hypertension, respectively, reported a trend toward an increase in cardiac output and decrease in pulmonary vascular resistance. However, no conclusive results could be derived since the studies were prematurely terminated due to slow enrollment.[32]

The Walk-PHaSST study that evaluated the use of sildenafil in SCD PH confirmed by right heart catheterization was prematurely terminated for safety due to an increased risk of crises events.[33] As a consequence, PDE5 inhibitors are avoided in this population. Riociguat has been examined in a limited case series of SCD CTEPH and an improvement in 6-minute walk distance, pulmonary vascular resistance, and cardiac output was reported.[34] In a small case series reporting inhaled, subcutaneous, and parenteral prostanoids in patients with SCD PH and SCD CTEPH, an improvement in right ventricular systolic pressures was reported with variable change in functional status and 6-minute walk distance.[35]

CONCLUSIONS

PH associated with hematologic disorders remains a heterogeneous and challenging group of clinical entities. The relative rarity and/or variable clinical presentation of many of these disease processes has made it challenging to study these entities in randomized clinical trials and make recommendations of a unifying treatment that can be applied broadly. While the main focus for therapy is the underlying disease process, greater understanding may be gained from future preclinical studies focusing on identifying

the pathogenic mechanisms of pulmonary vasculopathy and the development of prospective registries.

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Obesity and Pulmonary Hypertension: A Discussion With Deborah Jo Levine and Anna Hemnes

In this special discussion for the Pulmonary Hypertension Association, Editor-in-Chief Deborah Jo Levine, MD, Professor of Medicine, Pulmonary and Critical Care, Medical Director of Lung Transplantation, and Director of Pulmonary Hypertension at the University of Texas Health Science Center in San Antonio, spoke with Anna Hemnes, MD, Associate Professor in the Division of Allergy, Pulmonary and Critical Care Medicine at Vanderbilt University Medical Center.

Dr Levine: Today, I'm speaking to Dr Anna Hemnes, who is Associate Professor and the Associate Director of Pulmonary Hypertension at Vanderbilt University. Today, we are discussing how obesity affects pulmonary hypertension. I think it will be a really great discussion. I look forward to it. Welcome, Anna.

Dr Hemnes: Thanks so much, Debbie. I'm really excited to be here. Good afternoon to you, too.

Dr Levine: There's so many questions on this topic from all perspectives: from our patients, from our referring docs, as well as our own centers. How these 2 issues are related. The most frequent questions that comes to mind are, "Does obesity cause pulmonary hypertension? How are they associated with each other? Does obesity worsen PH?"

Dr Hemnes: I think that is the most fundamental question that we are trying to answer in our basic science lab, and also, people are trying to approach using epidemiologic studies right now. Certainly, it's clear that in cohorts of patients with pulmonary hypertension, obesity is common, which brought up this question of whether obesity predates pulmonary hypertension and whether obesity might cause it. The average BMI in most American, and even now European, cohorts of pulmonary hypertension patients is about 29 to 31, so it's pretty common.

In our lab, we have done experiments where we took normal mice and just fed them a high-fat diet and made them obese. We found that they do increase their pulmonary artery pressures just being fed a high-fat diet alone,[1] compared to mice that are eating standard chow, but that doesn't really answer the question about the epidemiology in humans. We obviously won't do a similar experiment in people because it would be unethical. There are, though, some large cohort studies that have followed patients over time, using echocardiography, and looking at how BMI might relate to right ventricular changes and estimated PA systolic pressure. There's a nice publication that was, within about the last year, in the CARDIA cohort, and they were able to show in that BMI correlated with higher echo estimated PA systolic pressure at baseline, so people who were at a higher BMI had higher PA systolic pressure, and probably more importantly, the more weight that people put on, the more their BMI went up, the higher their RVSP went, as they measured them echocardiographically over time.[2] Based on this, I would suggest that increasing BMI may very well correlate with rising RVSP on echocardiogram over time.

Then, there's a publication from Evan Britain and colleagues using the deidentified medical record at Vanderbilt that had linked genetic data. They used this genetic data to perform a Mendelian randomization study using a polygenic risk score and were able to find that higher BMI is a modifier of pulmonary hypertension severity on echo.[3]

I do think that there is accumulating evidence that obesity may at least contribute to pulmonary hypertension. I don't think we can say right now what kind of pulmonary hypertension it is, whether it's PAH or Group 3 pulmonary hypertension related to obesity, or whether there's some direct toxicity of some feature of obesity on the pulmonary vasculature.

Dr Levine: That is incredibly fascinating work. I just wonder how we can tease that out, especially in the first trial, about echocardiography and PH. We know there are challenges evaluating the RVSP or PASP in obese patients because of inadequate or difficult windows to assess. Knowing that, how confident can we be on the associations when we know the echo findings may be quite variable in this group of patients?

Dr Hemnes: Yes. I think that's a great point. The one nice thing about these studies, like the CARDIA study that I mentioned, is that the patients had highly standardized echocardiography, and that were usually overread by Central readers, so you know that the quality in those studies is pretty high, at least as high as you can get. We do have to acknowledge, as you said that being obese does make echo windows hard to read, sometimes. The studies like the one that I mentioned from Vanderbilt, where there's not a prescribed protocol and overread by a Data Coordinating Center, have a little bit less confidence, I think, in the echo findings. Certainly, in my clinic, we do find, sometimes, patients are referred with obesity, and it's really hard to get a sense of how good quality the echo is. Sometimes there's comments that it's a poor quality window and the RVSP might be elevated, or there might be right ventricular changes, but unfortunately, because of just the quality, technically, it's hard to tell. What is your experience with that?

Dr Levine: It is exactly the same situation you are describing. It makes it difficult to really know how accurate the reading is. I don't know if there's any

 DOI:10.21693/1933-088X-20.3.84

longitudinal studies with serial echoes looking at RVSP/PASP and morphology of the right heart before and after a large amount of weight gain. Have you seen any work of this nature?

Dr Hemnes: Very limited. I think just that CARDIA one is the only one that I can think of off the top of my head. The converse, though, is another interesting question, what about folks who have had massive weight loss, do their echocardiographic changes reverse? Probably the best way to study that would be in the group of patients who have a gastric bypass and have a pretty rapid weight loss? We are working in my lab right now trying to do that study here, and I think the data will be pretty informative, regardless of what we find.

Dr Levine: I think it'll be really important to really elucidate this association between obesity and PH, and really trying to elucidate what that means.

We know now that there is some kind of association, but do we know how obesity impacts the outcomes in PH, whether it be PAH or any of the other groups?

Dr Hemnes: Yes. That is a really interesting question to me. There have been a couple of recent publications that are relevant to that. The first I'll mention came from the Pulmonary Hypertension Association Registry, which is nice to see that that is producing really high quality and meaningful data. Using the PHA Registry, this is PAH patients specifically, Jeff Min and colleagues were able to show that obesity is associated with worse metrics and quality of life.[4] However, it was associated with improved outcomes, so people who were obese tended to live longer, even though they felt worse.

Then there was another study from the Veterans Affair cohort by Aaron Trammell and colleagues, that was recently published, that showed that the people in this Veterans Affair cohort that was essentially an untyped pulmonary hypertension. You couldn't say it was PAH rather it's unspecified pulmonary hypertension. They found that obese patients tended to live longer, and the people with the lowest BMI had the shortest survival.[5] Both of these, together, are pointing to this obesity paradox that has been described in other disease states and suggest that obesity, while it may be linked to development of disease, may actually be associated with better longevity when their disease was established.

I'm not saying that we should advocate for people with PAH or any kind of pulmonary hypertension to go out and gain weight so that they can improve their mortality because I don't think that that's true at all, but it may speak to the role that nutritional status plays in survival in pulmonary hypertension of all causes.

Dr Levine: That is so interesting, When you think about these patients who are obese, whether they have other characteristics of the metabolic syndrome, including heart disease, hypertension, diabetes, it really doesn't correlate to what you would think, in terms of survival.

Dr Hemnes: Yes, I totally agree. To me, I do think, though, certainly, people who have lower body weights sometimes are our sickest patients, but that may be that they're using so many calories to maintain their cardiac output and can't really maintain their nutrition. I don't think we have enough granularity yet to know whether it's these folks that are on the lower end of BMI that are driving the data or whether it truly is a survival benefit related to being obese.

Dr Levine: There is however, a big difference between overweight and obese, so how should we work with our patients in terms of losing weight. What are the expected effects of weight loss on PH? Even if they feel better because they have other improvements in their quality of life, should we be encouraging them to lose weight because of this data?

Dr Hemnes: My practice has been for people who are overweight or obese, to encourage them to lose weight. Probably like you, I did this mental calculation: if they're only able to pump so many liters a minute of blood, based on their fixed cardiac output, then having more body means that you're not able to deliver as much blood per unit weight as they would if they weighed less, and so they'd feel better if they lost weight. In fact, I've had a couple of patients who have lost significant weight, intentionally, and they have told me that they really feel markedly better despite no change in PAH therapy. They can do more, then they're less out of breath.

Sometimes, people tell me they also feel better for other reasons, like their osteoarthritis doesn't hurt as bad, or there are other disease comorbidities, so diabetes doesn't require as much intervention as it would otherwise. I have generally told people to lose weight if they're overweight or obese. I don't think these data are going to change my practice. I generally think we should aim for patients to have a normal weight. The same way, if I have people who were underweight, I try to encourage them to eat and maintain a normal BMI. It does call into question whether that advice is good advice, but I guess that's a personal decision about this issue of quality of life being worse for people who are overweight. What do you tell your patients?

Dr Levine: It's hard because I think we both live in states where there is a high proportion of overweight people. Sometimes, it is difficult to say what is a normal weight. It's hard because it is a spectrum. For our patients, it is hard because what's normal in terms of some populations is not normal for others. We know that obesity is a BMI greater than 30 or morbid obesity over 35. These are the patients that weight loss should help their quality of life and hopefully mortality.

If someone is just mildly overweight, I would say, just make sure you're still doing your physical rehab, trying to eat right. We already all counsel our patients on using a low salt diet, it is important we continue to talk to them about healthy eating in other realms as well.

I feel it's a patient-to-patient basis and, really, a spectrum. Where I do think it's important, is when a patient is obese and needs to be evaluated for lung transplantation. I think if we're thinking

one step ahead in this population, that's another thing to look at.

Dr Hemnes: Yes, that's a really good point. I often encounter that as well because, like you, we live in a state that has a lot of obesity, and it's particularly sad when you have people who are medically capable of having a lung transplant, but really, the only thing that keeps them from that is their BMI. It's an important concern.

Dr Levine: It is. If patients do have problems losing weight, and you feel like it's important, either for lung transplantation or just quality of life or decreasing other comorbidities, would you offer these patients, or do you have any experience with bariatric surgery in PH patients?

Dr Hemnes: I had a patient, probably about 10 years ago, who had a BMI of about 54, who, unbeknownst to me got to the point where she was getting ready to have bariatric surgery and came to me wanting medical clearance. I told her that I didn't think that was a great idea, and we generally didn't recommend elective surgery in our patients. She basically told me that she didn't care what I said, and she was going to have the surgery no matter what. We decided to support her and try to get her through surgery, which occurred without complications. We got a right heart catheterization and echo on her pre-op and also repeated these post-op. Within about a month of her gastric bypass surgery, before her weight loss had really occurred, she had rapid improvement of RV function on echo. Her PVR actually, over time, fell, while her cardiac output went up, which is the opposite of what you'd expect with weight loss.

Based on this, I have not become somebody who recommended gastric bypass surgery to my patients because I still think that there's risk associated with any surgery, but when patients come to me and say, "This is something that I feel like I need to do for my quality of life. I'm miserable being as overweight as I am," I no longer say, "I think that's a terrible idea." In our practice, we've probably had about 5 or 6 people who have had bariatric surgery, mostly by doing a gastric bypass. Some of them have had improvements in their pulmonary hypertension, but most of them have had improvements in their symptoms and their ability to walk further on the 6-minute walk test. I don't feel like the science is such that we would advocate for doing this as a treatment for pulmonary hypertension at all. I do think patients who do not have severe right heart failure or a lot of risk for poor outcomes associated with surgery may be candidates for a gastric bypass if they feel like that's appropriate for their own quality of life. Have you had any patients that have done this?

Dr Levine: Yes. Again, like you, they haven't been patients who are severe. They've been patients with more mild PH, some with moderate and none with severe. On this topic, there are so many different types of procedures performed on for weight loss now. Do we look towards the least invasive? Obviously, the severe patients, you're not going to advocate for that, but at what point would you start to discourage that type of procedure, in terms of their severity?

Dr Hemnes: That's a hard question. People who have more-than-moderate RV dysfunction, hospitalizations for heart failure, use of parenteral prostacyclins would make me nervous.

Dr Levine: I agree. I definitely agree.

Dr Hemnes: Those would be the main ones that I think.

Dr Levine: It's almost like you would want to recommend it early on in their progression, but you still want to see if they can lose weight on their own, but maybe sooner rather than later. These procedures seem to be improving, with less risk than they were even 5, 10 years ago, but it's still a procedure, it's still a surgery, and I still worry about it. I discourage it, probably, more than not, because, obviously, the people that you see, the people I see, are not going to be these people with a mean PAP of 22. These are people who've progressed farther. It is a difficult decision, and I think it comes up a lot.

Dr Hemnes: I think it comes up a lot in our clinic. I can think of several patients, off the top of my head, who I think their main limitation to their quality of life is their obesity, and yet, I don't recommend or bring up bariatric surgery because of my concerns about their operative mortality.

Dr Levine: How often, and not for a conditioning activity, but more for weight loss, how often are you prescribing or recommending pulmonary rehab for weight loss, specifically?

Dr Hemnes: I have not had success with getting people into pulmonary rehab for weight loss. I do recommend increased activity, joining SilverSneakers at the YMCA, getting outside and taking walks, being more active, and that sort of behavior change. I usually just recommend pulmonary rehab for getting people more active with pulmonary hypertension. Have you recommended pulmonary rehab for obesity?

Dr Levine: I don't know if it's always a pulmonary rehab program, but I do try to get them to do as much activity as they are able. If we can get them into a pulmonary rehab, because of their heart or lung disease, then I think it's almost like a really good jump-off point for them to do it on their own. Sometimes, that's what it takes. Some kind of organized course or class or monitored setting where they feel, "Okay. It's fun and I can do it," and then they maybe continue it when the course is over.

For pretransplant patients, whether it be PH or ILD or a different lung disease, the people who do pulmonary rehab once they go to it, they seem to carry on better after they've done it, than before trying to start it on their own. The big questions are "can you always get it paid for?", number 2, "will they go?" and number 3, "is there a facility convenient to their home?"

Dr Hemnes: I agree, though. The folks that have engaged in pulmonary rehab, almost universally, found it to be

tremendously helpful and set up a habit for them that they were able to continue and oftentimes have lost weight and feel a lot better. I recommend it pretty much to everybody. Not everybody feels like they have the time or the resources to be able to do it, but I really think it's beneficial.

Dr Levine: I think that's, nationwide, a big problem for our patients and other patients with end-stage lung disease, especially in smaller towns and places where there's not as many resources, not as many big hospitals or centers. Sometimes, trying to get them in cardiac rehab, something is so important but very difficult. Maybe we're putting our money in the wrong places.

Dr Hemnes: We just did a trial that was published in Chest, within the last few months, that looked at a mobile health intervention in patients with PH.[6] People were given Fitbits and randomized either to a text-based intervention to increase their step counts per day or just the usual care where we said essentially, "Walking is good for you." It looks like the text-based intervention did improve step counts by about 1500 steps per day in the intervention group compared to the placebo. There was a reduction in visceral fat in the intervention group.

I think we, as a country, and particularly our field, need to think creatively about how we can get rehab more accessible to people, and whether it's a telehealth delivery model or a text-based intervention. I think we need to recognize that it's hard for people to travel to rehab centers, or they don't have time, even if they lived in a big city and it's close to them. We need to think more creatively about how to deliver exercise to our patients.

Dr Levine: I agree, and I think that a lot of it comes down to motivation and how we motivate them. There's one patient I had who is 68 years old. Her daughter says, "You have to get 10 000 steps a day." She never likes to go outside, and she'd walk around her kitchen island, and she would not go to sleep until she had her 10 000 steps every day. Now that is motivation. I think it comes down to, how do we, not only find different tools, but how do we motivate them that this is really the right thing to do, and probably the best thing they could do for themselves to be able to use whatever oxygen they do have more efficiently? We've got to figure out a way too, to make that believable to them.

Dr Hemnes: Yes, I totally agree. To do a better job of conveying the benefits of exercise, like how much better people feel and the motivating features to do it.

Dr Levine: Exactly. That will be a great addition to the literature. I think all of those new tools, which all of us learned more about during the pandemic, are going to be useful for all of our patients, especially those that do live out in rural areas and don't have these opportunities that people who live in town do.

I'd like to ask you a couple of questions at the end of our session about trials of metabolic interventions, whether it'd be fatty acid oxidation inhibitors or metformin. Can you expand a little bit about that?

Dr Hemnes: Yes. Since we know that metabolism is important to the development of PAH, specifically, people that thought, "Well, there's metabolic therapies that are well-tolerated, that we could then give to patients with PAH and repurpose them and see if they could work. The first one that was published was a trial of dichloroacetate from Evangelos Michelakis' group.[7] They were able to show a benefit in about half of the patients. It seemed like it was mediated by different genetic polymorphisms related to metabolism, but there was a lot of side effects of DCA, like neuropathy in the patients. It seems like that drug probably won't move forward as a therapy for PAH.

We got interested in metformin as a treatment for PAH because of our interest in insulin resistance, how it could promote pulmonary vascular disease, and right heart failure. We just completed a pilot study of metformin in 20 PAH patients,[8] and we were able to show that it was well-tolerated and safe, which wasn't known before. Secondly, it showed that there was an improvement in RV function, as measured by the fractional area change on echo, and a reduction in RV lipid content, which we have previously shown was common in PAH potentially bad for their right heart.

Based on that, we are now enrolling in a multicenter trial of metformin that's funded by the NHLBI. After these data, we will know more definitively if metformin improves relevant endpoints like functional class and 6-minute walk distance. metformin, has many effects, and one is that it increases mitochondrial fatty acid oxidation. So we are looking at the effects of metformin on heart lipid content and other markers of fatty acid oxidation. There've been other groups that say metabolism of RV fatty acid oxidation is low in PAH, and glucose oxidation is impaired as well, so what we should do is further impair fatty acid oxidation to try to rev up the glucose metabolic pathway. There have been some trials using drugs like ranolazine in PAH patients, that have mixed results in their publications.[9-11] Those have not been widely adopted, and I'm not aware of those drugs moving forward into any phase 3 trials, presently.

The other question that comes up sometimes, is whether drugs like liraglutide, the GLP-1 class of antidiabetics, that have shown major impact in cardiovascular disease, whether they may have a role in treating pulmonary hypertension. We presently don't know the answer to that, but it's a really interesting question.

Dr Levine: Are you all planning to look at that in your cohort?

Dr Hemnes: Yes. We're looking at it in our basic science lab using mouse models, presently. I think we can, hopefully, in the future, translate that to patients with PAH pretty rapidly, given how well tolerated the drugs are in other populations.

Dr Levine: Well, that is fascinating, and I've been looking forward to seeing your results.

Dr Hemnes: Thanks. It makes me feel better that there might be some benefit

to these studies—that other people read them or are interested in the questions!

Dr Levine: What do you think about the genomics of obesity and PH?

Dr Hemnes: That's a good question. We don't know very much, right now, about whether genetic mutations that have been associated with PAH or pulmonary veno-occlusive disease are also associated with alterations in metabolism that could predispose to obesity. I also have not seen any publications on whether patients with PAH, like idiopathic PH, without a genetic mutation, have lower BMIs than those that do have genetic mutations, which is a really interesting question, and I've not seen anybody ask that yet. Good question, but little knowledge right now.

Dr Levine: It's another study for you to do.

Dr Hemnes: Yes. Thank you, that you feel that way.

Dr Levine: Anna, thank you so much for talking today, and I look forward to your continued work in this area.

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Obesity and Pulmonary Hypertension

Section Editor
Claire Parker, MS, CPNP-AC

Ai Jin Lee, RN, MSN, AGCNS-BC, CCRN
UCLA Pulmonary Vascular Disease Program
Los Angeles, CA

Rebecca Alonzo, RN, MSN
Western University of Health Sciences
Pomona, CA

Charlotte Lipsky, RN, MSN(c), CCRN
UCLA Pulmonary Vascular Disease Program
Los Angeles, CA

Yessenia I. Ortega, RN, MSN(c), PHN
Mount Saint Mary's University, Los Angeles
Los Angeles, CA

Shannon A. Salveson, RN, MSN, ACNP-BC
UCLA Pulmonary Vascular Disease Program
Los Angeles, CA

Kathy McCloy, RN, MSN, ACNP
UCLA Pulmonary Vascular Disease Program
Los Angeles, CA

INTRODUCTION

Obesity is a global public health problem that exacerbates the burden of many health issues including cardiovascular disease, stroke, diabetes, liver disease, and many cancers.[1] From 2017 to 2018 the prevalence of obesity in adults living in the United States was 42.4%.[2] Obesity is characterized by excessive adipose tissue resulting in increased body weight defined in terms of body mass index (BMI; kg/m^2). The World Health Organization defines class I obesity as a BMI of 30 to 34.9 kg/m^2, class II obesity as a BMI of 35 to 39.9 kg/m^2, class III obesity as BMI $\geq$40 kg/m^2, class IV obesity as BMI $\geq$50 kg/m^2, and class V obesity as BMI $\geq$60 kg/m^2. Epidemiological data support that there is a link between obesity and pulmonary arterial hypertension (PAH), as 30% to 40% of PAH patients are reported as obese.[1-3] One study showed obesity and BMI had no significance to overall mortality rate in patients with PAH) however, there is an age-obesity interaction. PAH patients < 65 years of age with morbid obesity had increased mortality rates.[4]

Adipose tissue is now understood to be an endocrine organ. Excessive amounts of adipose tissue leads to derangement of adipose function and creates the pathological conditions of systemic low-grade inflammation, insulin resistance, and oxidative stress that may contribute to the progression of vascular remodeling associated with PAH.[4] Obesity exacerbates cardiac and pulmonary pathologies that precipitate pulmonary hypertension (PH) secondary to left heart disease and PH secondary to hypoxemia as seen in obstructive sleep apnea and obesity hypoventilation syndrome. Hemodynamic, neurohormonal, and metabolic abnormalities associated with obesity can lead to morphological alterations of the cardiac system, predisposing individuals to right and left ventricular dysfunction.[5] Caring for a PH patient with obesity requires a collaborative approach that involves the patient, family, and multidisciplinary team for improved outcomes, quality of life (QoL), and resilience.[1,6,7]

NUTRITION

While there is limited research on the impact of nutrition and lifestyle interventions for PH patients, there are well-established nutrition and lifestyle modification recommendations for patients with heart failure and evidence that these interventions improve prognosis.[4,6,8] Although the pathophysiology of PH and heart failure are different, both diseases often result in malnutrition and muscle wasting, which are linked to exercise intolerance, fatigue, and muscle weakness.[6,8,9] There are no established dietary recommendations or nutrient supplementation for PH patients; however, it is recommended that patients with heart disease follow a diet rich in grains, fruits, vegetables, and lean protein; low in sodium; and with restricted fluids and alcohol.[6,8,10] Consultation with a registered dietician or nutritionist may be warranted to further optimize weight and prevent nutritional deficiencies.[4,6,7,11]

NUTRITIONAL DEFICIENCIES

There is evidence that PH patients may be likely to suffer from nutritional deficiencies due to a variety of factors including right ventricular (RV) dysfunction, inflammation, and comorbidities such as connective tissue disease which may ultimately contribute to gastrointestinal edema and subsequent malabsorption of nutrients.[6,8]

Vitamin D and iron deficiencies are more prevalent among PH patients and may lead to disease progression.[10] Vitamin D deficiency is also related to infection, cancer, and respiratory and cardiovascular diseases.[6,10,11] In one study, PH patients received vitamin D (cholecalciferol) supplementation at a dose of 50 000 IU weekly for 3 months. Results showed significant improvements in 6-minute walk distance and RV size.[12]

Finally, some PH medications, such as prostacyclins, may contribute to nutrition deficiencies in PH patients due to side effects including anorexia, nausea, and diarrhea.[6] Diuretics are associated

Key Words--pulmonary hypertension, obesity, nutritional deficiency, exercise, wearable technology, liquid diets, bariatric surgery
Correspondence: mmccloy@ucla.edu

with thiamine deficiency, impacting energy and carbohydrate regulation, as well as electrolyte imbalances.[10]

EXERCISE

General exercise recommendations for adults include at least 150 minutes of moderate physical activity or at least 75 min of high-intensity physical activity every week.[13] A formal exercise program not only aids in weight-loss efforts, but can improve functional status, slow chronic disease progression, and increase QoL.[14] In PH patients, benefits from exercise programs have been demonstrated by increases in exercise capacity measured by maximal oxygen consumption; increases in 6-minute walk distance; decreases in RV systolic pressure, mean pulmonary arterial pressure, and pulmonary vascular resistance; and improved QoL scores.[15]

Previously, the overall consensus for patients with PH was that exercise should be avoided. This stemmed from the belief that it was unsafe for patients with PH to exercise, primarily due to fear of dangerous decreases in cardiac output or even sudden death.[9,14,16] However, recent guidelines set forth by the European Respiratory Society,[17] as well as recommendations from the 6th World Symposium on PH, emphasize the safety and stress the importance of a regimented exercise program for patients' overall health and well-being.[18]

Despite these new recommendations, many studies have demonstrated that patients with PH do not meet the daily physical activity requirements, leading to physical deconditioning. For those patients with a history of obesity, this further exacerbates their sedentary lifestyle.[9,13,16] Therefore, it is important for providers to encourage and promote exercise training into the patient treatment plan, particularly for those that are overweight.[9]

Pulmonary rehabilitation (PR), is a regimented program that incorporates supervised exercise training based on a multidisciplinary approach to improve a patient's physical and cognitive health, as well as foster long-term, healthy lifestyle changes.[14,16] The PR structure allows for patients to safely learn appropriate exercise techniques in a controlled environment, focusing on a patient's personal physical capabilities, as well as recognizing their limitations.[16] Multiple studies suggest that PR programs using a combination of aerobic exercise, resistance training, and inspiratory breathing techniques promote significant benefit in terms of exercise tolerance and functional capacity, which leads to longstanding compliance and sustainability.[14,16] Despite the known benefits of PR, not all patients have access to such programs, whether it be due to insurance or financial limitations, geographic availability, or even lack of provider support.[9]

When PR is not an option, or after a patient completes PR, there are many innovative technologies in the current market that allow for patients to track their daily physical activity. One such technology is in the form of wearable technology (WT), which allows for daily measurement of total steps, calories, distance travelled, and exercise intensity.[19,20] These data can be transferred and accessed by a patient's smartphone, watch, or wristband.[20] Studies have shown that WT is easy to use, promotes patient self-monitoring and compliance, and increases overall daily movement.[19,21] One meta-analysis performed by Kirk et al[20] found that patients who used WT compared to control groups averaged more than 2500 steps per day, and spent 30 more minutes a day walking, with all WT participants reaching 10 000 steps per day. Increased weekly step counts and total active minutes per week both strongly correlate with increased weight loss overall.[19]

Patients with PH and obesity will benefit from an exercise regimen of some form. However, it must be emphasized that all patients participating in any form of exercise training should be optimized on PH medical therapy prior to starting. This is not only for success in the benefits of training, but for safety concerns as well.[14,16,18] Guidance and support from the patient's entire medical team, as well as patient motivation and social network encouragement, is crucial in the success of an exercise-based weight loss program.[9]

LIQUID DIETS

For some PH patients who have difficulty losing weight, a medically supervised meal replacement program that consists of a calorie-restricted liquid diet may be appropriate. One study done in the United Kingdom showed that a liquid diet was effective in a 12-month weight maintenance program for morbidly obese patients and that patients were able to maintain a weight loss of over 15 kg throughout the study period.[22] The diet followed by the participants included an 810 kcal/d liquid diet for 12 weeks followed by reintroduction of low-calorie solid foods that included 30% of energy from fats. Management by a physician specializing in clinical nutrition as well as involvement of a registered dietitian should be incorporated into the plan of care to ensure weight loss is safely achieved.

THE ROLE OF BARIATRIC SURGERY

Bariatric surgery (BS) is an effective therapy for morbidly obese patients, resulting in significant weight loss.[23,24] This is particularly important in patients who struggle with meaningful weight loss and in select cases where candidacy for eventual lung transplantation may be denied due to morbid obesity.

PH patients may not be considered candidates for BS as they are considered medically high risk for adverse outcomes following noncardiac surgical procedures.[24,25] However, case reports and recent studies have shown improved outcomes following BS in carefully selected patients with PH, including reducing the need for PH medications, recovery of RV function, and improvements in oxygen requirements, functional status, and insulin resistance.[26-29] In a retrospective study, Sheu et al[28] compared patients who underwent BS to BMI-matched individuals. Primary outcomes in this cohort were significantly improved in the surgical group (those with BS) which consisted of decrease in the use of pulmonary vasodilator and diuretic medications, decreased need for home oxygen, and improvement in mean pulmonary arterial pressure. Although there were 7 significant postoperative complications cited, there were no mortalities. Similarly, Hanipah et al[29] reported favorable results in a retrospective review of 61 patients with PH and a mean BMI of 49 who underwent gastric bypass. All patients had a mean RV systolic pressure ≥ 35 mm Hg on Doppler echocardio-

gram. The 30-day complication rate was 16%, with 3 patients having major early pulmonary complications: respiratory failure (2 patients) and pulmonary embolism (1 patient). There was no 30-day mortality reported. One year follow-up showed a reduced mean BMI of 36 kg and a significant improvement in echocardiographic RV systolic pressure from 44 to 40 mm Hg. Employment of a multidisciplinary approach at an experienced center, including a bariatric surgeon, pulmonologist, cardiologist, cardiac anesthesiologist, dietician, and psychologist was cited as a possible factor related to the positive outcomes reported.[29]

SUMMARY

Obesity is a global health epidemic that affects a large portion of patients with PH, negatively affecting QoL. Meaningful weight loss can be difficult to achieve for this patient population; thus, a multidisciplinary approach should be employed when designing a weight loss program for PH patients. Interventions should include strategies that incorporate both nutrition and safe exercise training. WT has proven to be effective in improving patients' awareness of their physical activity habits and overall compliance. Implementation of a medically supervised liquid diet and/or BS have proven successful in select cases of morbid obesity. Providers should incorporate weight loss strategies for the obese PH patient to include exercise and nutrition as part of a holistic approach to improve overall health outcomes.

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PH and COVID-19 as a Systemic Infection

This summer our Guest Editor, Ioana Preston, MD, Director of the Pulmonary Hypertension Center at Tufts University School of Medicine, gathered with Harrison (Hap) Farber, MD, Director of the Pulmonary Embolism Response Team (PERT) at Tufts University School of Medicine; Karen Fagan, MD, Chief of the Division of Pulmonary and Critical Care Medicine at the University of South Alabama; Ron Oudiz, MD, Director of the Liu Center for Pulmonary Hypertension at the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center; and Panagis Galiatsatos, MD, Assistant Professor in the Division of Pulmonary & Critical Care Medicine at John Hopkins Medicine, to discuss the impact of COVID-19 infection on the pulmonary vasculature in general and the PAH lung in particular.

Dr Preston: Welcome to this month's roundtable titled: PH and COVID-19 as a Systemic Infection. We are fortunate to have today a group of wonderful PAH experts who, over the past year and a half, have encountered in both acute care and outpatient settings the various aspects of COVID-19 infection and its effects on the lungs and heart.

Let's start with the notion that COVID-19 infection has a predilection towards the pulmonary vasculature. What is your take on that?

Dr Fagan: I think one of the reasons that the concern for a developing pulmonary vasculopathy in COVID infection stemmed from some of the early observations of coagulopathy and the concerns about potentially having coagulopathic events within the pulmonary circulation, either macrovascular events like a venous thrombosis in a PE or microvascular in situ thrombosis and the potential impact that that could have.

I think that has been difficult to ascertain whether or not that's been the case, although I think most of us have certainly seen the incidence of PE in these patients is higher than in our normal patient population, even with appropriate prophylaxis. I think most of us adopted early on a pretty aggressive anticoagulation strategy as a preventative for venous thromboembolism for our hospitalized COVID patients.

At least the tact that we took was to be more aggressive than we normally would be for a hospitalized patient. I think that over time, as we've learned more about COVID, we've learned about some of the different pathways that seem to be important in either potentiating or even hindering things like some of the inflammatory cascade. IL-6, which has been a long-implicated potential mediator of pulmonary vasculopathy for lots of different reasons.

We know that IL-6 is an important component of the inflammatory response to COVID infection and even anti-IL-6 therapy is now recommended in some situations for hospitalized patients. Again, how that may or may not directly affect a pulmonary vasculopathy remains to be seen, but there's a lot of potential reasons why the COVID infection is something that we should look at carefully, because it may not only help us understand the pulmonary complications of COVID, but it may also help us understand PAH.

We may get some insights in mechanistically and potentially therapeutically. The anti-IL-6 therapy is something that I've been interested in for a long time as a potential for PH. To see it used in this population with good safety is something that we maybe would be able to think about, revitalizing that particular line of investigation as a therapeutic in our patients as well.

I will say clinically, the most important finding that I've seen in our patients, who are still symptomatic, particularly long-haulers who come in, is that most of their ECHOs have been very normal-looking. But if there was a common abnormality that I've seen on PFTs, it's been a decrease in the diffusing capacity for carbon monoxide.

That's quite predictable in many of these patients, which does suggest some type of underlying, potentially vascular complication. We know they're not particularly anemic. We know their other lung function looks good in their imaging—once the initial infection is resolved, it looks good.

That leaves us with pulmonary vascular insufficiency as a potential cause for a decrease in DLCO. I've seen it persist in patients. Granted, we're still pretty early in this, but I've seen that as the most common abnormality. Hap you are shaking your head to that as well.

Dr Farber: Yes. I would agree with that. We now have a group of people that seem to have a fairly common abnormality: it's their diffusion capacity. Just to what you said, Karen, I have 2 questions for you. First one is, do you think that this vasculopathy or these clots or whatever they get, do you think this is true VTE with PEs or this is in situ damage to their vessels within the pulmonary circulation and just in situ clotting because this is a vascular virus?

Dr Fagan: I think macrovascular VTE events are probably not the issue here. I think that most of the patients, particularly with these low DLCOs, don't have a history or they were prophylaxed appropriately for macrovascular events. I do think this potential for microvascular coagulopathy contributed, is possible.

I think there were a few autopsy series that showed some in situ thrombosis in patients who passed from COVID, but I think that we don't really know, and whether or not the virus itself creates an inflammatory endothelial injury that could lead to remodeling or longer-term vascular complications, remains to be seen. I just don't think we have enough time and enough information yet.

 DOI:10.21693/1933-088X-20.3.92

Dr Farber: That leads to the second question. That leads to the point that obviously any coagulation in these people has become ridiculously controversial, whether you fully anticoagulate them, whether you overprophylax them or whatever. If it's mostly microvascular, I would be surprised if anticoagulating them is probably going to do much.

Dr Fagan: I agree with you, but, in these patients, I don't think that macrovascular events are uncommon. I just don't think that they're the primary cause of this long-hauler, low-DLCO kind of thing. I think that they are more common in these acutely hospitalized patients than other patients that are acutely hospitalized. I agree with you.

I think that for my practice, we are anticoagulating fully for these patients unless there's a contraindication to prophylax them from macrovascular events, but I'm not certain that that's necessarily preventing any of the microvascular potential complications. We do know that our experience has been that they've had more macrovascular events, so preventing those is important just for their overall outcome, but whether or not it's doing much for the microcirculation, I don't know.

Dr Preston: Ron, what's your experience?

Dr Oudiz: Actually, I was going to ask Karen a question with respect to these people who we think have microvascular disease based on symptomatology and the long-haulers and the low DLCO and others. Has there been any attempt to quantify the capacity of the pulmonary circulation?

In other words, something like CPET or even just generically-exercised capacity, because you can actually quantify the amount of pulmonary blood flow that increases or the blunting of that increase. If there is an impairment, then, of course, it sets you up for possible therapies, some of which apparently already exist.

Dr Fagan: We have only recently begun to start ordering cardiopulmonary exercise testing on some of our patients to really look at that, because, again, as we've had more of these long-haulers come in, who are symptomatic, particularly with the exercise and have PFTs that may have a low DLCO or may not, trying to quantify what their exercise limitation is something that we're more recently doing.

Before we were saying, "Maybe we need just a little more time," but now we're seeing that some people with time, have their symptoms resolve and they get back to what is normal for them. There's a cohort of these people who just have persistent symptoms. We're starting to try and actually look at exactly what you suggested, which we see if we can quantify what is their exercise limitation, and is that a ventilatory defect that we're just not picking up on routine PFTs? Is it a perfusion defect, or a cardiac defect? Those are all important questions. I think that that's a really interesting area as we begin to develop these cohorts of long-haulers that how we're going to phenotype them and what we're going to look at to see what's the cause of their exercise impairment or their functional limitation. I think we've still got a lot to learn, but it's a terrific plan.

Dr Farber: In addition**,** there are both autopsy and the cardiac MRI data to show that many of these people, surprisingly, are limited, that they actually have what looks like a myocarditis or inflammatory cardiac disease from COVID-19. It's interesting that this has been reported, whether it's actually true or not.

Who are these people who are basically younger and incredibly athletic who may develop this myocarditis? The classic one here is one of the pitchers for the Red Sox and all this stuff that they had what seemed like mild disease, some of them not even sick enough to go to the hospital, and yet, six months later, they got this cardiac injury from it presumably.

Dr Preston: Yes. I think the reports on cardiac MRIs were not all coupled with symptomatic patients. Some of the MRIs were in asymptomatic patients that showed some level of cardiomyopathy if you would, or myocardial inflammation. I'm not sure if we're quite ready to correlate the involvement in cardiac disease with symptoms.

Dr Farber: Ron is the cardiologist. Have you guys seen this stuff?

Dr Oudiz: We, as a division and as a department really, recently talked about the long-term sequelae and what we're seeing and what we're not seeing. For some reason, we just have not seen what others are seeing in our division. The pulmonary division, of course, has the long-haulers that everyone is seeing, but certainly not in my PH clinic either. We haven't talked about this yet but the PH clinic, per se, is a unique group of patients because they hide and they have been paranoid for the last year and a half.

Dr Preston: Yes.

Dr Oudiz: Now that they're vaccinated, they're still not coming out. They're still at home wearing their masks and not even want to come to the clinic many times.

Dr Preston: That leads me to my next question. What is your experience in your PH patient community and how many of your PH patients have been infected with COVID?

Dr Fagan: I can say that I've only had 1 patient that was hospitalized with COVID, and that was probably actually more related to her PH than COVID itself because I think she just got very nervous and was not quite as good about managing her PH during the time that she got sick. She responded to nothing but diuresis in the hospital and got better.

I've had maybe 1 or 2 other patients with very mild disease who were managed at home. I do think that the commentary about these patients going into hiding and that were very, very self-protective is true. I think that one thing we did as a community was to get these people early on to recognize the seriousness of the infection and the potential for adverse outcomes.

Our community took that to heart and really protected themselves. There's biological possibilities as to why our patients may or may not have more severe disease, but I think the biggest reason I didn't see in my patient population was that they were very, very careful about exposure.

Dr Preston: Ron, what's been your experience?

Dr Oudiz: We've had patients who have definitively gotten symptoms, sometimes severe symptoms, but never got hypoxemic. Even with fevers and headache and the usual constitutional symptoms that they've gotten, they've not gotten more hypoxemic. Most of the time, they've stayed at home or if they've come to the ED, they've just been sent home.

We've had some patients with comorbidities, for example, our porto-pulmonary hypertension patient whose liver disease got worse and passed. I think we were initially surprised that the underlying disease for most of our patients is pretty severe. PH is one of the worst diagnoses one can have in life, and the majority of patients not only were not dying but weren't even getting hospitalized.

Dr Preston: Can you make a comparison with heart failure patients, since you're our cardiologist on the roundtable? There's been a higher incidence of hospitalization from COVID from heart failure folks.

Dr Oudiz: We did see a bump there. I think they are a little bit different. A lot of the heart failure patients were decompensated, of course, those that got infected. Our service was busy, not just with COVID patients that had other cardiac diagnoses but a lot of heart failure. Without epidemiologic numbers, it's difficult to say anything other than this observation. It does seem to be different than in my clinic, PH patients with their right heart failure.

Dr Preston: Hap, were you going to add something?

Dr Farber: No, I would echo what everybody else has said. I've been amazingly impressed with how few PH patients have ended up in a hospital during this. I could think of only 2, and neither one of them ever ended up in an ICU. Most of the people who got infected, and they were very small numbers that stayed at home and were okay.

As Karen pointed out, we all tried to make some biological argument for why they didn't do poorly. Either vessels were all damaged already so the virus could not get into it, or these people are really good at hunkering down and hiding.

Dr Preston: Karen, how were you able to follow them from the distance, your PH patients, during the pandemic?

Dr Fagan: Initially, our hospital shut down our clinics for the most part, and so we were forced to pretty much do everything virtually. The patient population that I serve down here, a fair number of them are very under-resourced and have very limited, if any, access to internet technology like Zoom and other things like that.

I would say that 75% of our virtual visits were conducted over the phone, while the ones that we were able to do via Zoom left me a little bit more comforted that I was able to at least see our patients and have a little more visual impression of what they look like and things like that, than on the phone.

When we were able to go back to live visits, the vast majority of our patients came back immediately to in-person visits. I think because again, part of it is an access issue to technology in some of the patients that we serve. It was difficult because so much of what we do when we're with a patient is visual. So much of our assessment in our exam even occurs without ever touching a patient.

It's about looking at them, seeing how they're sitting, seeing what their nail beds look like while we're chatting, and doing other things. So much of that was hard to interpret over the phone for us. In the virtual visits, it was hard, too, but at least there was a little bit more that we were able to get.

I understand and appreciate the need for that. Hopefully, we'll never have another pandemic that will force everyone in the same way, but there were some limitations. I was grateful to at least be able to interact with my patients at all and to at least get some assessments.

Dr Preston: Ron, what's been your experience, and what were your hurdles during distance and tele-follow-up?

Dr Oudiz: In our county clinic, we had phone visits only. We didn't have video. That I think is huge in trying to assess right heart failure because you can't look at the edema. You can't even really do the eyeball test to just see how the patient looks. There have been some cases where when we did have phone visits, I said "You need to come in."

In part because of the history, of course, what they verbally told me, but also how they looked. If you know your patients, you can see sometimes subtly, sometimes obviously, that things aren't going so well. That wasn't great. I just phoned a patient yesterday who I haven't physically seen in over a year.

We're vaccinated, they're vaccinated, they just don't want to come in. In this case, to be fair, part of it was transportation. She's married, her husband works, and she doesn't have any family or friends that can drive her on the days we gave her. My instructions were, "You're coming in next time because we need to see you. There are serious, active problems." Even if there aren't active problems, it's a long time. Normally we see stable patients every 3 months. A year is really just way too long to not have set your stethoscope and hands on the patient.

Dr Preston: Hap, what has been your experience with your patients? Many of them are underserved. They're socially not a wealthy population or a well-off population. How did they behave?

Dr Farber: I think obviously we had similar experiences to what Ron and Karen have already talked about. I think a couple of the things that I think need to be emphasized was that doing it by phone alone was just—you just couldn't tell anything. I think, Ron, you probably had this too. When you call them up on the phone, they tell you they are ok. Because they want you to think they're

doing great, they tell you they're doing great no matter what. Whether they're doing good or bad, they're telling you, "Yes, I'm fine."

We do ours through Doximity here. Most of the time it works pretty well because you can at least see the patient, which is helpful. We've also gotten spouses or significant others on Doximity with the patient. We have taught their significant others or their spouse how to put their thumb on the patient's leg so I can see if they have edema or to see on the phone if they look any different. I think the hardest part has been 2 things. One is that oftentimes, especially if you can't see them or can't see them well, it's very hard to tell whether they've gotten worse because their disease is worse or whether they've just been inactive because of COVID and haven't done any physical activity.

Dr Farber: The other part of that equation is most of them have gained weight because they've been less active. They tell you their weight is up 10 pounds. It's hard to determine, is it fluid? Is it because they've just been sitting in front of the refrigerator? It's hard to tell.

The third thing we're faced with now, a lot of our patients live far away. They had gotten so used to this Doximity and tele-thing. They don't want to come in now at all. They want to do everything over telehealth because that way they don't have to drive 4 to 6 hours. They say, "No. We're not coming in. We're doing this forever." Like Ron, there are patients I haven't seen in, God knows how long, a year, a year and a half, 2 years. That's worrisome. Ron, I guess these people have proven they're survivors. They're still out there in a year and a half.

Dr Preston: That tells us how much we do for them…

Dr Farber: Yes.

Dr Oudiz: They're there and then they're not. Who's to say what's going to happen tomorrow?

Dr Preston: That leads me to my next question. There is a tendency now to try to incorporate telemedicine as a part of our outpatient clinic, whether it's PH clinic or not. How do you guys see that as a complement to in-person visits? Is it helpful if we're implementing a mix of telehealth and in-person visits?

Dr Fagan: We, fortunately, have not been pressured to try and make telehealth—We're still being very much encouraged to have everyone in person. I will say that I had an experience with a patient in my office on the phone with a consultant. I was there. It was really a telehealth visit for this patient and a consultant in another city.

I was there to feed additional history, to feed the exam, to do those things. That worked out really well actually because it saved her a 5-hour trip to go see someone else. The patient and I together were able to see that consultant.

I think that that's something that I may want to try and look at a little bit more. I think having a health professional with the patient physically during a telehealth visit, it was really a powerful experience because we were able to really collaborate in the care of that patient. The patient was there, and we were able to have a really functional full visit.

Dr Oudiz: That's Nirvana I think. If we can have that everywhere, that would be a perfect world.

Dr Fagan: It was really nice. Maybe I'm spoiled now, and I can't think of any other way to do it.

Dr Preston: Ron, are you going to implement a mix of telemedicine and in-person clinic?

Dr Oudiz: You mean what Karen was talking about? I wish I could. We have limited resources. That's the problem.

Dr Preston: No, not necessarily to have a multidisciplinary visit, but I was thinking more to do in-person alternating with televisits for the same patient.

Dr Oudiz: I think that's going to stay. I think even in the corporate world. We heard Apple yesterday is going to have some of their workers now work from home. What before was taboo to put on your time card that you were working from home and even though you weren't in the office you get your paycheck, the same thing for patients.

We're never going to really go back to 100% in-person visits as long as the precedent has now been set and this concept is reasonable. I think that we see patients every 3 months and that's the standard for the stable patient. It's up to us and our staff and our nurses and nurse practitioners and allied health to determine whether or not there is appropriateness of that visit. If you chose wrong and you had a telehealth visit, then you bring them in soon.

Dr Preston: Do you use any devices to monitor them? Do you make them do 6-minute walk tests at home?

Dr Oudiz: A lot of them have pulse oximeters. I find it very useful if they're doing daily weights and they can measure their blood pressure and pulse with an automated machine and get me a pulse ox. That's pretty good. Then show me their feet and see what kind of swelling they have.

Dr Preston: There are also apps on the iPhone that can record an EKG strip. Have you used those?

Dr Oudiz: No. I was actually working with a developer of an idea like that long before they got FDA approval for the one device that currently exists. It's a really novel approach. It's just not ready for prime time yet. There are a bunch of issues with noise and with overcalling. Every couple of hours, we're going to get a call from our patients or even their PCPs saying, "You've got to see this patient. They're in a fib," and really all it was they were brushing their teeth.

Dr Preston: Hap, are your patients device savvy?

Dr Farber: Some are, some aren't. I think what Ron alluded to and I think what Karen alluded to, it is clear from this pandemic that telehealth is not going away. There's no question that it's now going to become an integral and

even a larger part of, just as Ron pointed out, business, medicine, everything.

If we're going to accept that fact, then the idea that we need to start working on is how to make these telehealth visits at home better. There are several apps under development to create a 6-minute walk at home, which might be helpful. We'll see if they work, but this is the whole concept now.

The idea, as Ron pointed out, that you can record EKG is not granted. All this stuff is in its infancy and probably has a lot of issues, but you got to figure it's going to get better. Like I talked about, we've taught patients, significant others, how to stick their thumb in somebody's legs so we can see if they have edema.

We can look at their infusion lines with the phone and stuff like that. I think the onus is on us and obviously, the technical people who do all this stuff, to come up with better ways to monitor people at home. It's the same thing as we pointed out. Some patients love it, and they're going to not come in all the time, so you have to have ways to effectively monitor them at home.

Dr Preston: Great, thank you. I do have another question that we could piggyback to the vasculopathy in the beginning. We recognized that our severe COVID patients ending up in the ICU with acute respiratory distress syndrome have different phenotypes. There's one type that has very high oxygen requirements, but their lungs are not very stiff, right? Their compliance is almost normal, versus those who are more typical ARDS patients in whom compliance is very low. My question is, do you think that the first phenotype is maybe more associated with vasculopathy, and are those patients the ones who will develop long-term symptoms after they recover from COVID, should they recover, or is it not clear?

Dr Oudiz: I think it's not clear.

Dr Preston: Has anyone looked at what were the acute phenotypes during the acute infection in those long-haulers?

Dr Farber: It's interesting, Ioana, we've seen a significant number of these long-haulers, which are now called PACS, post-acute COVID sequelae, who weren't even sick enough to be in a hospital. They never got admitted. They were never intubated. They never had "ARDS", they just were sick at home and never got better and in fact got worse.

Dr Preston: I see.

Dr Farber: I would agree with Ron. I don't know that the data are good enough to tell us what phenotype precedes long-term sequelae from COVID.

Dr Preston: Or if you had severe disease, you're at higher risk of becoming a long-hauler or PACS?

Dr Farber: It doesn't seem that severity matters, at least in the people that we've seen so far with PACS, at least anecdotally off the top of my head. I can't make a correlation between the severity of their initial disease presentation and what happens down the road.

Dr Oudiz: It's not obvious.

Dr Farber: It isn't obvious, which is fascinating. You would think that the people who would be more likely to develop ongoing symptoms would be the people who had the most severe disease, but it doesn't appear to be that way.

Dr Preston: Yes. More research needs to be done.

Dr Farber: Ron and Ioana, do you think that the morbidity and mortality among the PH patients has gone up during this year and a half?

Dr Preston: I think the opposite. The way my experience has been in the ICU in the second part of the pandemic, it looks like the population has changed into younger COVID-infected population and maybe just because of the age, but I've had better success at keeping them alive.

Dr Farber: No, what I meant was just PH patients in general over the last year and a half with all that we've talked about, the pandemic plus not being able to see them as frequently or at all. Do we think that if we went back and did morbidity and mortality statistics that the numbers would be different than they've had been, say, the year or two years before this?

Dr Oudiz: We have data, and I'm sure the PHA's registry will be able to actually answer that question leading up to the pandemic and during the pandemic and then now post. I think that they'll be able to get some meaningful numbers because they have so many in their registry.

Dr Farber: Ron, just out of curiosity, do you think among your patients, do you think it's changed at all?

Dr Oudiz: No, I haven't seen it. You know, the problem is that we don't have a ton, we have a couple 100 patients. The problem with a couple 100 patients is sometimes you have a cluster of 3 or 4 who, all of a sudden get hospitalized, and one of them dies and your staff is looking at you like, "What's wrong with us?" Then months go by and nothing happens. That's why I think the registry with more numbers and more diverse centers that are putting into that registry is more realistic to give us an answer.

Dr Preston: Panagis, how were you connected with your patient community, and what was your experience with remote visits during the pandemic?

Dr Galiatsatos: It was tough. I think it works for the right patients, and I think it doesn't work for others. When I say the right patients, there's a lot. There could be a social conversation where some patients may not have the equipment to do a virtual visit, they have to rely on a phone, or their digital literacy just doesn't allow them to really access it well. I think of my 74-year-old mother, she has no idea how to run a computer. She can make a good baklava, but she has no idea how to run a computer.

Dr Farber: That's more important.

Dr Preston: Exactly. We should talk, right?

Dr Galiatsatos: There are some patients that I think a telemedicine visit is perfect. We'll talk about a few medications. Others have a hard time expressing their problems: "I'm having this symptom." In those, I really wish I could examine them.

I'm a lung doctor, and so oxygen level checks are important. Let me put it this way, I think that telemedicine visits were better than nothing, even if they were just used as a checkpoint. I do think there's value in them moving forward, where I think certain clinic visits can be accomplished nicely through that. I'm going to now just take this to a different level.

This is where I would scream that we need advocacy at the government level to allow a universal medical license. Many patients that I see aren't based in Maryland, and for a lot of them, our checkpoints are fantastic. They say: "I love that I could just do this visit with you, from where I live in Maine."

Just an FYI, there's a way to advocate for a universal license because the doctors who specialize in very rare diseases, a telemedicine visit can be really easy for patients. Nonetheless, Ioana, you asked me a great question, and to some extent, and added one more thing to that.

Dr Preston: I think it's a very important thing, and maybe we should gather forces to be heard to advance the care of rare diseases like PH on a global scale, not only country, but in remote areas of the of the world, because there are countries and areas where there are no PH specialists.

Maybe we can offer our expertise on a global scale. Now, talking about disparities, and those patients who do not have access to remote connections, internet, computers, smartphones, and whatnot, have you seen worsening of the disease, more ER visits, hospitalizations from PH, Panagis?

Dr Galiatsatos: The group that I specifically work with are patients with HHT that sometimes renders them with PH. I feel like my comment is going to come across a little biased at the moment because of the patient I'm thinking of is right now admitted to the hospital, we couldn't get her to a telemedicine visit. She's of minority race and coming from a very socioeconomically disadvantaged neighborhood.

I would say the majority of the patients that I've seen are more affluent and more likely nonminority races. Potentially, I think there is some impact from a health equity standpoint. I will say the other challenge is sometimes that patients may have the devices, but maybe not have the digital literacy to use them. That's a big portion of this conversation too.

This isn't an easy step-up approach for a lot of patients to use the software on the EMR to navigate this properly. I think it's a combination between lack of access to technology and how to access it. That probably contributes a lot to health equities. I know that I'm coming across from my own bias of what I've seen.

It seems to be still a bit of the norm for other providers that I've talked to. I think this can be a big advocacy. If we really want to make telemedicine part of the staple of medicine, I think, in the right way, it can be used very well. We just need to make sure that we're not contributing to health inequities, and any that would exist, we have to be prepared to combat them.

Dr Preston: What's your experience, Ron, in different socioeconomic layers in your patient community?

Dr Galiatsatos: I have a mix about half of which are referred patients in a private clinic and the other half are part of the safety net hospital. There are definitely differences. As far as telehealth and access to that kind of stuff, though, I'd say most of them have at least a cell phone, and most of them have a smartphone, but it's glaringly different for those that don't.

There are still some that really are just not technically enabled. Getting around in LA, especially if you're impaired, isn't so easy. Our public transportation system is really bad. Three hours for one-way bus ride for some of our patients, and I've been on those buses myself just to see what it was like to get from my home to my clinic. It took me two and a half hours, and it's 11 miles.

Dr Preston: Maybe we can all team up with the PHA association and try to find solutions to combat these differences in care for our PH patients.

Dr Farber: A lot of it is somewhat generational, and I think it's been alluded to. Even those people who have a cell phone or a smartphone, or even have an iPad or computer access to it, there are a lot of them, especially older patients, who still have no idea how to use it or what to do with it.

For the Doximity thing, you send them a text, then all they have to do is hit on the text and say, "Yes," to access their phone and their camera, and you can see them, but we have a lot of patients who cannot figure out how to do that, unless their grandkid's in the room.

Dr Preston: I can tell you, my parents do not know how to text.

Dr Farber: They don't feel comfortable with it. They've not grown up with it, they don't know how to use it, and they don't plan to learn how to use it.

Dr Preston: Yes. Any other questions from you guys to the group before we wrap up? I think we've touched upon very interesting aspects of COVID-19 and its impact on pulmonary hypertension and vice versa. We've all went through a painful experience in the past year and a half. We hope we will be better at providing care for our PH patients during the pandemic and outside. Thank you all.

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