Pulmonary Hypertension Overlap Syndromes

A Real Entity?*

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The most widely accepted classification of pulmonary hypertension (PH) has relied on a series of conferences termed the World Symposia on Pulmonary Hypertension. The first World Symposia on Pulmonary Hypertension took place in 1973 in Geneva, Switzerland (1), under the auspices of the World Health Organization, and was followed 25 years later by the Evian (France) symposium of 1998. The Evian classification was comprehensive and took both pathophysiological and therapeutic aspects into consideration. At subsequent meetings in Venice, Italy (2003) (2), Dana Point, California (2008) (3), and most recently Nice, France (2013) (4), updated classifications were adopted. Although there have been significant changes over the years in the classification system, 5 general groups have remained intact: group I, pulmonary arterial hypertension (PAH); group II, PH secondary to left heart disease; group III, PH secondary to lung disease; group IV, PH secondary to chronic pulmonary thromboembolism; and group V, PH with unclear multifactorial mechanisms.

Accompanying the classification of PH is a series of hemodynamic and clinical definitions that help in classifying patients. PH in general is (somewhat) arbitrarily defined as a mean resting pulmonary artery pressure ≥25 mm Hg with pre-capillary PH characterized by a pulmonary artery wedge pressure of ≤15 mm Hg (5). Pre-capillary PH is prototypic of PAH (group I), while being present in most other forms of PH, with the notable exceptions of group II PH. The transpulmonary gradient, the difference between mean pulmonary artery pressure and the pulmonary capillary wedge pressure (PCWP), is elevated in pre-capillary PH (6).

Group II PH comprises the largest group of patients with PH, and the presence of PH markedly affects the prognosis of patients with left-sided heart failure (HF). Both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) may be accompanied by PH (6). In a community cohort of patients with HFpEF, the presence of PH was highly prevalent, was severe, and distinguished patients with symptomatic HF from patients with hypertensive heart disease without HF symptoms (7).

The presence of elevated left atrial filling pressure, reflected in the PCWP, contributes directly to elevations in pulmonary pressure through passive transmission. This pressure elevation does not result in an elevation in the transpulmonary gradient. In some group II patients, however, an additional “active” component of pulmonary arterial reactivity develops. Pathophysiologically similar processes may be operative to those in PAH, including endothelial dysfunction, vasoconstriction, overexpression of endothelin, and increased transforming growth factor-beta signaling (8–10). In the setting of any elevation of pulmonary pressures, reflective waves may affect pulmonary artery compliance, an emerging component in the progression of PH (11).

There may, therefore, be common pathways that are operative in all PH cases, with ultimately similar pathology. In group II patients, the resulting arterial
remodeling in the small resistance vessels of the pulmonary circulation leads to PH that appears to be “out of proportion” to the elevation in left atrial pressure. It has, therefore, been proposed that the PH itself in group II patients may be a target of therapy, and given the common pathophysiological mechanisms to PAH, PH-specific therapies may be appropriate and of benefit in this group of patients, particularly when there is a significant “active” component of the PH.

In this issue of the Journal, Opitz et al. (12) present data from COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), an ongoing European registry of patients receiving PH-specific therapies. They divided the patients in the register to those with “typical idiopathic pulmonary arterial hypertension (IPAH)” (2 or fewer risk factors for left heart disease), with “atypical IPAH” (3 or more risk factors for left heart disease), and with a diagnosis of HFpEF. Not surprisingly, the patients with atypical IPAH and HFpEF were older, had more comorbidities, and had lower 6-min walk test scores, although pulmonary pressures were similar. Patients in all 3 groups responded to PH-specific therapies, but there was a gradient in response: patients with typical IPAH responded the best, those with HFpEF responded the least, and those with atypical IPAH were in-between. The authors conclude that there is a continuum among these 3 conditions, and that individual patients may belie the neat classification into group I versus group II as envisioned in the PH classification.

The strength of the authors’ analysis is 2-fold. First, they provide a real-world assessment of patients with PH and their response to current-day therapies. In addition, their analysis highlights important limitations of our current classification of PH with implications for diagnosis and treatment.

There are, however, significant limitations to the data, which should be taken into account. The patients were by definition selected by having been prescribed PH-specific therapy, and therefore are not reflective of the universe of patients with PH. The hemodynamic parameters of the patients were site reported without the benefit of a core laboratory and without monitoring of the accuracy of the measurements. Right heart catheterization measurements can be challenging with issues of accurate determination of the zero value (should be measured at the level of the right atrium), respiratory variation, and catheter fling. A common error is to record the computer-generated mean PCWP rather than measure the end-expiratory PCWP. In addition, variations in patient hydration status and influence of diuretic therapy may affect hemodynamic measurements. Indeed, in patients with diagnostic uncertainty, maneuvers such as a fluid challenge may help distinguish between group I and II patients, and should be performed in atypical patients, particularly if on diuretic therapy.

Despite these limitations, the authors should be commended for raising a provocative issue and challenging accepted dogma. Most importantly, their analysis has implications for therapy of patients with atypical presentations as well as HFpEF with PH, suggesting that PH-specific therapies may be considered in such patients. Historically, however, therapies that were proven to be efficacious for PAH were often ineffective in HF, and vice versa. The endothelin receptor antagonists have generally not been beneficial in HF, despite amelioration in hemodynamic parameters. For example, the large ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trial of bosentan, a nonselective endothelin blocker, in patients with HFpEF not only showed no mortality benefit, but showed that hospitalizations for HF actually increased (13). Conversely, angiotensin-converting enzyme inhibitors as well as other systemic vasodilators typically indicated in HF management are not generally of benefit in PAH and may cause significant hypotension due to selective vasodilation of the systemic circulation (14). Beyond a lack of sufficient evidence for their efficacy, PH-targeted therapies theoretically may increase pulmonary flow and induce pulmonary congestion in the setting of increased left atrial pressure.

The authors point out that the results of their analysis from COMPERA are at least partially supported by recent observations from the AMBITION (AMBrilsentan and Tadalafil in Patients With Pulmonary Arterial Hypertension) trial of combination therapy versus monotherapy in PAH (15). In the AMBITION study, we, along with the rest of the trial leadership, noted that a significant minority of the patients, although formally meeting the hemodynamic definition of group I patients with PH and PCWP <15 mm Hg, were not typical group I patients with PAH—they were older, many were male, and some not only had cardiac risk factors, but also had a history of coronary artery disease. The concern was that these patients may have met the entry criteria (e.g., due to high-dose diuretic treatment) but did not actually have PAH, and thus were not the intended patient population. A protocol amendment was implemented that further tightened the entry criteria in the study and excluded these patients from the

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primary analysis set. This change was implemented before unblinding of any data and therefore did not introduce any bias into the study. Interestingly, at the conclusion of the study, these “atypical” patients also responded to combination PH therapy in comparison to PH monotherapy, although they did have a higher discontinuation rate and somewhat attenuated response.

Several PH-specific therapies are currently being evaluated for efficacy in left HF patients with PH, with both HFpEF and HFrEF being studied (10). While awaiting the results of these studies, should PH-specific therapies be instituted in these patients? The results of the COMPERA registry should be regarded only as hypothesis-generating as they are uncontrolled. Given the potential for harm, previous lack of benefit in randomized studies, and high costs of these therapies, routine use of PH-specific therapies cannot be recommended at this time.

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**REFERENCES**


