Challenges in Pulmonary Hypertension: Controversies in Treating the Tip of the Iceberg

A Joint National Institutes of Health Clinical Center and Pulmonary Hypertension Association Symposium Report

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The Critical Care Medicine Department of the National Institutes of Health Clinical Center and the Pulmonary Hypertension Association held a joint symposium to discuss "Challenges in Pulmonary Hypertension: Beating, Breathing, and Beyond." Communities of interest including patient advocates, clinicians, and academic investigators gathered together to raise awareness and highlight the challenges in diagnosing and treating pulmonary hypertension (PH). While agreeing there is a need for treatments that can cross World Health Organization (WHO) PH classifications, the symposium clearly pointed out that improved phenotyping is still needed to better determine who will benefit from these therapies.

PH, defined hemodynamically as a mean pulmonary artery pressure (mPAP) of 25 mm Hg or greater (1), can arise from pulmonary vascular disease, left heart disease, lung disease, chronic thromboembolic disease, and other causes, forming the basis of WHO classifications (2). The symposium focused on whether or not pulmonary arterial hypertension (PAH) (WHO group 1)-specific treatments are warranted as therapies for heart failure with preserved ejection fraction and PH (HFpEF-PH; WHO group 2.2), interstitial lung disease with PH (ILD-PH; WHO group 3.2), and pulmonary venoocclusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH) (referred to as PVOD for simplicity; WHO group 1′). Like icebergs in the water, the tips of these specific WHO subgroups can seem similarly menacing, showing elevated pulmonary arterial pressure and right ventricular (RV) dysfunction (Figure 1). Importantly, apart from addressing the underlying substrate in patients with HFpEF-PH and ILD-PH or lung transplant in patients with ILD-PH and PVOD, there are currently no approved evidence-based therapies that specifically address pulmonary vascular disease or a failing RV in these patients (3). Practitioners, in their haste to steer clear of right heart failure, can be conflicted as they navigate a path between the need to treat and the desire above all, to do no harm (*primum non nocere* [4]).

We need only look to early inotropic strategies using oral milrinone, vesnarinone, and xamoterol in heart failure with reduced ejection fraction to remind ourselves that treating hemodynamics without targeting the underlying pathophysiology does not necessarily improve survival. In fact, these treatments, although occasionally providing symptom relief, uniformly reduced survival (5–7). To avoid therapeutic misadventures, we need to dive

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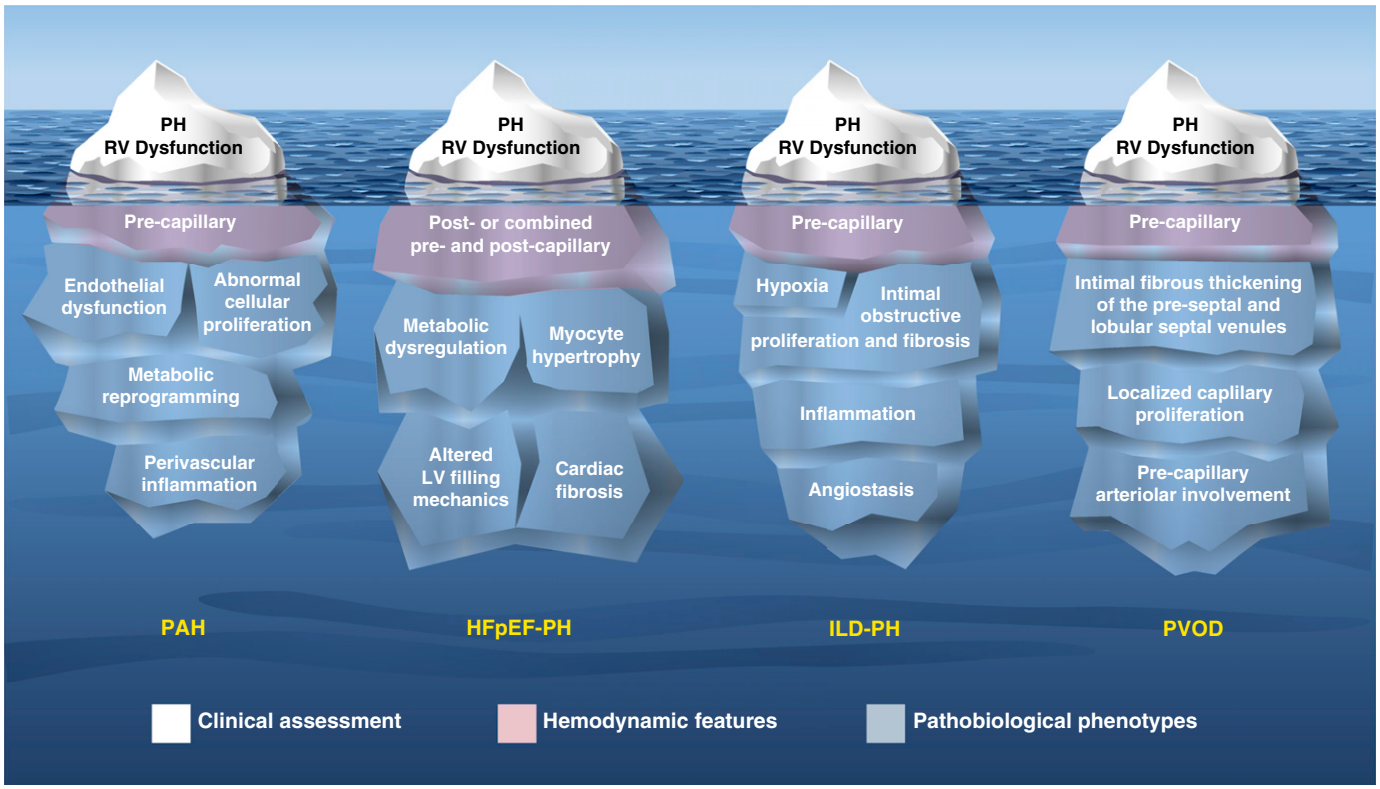

Figure 1. Iceberg models illustrating the substrates underlying pulmonary hypertension (PH) due to pulmonary arterial hypertension (PAH), heart failure with preserved ejection fraction (HFpEF), interstitial lung disease (ILD), and pulmonary veno-occlusive disease (PVOD). LV = left ventricular; RV = right ventricular. Illustration by Jacqueline Schaffer.

deeper to see the phenotypes beneath the surface (Figure 1). PAH is characterized by endothelial dysfunction, abnormal cellular proliferation, metabolic reprogramming, and perivascular inflammation of the precapillary pulmonary arterioles (8–11); HFpEF-PH by metabolic dysregulation, myocyte hypertrophy, cardiac fibrosis, and ultimately altered left ventricular filling mechanics with adverse vascular remodeling involving the postcapillary pulmonary venules and, to varying degrees, the pulmonary capillaries and precapillary pulmonary arterioles (12, 13); ILD-PH by hypoxia, intimal obstructive proliferation and fibrosis, inflammation, and angiostasis (14); and PVOD by extensive occlusion of the postcapillary pulmonary veins by fibrous tissue, intimal thickening of venules in the lobular septa, localized capillary proliferation, and varying degrees of involvement of the precapillary arterioles without plexiform lesions (15).

Although these major phenotypes of PH are statically classified by the World Symposium on Pulmonary Hypertension, they are dynamic over time. A major challenge facing practitioners is that individual patients may have elements that cross phenotypes.

Should You Treat HFpEF-PH with PAH-Specific Therapies?

WHO group 2 PH is by far the most common form of PH, accounting for more than 65% of all PH seen in the clinical arena (16, 17). Examining prevalence data from the perspective of heart failure, between 50% and 80% of patients will have some echocardiographic evidence of PH (18–24). If there are 5.7 million patients with heart failure in the United States, then 2.9 to 4.6 million have some degree of PH (25). In addition, mortality rates in heart failure are related both to the presence and degree of PH (3, 18, 26, 27). These numbers and mortality trends emphasize the clinical burden of group 2 PH in our society. Yet, there are currently no approved evidence-based medical therapies for PH complicating heart failure. The search for such therapies has been confounded by the phenotypic diversity of the left ventricular (LV) dysfunction and the uncertainty of the degree to which PH is a marker of severity of the underlying LV dysfunction versus a target for treatment. In light of this, it makes logical sense to first identify amenable phenotypes of HFpEF and then develop strategies to target the PH remaining once the underlying substrate has been optimally managed.

Although group 2 PH arises from elevations in left atrial pressure (LAP), it may present in an occult fashion with a relatively normal baseline pulmonary artery occlusion pressure (PAOP) of less than 15 mm Hg. Provocative testing, such as a fluid challenge or exercise during right heart catheterization, could reveal an elevated PAOP, and thus may provide additional information toward accurate diagnosis and classification (28, 29). Yet, several unanswered questions regarding these tests remain. How best to implement the fluid challenge, and what defines an abnormal response given that increases in filling pressures with volume loading have been reported in healthy volunteers (30, 31)?

Determining an optimal PAOP cutoff will have important therapeutic implications. For example, 7% of patients with PAH and 8% of control subjects without suspected PH were reclassified as having postcapillary PH using a PAOP cutoff of greater than or equal to 18 mm Hg after rapid saline infusion (29). In comparison, 15% to 22% of patients with precapillary PH were reclassified as postcapillary PH using a fluid challenge–induced PAOP cutoff of greater than 15 mm Hg (28, 29). Questions also remain when considering exercise as a provocative challenge, including the appropriate mode and intensity as well as rigorously defining normal responses across various age and body mass index strata (32, 33). Finally, investigations comparing acute fluid loading to exercise are an important first step to determining the sensitivity, specificity, and predictive values of these techniques (31, 33).

Hemodynamic evaluation can further parse group 2 PH into two distinct phenotypes defined by the recent World Symposium on Pulmonary Hypertension and highlighted in the recent European societal PH guidelines (3, 34): isolated postcapillary PH (Ipc-PH), in which the PAOP is 15 mm Hg or greater and the diastolic pressure gradient (difference between the pulmonary arterial diastolic and occlusion pressures) is less than 7 mm Hg; and combined pre- and postcapillary PH (Cpc-PH), in which both the PAOP and diastolic pressure gradient are elevated. We are just starting to understand the broader phenotypes encompassed in these hemodynamic definitions. In terms of clinical phenotypes, although patients with Cpc-PH, Ipc-PH, and PAH frequently have diabetes and systemic hypertension, these metabolic syndrome comorbidities were more prevalent in patients with Cpc-PH than in patients with PAH (35). In addition, genotyping data in patients with Cpc-PH revealed that these patients share a large number of genetic variants commonly identified in patients with PAH. When subjected to a gene ontology analysis, these variants were found to be enriched in cytoskeletal genes and genes regulating inflammation, potentially suggesting a shared molecular etiology between PAH and Cpc-PH that is different from Ipc-PH (35).

Although the principal recommendation for managing group 2 PH is to aggressively treat the underlying etiology (i.e., manage the substrate) (3), there has been recent interest in the use of PAH-specific pharmacotherapies to treat PH in patients with HFpEF-PH. However, PAH-specific drugs target the endothelin, nitric oxide, and prostacyclin signaling pathways that are dysfunctional in PAH and have been implicated in the adverse precapillary pulmonary arteriole remodeling and plexiform lesion formation pathognomonic for the disease. In contrast to PAH, the pathophysiology underlying HFpEF-PH is related to left heart dysfunction with left atrial overload, left ventricular hypertrophy, fibrosis, and increased stiffness. Impaired left heart function, in turn, promotes postcapillary pulmonary venule remodeling as a result of backward transmission of elevated filling pressures (36). Although significant knowledge gaps remain in understanding the pathobiology of pulmonary vascular remodeling in HFpEF-PH, the recent development of HFpEF-PH preclinical animal models is an important initial step forward (37, 38).

Recently, data from the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry evaluating PAH therapy in HFpEF found these patients were most frequently prescribed a phosphodiesterase-5 inhibitor, and 7% were on combination therapy at 1 year (39). Further analysis examining the tolerability and efficacy of PAH-specific drugs prescribed off-label to patients with HFpEF-PH found that among patients with follow-up data, 18.4% discontinued a phosphodiesterase-5 inhibitor and 42.9% discontinued use of an endothelin receptor antagonist because of either efficacy failure or side effects. In addition, compared to idiopathic PAH (IPAH) patients treated with targeted PAH therapy, HFpEF-PH patients were less likely to be WHO functional class I/II at 1 year (39). Thus, off-label use of PAH-specific drugs in patients with HFpEF-PH was less effective and often discontinued (39).

Patients with systemic sclerosis (SSc) warrant specific mention, because they can present with varying elements of parenchymal lung disease, pulmonary vasculopathy, and left heart disease. In the PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) cohort, 20% (59 of 298) of the patients with SSc-PH had a PAOP of greater than 15 mm Hg (40). Nearly all of these patients had HFpEF-PH, and a third were classified as Cpc-PH. The fact that most patients with Cpc-PH (86%) and half of the patients with Ipc-PH were treated with PAH medications likely reflects practitioners' awareness of the potential for pulmonary arteriopathy in SSc, and therefore standard HFpEF-PH treatment paradigms may not be sufficient.

Randomized, controlled trials of PAH-specific drugs in patients with HFpEF-PH have yielded mixed results. Contemporary, single-center studies have reported conflicting effects of inhaled prostanoids on the PAOP in stable patients with HFpEF-PH, with one showing a reduction and the other showing an increase in PAOP (41, 42). On the other hand, acute administration of inhaled nitrite increased pulmonary artery compliance and lowered right atrial pressure, mPAP, and PAOP, more so in patients with HFpEF-PH than in patients with group 1 or 3 PH (43). Endothelin receptor antagonists have also been studied in patients with HFpEF-PH in two clinical trials, with disappointing results. The Safety and Efficacy Trial to Treat Diastolic Heart Failure Using Ambrisentan was terminated early because of poor enrollment, and the BADDHY (Safety and Efficacy of Bosentan in Patients with Diastolic Heart Failure and Secondary Pulmonary Hypertension) trial was stopped early when an interim analysis favored placebo (44). In the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial, sildenafil for 24 weeks compared with placebo had no effect on the change in peak oxygen consumption, and there was no difference in 6-minute-walk distance (6MWD) (45). However, in a single-center study of patients with HFpEF with Cpc-PH and severe RV dysfunction documented by right heart catheterization, sildenafil significantly improved hemodynamics, RV function, and quality of life (46). Notably, the RELAX study included a broader population of patients with HFpEF and did not specifically examine patients with HFpEF-PH or those with Cpc-PH and severe RV dysfunction (45, 47). In line with the RELAX study, a recent single-center study in patients with HFpEF with predominantly Ipc-PH documented by right heart catheterization, sildenafil failed to improve hemodynamics, exercise capacity, or quality of life (48). In addition, riociguat, a soluble guanylate cyclase

stimulator, failed to acutely lower mPAP compared with placebo in patients with HFpEF-PH (49).

To date, there is no multicenter, randomized trial of a PAH-specific drug in HFpEF-PH that has met their primary endpoint (13). Failure to adequately address patient volume status (i.e., control LAP) and account for prominent pulmonary venous remodeling likely contributed to the suboptimal results of these pulmonary vasodilator trials in HFpEF-PH. Does this mean there are no patients with HFpEF-PH who could benefit from PAH-specific therapies, or does it instead imply that we have yet to identify the appropriate HFpEF-PH phenotype to study in these trials? The latter concept is supported by the observation that patients with HFpEF-PH with more advanced disease were more likely to respond to PAH-specific therapy in these trials (46, 50). Interestingly, although the initial trigger (i.e., elevated LAP) for Cpc-PH is distinct from that of PAH, the secondary mediators and mechanisms underpinning this disease, as well as the pathological remodeling of the pulmonary arteries, share some similarities (35, 51). For example, it is reasonable to hypothesize that the Cpc-PH phenotype of HFpEF-PH may represent a unique subgroup that would benefit from PAH therapies once volume status and LAP have been optimized. However, this approach needs to be examined in carefully controlled clinical trials.

At present, HFpEF-PH should be managed according to guideline-accepted therapies (52) with diuretics, risk factor modification to impact the underlying substrate, and treatment of comorbidities (e.g., sleep-disordered breathing). The question now is, "What algorithm can be developed to study the effect of PAH-specific drugs in HFpEF-PH in the context of optimal control of LAP?" Choosing the right timing to introduce a PAH-specific therapy may be critical. Novel and aggressive unloading strategies at the level of the left atrium (53) may pave the way for safe, effective pulmonary vasodilator trials in Cpc-PH. Aggressive left atrial decompression has the potential to drive favorable venous remodeling. In conjunction with modification of risk factors and comorbidities, long-term decompression of LAP might allow for adequate pulmonary venous and arterial unloading and gradual venous remodeling. The subsequent introduction of PAH-specific therapy may promote further arterial remodeling in an "unloaded" venous system, thus mitigating the likelihood of alveolar leak and pulmonary edema. It is in this context that PAH therapies might hold promise for improving the disease process and RV performance.

Should You Treat ILD-PH with PAH-Specific Therapies?

The prevalence of severe ILD-PH varies by the underlying cause of parenchymal lung disease, method of detection (echocardiography vs. cardiac catheterization), and cohort studied (unselected ILD clinic vs. patients referred for lung transplantation) (3, 14, 54–57). Yet, when detected, even mild PH is associated with increased morbidity and mortality in patients with ILD (58–63). Unfortunately, despite the explosion over the past two decades of new medications for PAH, there are currently no approved evidence-based therapies for PH complicating chronic lung diseases. Pirfenidone and nintedanib, recently approved by the U.S. Food and Drug Administration for the treatment of idiopathic pulmonary fibrosis (IPF), modestly slow loss of lung function, although their effects on PH in these patients was not specifically examined (64–66). Therefore, in patients with advanced ILD and established PH, where lung transplant remains the only effective treatment option, PAH-specific drugs become a tempting therapeutic opportunity. However, because of the lack of convincing data that pulmonary vasodilators are beneficial in this patient population (67, 68), the most recent PH treatment guidelines clearly state that "the use of drugs approved for PAH is not recommended in patients with PH due to lung disease" (3). This recommendation appears justified after the recent termination of a phase 2 ILD-PH study because of a higher rate of death and other serious adverse events noted in patients randomized to riociguat compared with placebo (69). However, extrapolating these results to all other subtypes of patients with ILD-PH is problematic, because this study included only patients with symptomatic PH associated with idiopathic interstitial pneumonias.

So, how to treat a patient with chronic lung disease who develops PH, or even more importantly, what constitutes clinically significant PH that warrants therapy in these patients? A closer look at the studies examining the efficacy of pulmonary vasodilators in patients with ILD leaves one wondering whether there is truly "evidence of absence" or merely "absence of evidence." Studies published to date have largely included an unselected IPF patient cohort (i.e., those with and without PH) (70–75) or were uncontrolled (76–82). Notably, only one randomized, double-blind, placebo-controlled trial of PAH-specific therapy has been completed exclusively in patients with ILD-PH, and although this study failed to demonstrate efficacy, it was rather small and included only patients with IPF with PH (83). In light of these shortcomings in the available data, a survey of current practice patterns suggests that PAH-specific therapies are prescribed to patients with WHO group 3 PH at most U.S. PH referral centers despite current guidelines (84). The majority of PH physician specialists, with an average ($\pm$SD) of 16.5 $\pm$ 5.8 years of experience treating patients with PH, reported that evidence of RV dysfunction or failure was a significant factor influencing their decision to treat patients with WHO group 3 PH with PAH-specific therapy (84). In support of this practice, a *post hoc* subgroup analysis of the STEP-IF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial demonstrated that patients with evidence of RV dysfunction by echocardiography were the most likely to benefit from therapy, with a mean increase of 99.3 m (95% confidence interval, 22.3–176.2 m) in their 6MWD at 12 weeks compared with baseline (85). Therefore, evidence of a possible circulatory limitation to functional capacity, as opposed to predominantly a ventilatory limitation, may identify a subset of patients in whom studies of pulmonary vasodilator therapy should be focused. However, such an approach needs to be validated prospectively. In addition to the limitations of the available evidence, there is also a concern for potential hypoxemia due to worsening $\dot{V}/Q$ mismatch with systemically administered pulmonary vasodilators in patients with advanced parenchymal lung disease (76, 77). However, oxygenation was not adversely affected in an uncontrolled

study of patients with advanced ILD-PH awaiting lung transplant treated for 12 weeks with intravenous treprostinil (82). Whether the impact of $\dot{V}/\dot{Q}$ mismatch is offset by improvements in RV performance and cardiac output in a subset of patients with ILD-PH with symptoms and exercise intolerance due to circulatory limitations should be tested in a properly controlled clinical trial.

Indeed, current guidelines acknowledge the need to further subtype patients with group 3 PH (3, 67). On the basis of hemodynamics obtained by right heart catheterization, "severe" PH is defined as mPAP greater than 35 mm Hg or greater than or equal to 25 mm Hg in the presence of a low cardiac index ($<$2.5 L/min/m^2) (3). Likewise, guidelines suggest that pulmonary vasodilator therapy may be considered when "severe" PH is present in the setting of "mild" lung disease (3). However, these distinctions are easily blurred in clinical practice, when patients present with other relevant comorbidities associated with the development of PH (e.g., HFpEF and obstructive sleep apnea). Similarly, patients with connective tissue disease, especially those with SSc, represent a unique challenge because of the potential coexistence of parenchymal lung disease and pulmonary vasculopathy. Thus, a "one-size-fits-all" approach for determining those patients with ILD-PH who are appropriate to treat with pulmonary vasodilators may be inadequate (86). For instance, in a retrospective cohort study of treatment-naive incident cases of chronic lung disease–associated severe precapillary PH, as defined above, PAH-specific therapy did not result in significant improvements in New York Heart Association functional class or 6MWD (87). Moreover, data from the COMPERA registry did not demonstrate any significant difference in the proportion of patients who improved their 6MWD or functional class with PAH-specific therapy in patients with ILD-PH who fulfilled the definition for severe PH versus those who did not (88). In addition, treatment of patients with SSc ILD-PH with PAH therapy has demonstrated mixed results in retrospective cohort studies (89, 90). However, given their dismal prognosis and the possibility of a separate and potentially "responsive" pulmonary arteriopathy, patients with SSc ILD-PH are often given a trial of pulmonary vasodilators with close follow-up at expert centers.

Perhaps we should be asking not when is it appropriate to treat PH associated with ILD, but rather what are we treating? Although hypoxia was traditionally believed to be the major driver of PH in patients with ILD, there is evidence that PH can develop independent of hypoxemia (91, 92). In addition, the fact that PH only occurs in a subset of patients with established ILD and is weakly associated with either lung function or radiographic fibrosis scores also hints at the complexity of this disease (56, 93). Currently recognized subtypes of ILD-PH are based on the degree of elevation in mPAP and the presence of RV dysfunction but do not further delineate between patients with reduced functional capacity due to a circulatory versus a primarily restrictive ventilatory impairment. Evidence of circulatory limitation by cardiopulmonary exercising testing has been previously reported in patients with ILD-PH (94, 95) and offers a means for further enriching clinical trials with subjects who may have the most to gain from pulmonary vasodilator therapy. Furthermore, recent technical advances have increased the feasibility of cardiac magnetic resonance imaging in patients with significant pulmonary disease (96–98), thus enabling more precise clinical phenotyping in patients with ILD-PH through high-resolution quantification of RV function as well as noninvasive determination of mPAP and pulmonary vascular resistance (99–103).

Whether a subset of patients with ILD-PH will benefit from PAH-specific therapy remains an untested hypothesis. Thus, at this time, optimizing oxygen delivery, treating the underlying lung condition as well as associated comorbidities (e.g., left heart disease, volume overload), and referral of eligible patients for lung transplant remain the only valid recommendations for patients with ILD-PH (3).

Are You Treating Unrecognized PVOD with PAH-Specific Therapies?

Idiopathic and heritable PVOD and PCH are rare, difficult-to-diagnose, overlapping variants with an estimated prevalence of 1 to 2 cases per million (104, 105). However, this estimate does not account for PVOD associated with connective tissue disease (mainly SSc) or other associated risk factors (e.g., chemotherapy or exposure to organic solvents), nor does it account for patients misclassified with IPAH (104–106). Indeed, PVOD can masquerade as IPAH, and distinguishing between the two on clinical grounds is challenging because of broadly similar physical and hemodynamic findings (107). PVOD is characterized by a progressive clinical course, the lack of long-term response to PAH medical therapies, and possible occurrence of vasodilator-induced pulmonary edema, resulting in the need for early lung transplantation in eligible patients (104). On the basis of these observations, PVOD is classified under a separate subgroup category in the PH classification (3). The recent identification of an autosomal recessive form of PVOD and PCH due to biallelic mutations of the *EIF2AK4* (eukaryotic translation initiation factor 2 α kinase 4) gene (15, 108, 109) further supports these entities as overlapping variants in the current classification.

Although histology is necessary to make a definitive diagnosis of PVOD, histological confirmation is usually only available on postmortem or explanted lung specimens because of the inherent risks of lung biopsy in this patient population. Therefore, a systematic, noninvasive strategy integrating results from high-resolution computed tomography, D_{LCO}, arterial blood gas analysis, and 6MWD testing with pulse oximetry is necessary to identify PVOD as the cause of precapillary PH (107). Importantly, each of these clinical tests is currently recommended as part of the diagnostic workup in all patients with PH (3). In the largest case series to date, patients with histologically proven PVOD had significantly lower D_{LCO} and Pa_{O_2} as well as more severe exertional oxygen desaturation than patients with histologically confirmed IPAH, heritable PAH, and anorexigen-associated PAH (107). Furthermore, the presence of two or more abnormalities on high-resolution computed tomography, including centrilobular ground-glass opacities, thickened interlobular septa, and mediastinal lymphadenopathy, was strongly associated with PVOD, although their absence did not rule out PVOD. Importantly, patients with PVOD have a normal PAOP and are otherwise hemodynamically indistinguishable from patients with other forms of precapillary PH (15, 104, 107). Although acute

vasodilator testing with relatively low concentrations of inhaled nitric oxide (10 ppm) did not cause pulmonary edema in patients with PVOD, it also did not identify the approximately 20% to 40% of patients who would eventually develop pulmonary edema with chronic use of PAH-specific therapy (15, 107).

Although encountered much less frequently in clinical practice than ILD-PH, HFpEF-PH, and even PAH, a high index of suspicion for PVOD is essential to avoid potential adverse effects (e.g., pulmonary edema with pulmonary vasodilators) and delays in definitive therapy (i.e., lung transplantation) (104). Similarly, in patients with presumed IPAH who are not responding well to therapy, clinicians should consider whether they have adequately ruled out PVOD. This is particularly true in the setting of PH due to SSc, where PVOD has been recently described in a significant proportion of patients (110, 111). Notably, up to 10% of patients diagnosed clinically with IPAH are ultimately found to have histological evidence of PVOD on lung biopsy or at autopsy (112). Thus, in contrast to the quandary of whether there is a subset of patients with HFpEF-PH or ILD-PH who could benefit from PAH-specific therapy, here the challenge for clinicians is whether or not the patients with "PAH" they are treating have been thoroughly evaluated for suspected PVOD before initiating therapy. Recently, whole-genome sequencing of more than 800 patients diagnosed clinically with IPAH or familial PAH revealed a small subset of patients with biallelic *EIF2AK4* mutations (113). Compared with patients with PAH without *EIF2AK4* mutations, those with mutations had a lower transfer coefficient for carbon monoxide and were diagnosed with PAH at a younger age (median [interquartile range], 29 [23–38] years). Similar to patients clinically diagnosed with PVOD, patients with PAH with biallelic *EIF2AK4* mutations ($n = 9$) did not improve their functional status with pulmonary vasodilators and had a shortened survival. Therefore, genetic testing for biallelic *EIF2AK4* mutations should be considered in younger patients clinically diagnosed with IPAH but with a low diffusing capacity to prompt consideration of early referral for lung transplantation. Reduced expression of GCN2 (general control nonderepressible 2), the protein product of the *EIF2AK4* gene, in patients with IPAH and heritable PAH with *BMPR2* (bone morphogenetic protein receptor type 2) mutations, further highlights a previously unrecognized link between PVOD and PAH pathobiology (114).

Similar to HFpEF-PH and ILD-PH, there is no currently approved medical therapy for PVOD. However, in addition to supportive therapy with diuretics and oxygen, the approach to treatment of patients with PVOD with PAH-specific therapy is complex and potentially life threatening and therefore should only be initiated at a PH center with experience in caring for these patients (3).

Conclusions

Although finding promise for treatments that might eventually cross PH WHO groups, the symposium clearly pointed out that improved phenotyping is still needed to better determine who will benefit from these therapies. In addition to well-planned, randomized, double-blind, placebo-controlled trials, efforts such as the NHLBI Pulmonary Vascular Disease Phenomics Program (PVDOMICS) are needed to move the field forward from our "one-size-fits-all" PH strategy toward a precision medicine approach that will lay the groundwork for the development of appropriate and effective therapeutic interventions. Similarly, large, contemporary epidemiological studies are providing further evidence that pulmonary vascular disease exists on a continuum rather than simply above a threshold resting mPAP (115). In conjunction with more refined clinical and physiological phenotyping, integrated "omics" approaches and large data analytics offer the opportunity to *1*) deconstruct our current classification of PH subtypes; *2*) improve our understanding of molecular mechanisms leading to pulmonary vascular disease in the context of complex, multifaceted conditions, such as left heart disease and chronic lung diseases; and *3*) characterize treatment responders versus nonresponders in future clinical trials (86, 116). As the field moves from population to precision medicine (86, 116, 117) and focuses future resources on deep phenotyping (advanced imaging, transcriptomics, proteomics, and metabolomics), we may eventually realize our potential to identify relevant clinical and molecular features, shattering our icebergs into more granular groupings of phenotypically distinct crystals of varying shapes and sizes. ■

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