Defining the Phenotypes for Pulmonary Hypertension Associated With Diastolic Heart Failure

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Pulmonary hypertension (PH) is well known to be associated with left heart failure, which is probably the single most common cause of abnormally elevated pulmonary arterial pressure (>25 mm Hg by consensus). Estimates range up to 250,000 patients with PH associated with heart failure in the United States today, making it far more prevalent than other forms of PH. Consistent with this, more than three-quarters of unselected patients referred for cardiac ultrasound to a single community-based center and found to have an elevated estimated pulmonary arterial (PA) systolic pressure were subsequently determined to have a left ventricular (LV) cause. Despite its prevalence, though, the pathophysiology and phenotypic characteristics of PH associated with left heart failure are not well understood.

By expert consensus, the World Health Organization has classified PH into 5 groups, based partly on pathophysiologic and hemodynamic characteristics. Group 1, referred to as pulmonary arterial hypertension (PAH), includes idiopathic and hereditary varieties as well as PAH associated with connective tissue disease, congenital heart disease, portal hypertension, HIV, and others. PH owing to elevated left heart filling pressure is classified as group 2 (pulmonary venous hypertension), including PH attributable to LV systolic dysfunction, LV diastolic dysfunction, and valvular disease. Some prefer the term “heart failure with a preserved LV ejection fraction” (HFpEF) over “diastolic” heart failure because not all such patients necessarily have evidence of diastolic dysfunction, but the terms are often used interchangeably.

An elevation in mean PA pressure is expected when LV filling pressure increases because this is necessary to maintain blood flow. Most of the time, the increase is “proportionate” or “passive”—enough to maintain the transpulmonary gradient (TPG), the pressure difference between mean PA pressure and the pulmonary capillary wedge pressure (PCWP). However, in an estimated quarter to third of cases (depending on the definition), the elevation in mean PA pressure is greater than that necessary to maintain the TPG and becomes “disproportionate” or “reactive,” giving rise to an elevated pulmonary vascular resistance (Figure). This phenomenon was first described in association with mitral valve disease and was thought to be a mechanism for protecting the capillary bed from higher pressures as the pulmonary arteries become restricted and remodeled.

The mechanism for this disproportionate elevation in mean PA pressure is poorly understood but appears to involve at least some of the same pathophysiologic mechanisms as described in PAH, including endothelial cell dysfunction, increased circulating endothelial levels, and decreased release of nitric oxide. Initially, the process is thought to be reversible and PA pressure drops in response to vasodilators, but “fixed” disease, unresponsive to acute vasodilator administration, is thought to occur eventually. Although clinical characteristics of “disproportionate” PH associated with HFpEF (PH-HFpEF) have been previously described and despite the commonness of the condition, the most recent update of the World Health Organization classification retained a single category for “diastolic dysfunction” and did not include a separate category for PH-HFpEF.

In this context, the report by Thenappan et al. in this issue of Circulation: Heart Failure is noteworthy because it provides a more complete characterization of PH-HFpEF than previously reported and is based on a sizable number of patients. It also compares PH-HFpEF not only with PAH but also with HFpEF, both entities that are important to distinguish from PH-HFpEF. Not surprisingly, because the previous reports have made similar observations including the association of PH-HFpEF with the metabolic syndrome, the authors found that compared with PAH, PH-HFpEF is associated with more advanced age and a number of comorbidities (diabetes, obesity, hypertension, coronary artery disease). The ability of left atrial enlargement by ultrasound (more often seen with PH-HFpEF) and right atrial enlargement (more often seen with PAH) to differentiate between the entities is also not surprising.

More remarkable is the strong association of PH-HFpEF with female sex compared with HFpEF, something not observed in some previous studies. The association was as strong as the well-known association between PAH and female sex, raising the possibility of a shared sex-related predisposition, perhaps genetic or hormonal. However, this also highlights a significant weakness of the design, which was to compare PH-HFpEF patients derived from referrals to an outpatient practice accrued retrospectively and then prospectively over more than 20 years with HFpEF patients obtained prospectively by screening patients for heart failure over a 1-year period. Because this introduces potential bias, it is conceivable that the sex differences are more reflective of differences in patient accrual than the disease subsets themselves.
A surprising omission from the list of characteristics associated with PH-HFpEF in the Thenappan study is obstructive sleep apnea. Considering its well-known association with the metabolic syndrome and pulmonary hypertension and the fact that 46% of PH-HFpEF patients were obese as opposed to only 15% of the PAH patients, it seems possible that obstructive sleep apnea was associated with PH-HFpEF in the Thenappan study. Yet, the authors do not comment on it, perhaps because obstructive sleep apnea was not captured in their data base. If so, this is unfortunate because it is conceivable that its inclusion might have improved the ability of clinical characteristics to differentiate between the different PH entities.

The hemodynamic differences between the groups are also notable, although some of them were predictable, based on the hemodynamic criteria used to distinguish the different subsets. Thus, higher LV filling pressures and TPGs in the heart failure groups were expected. The higher aortic systolic pressure in the PH-HFpEF than in the PAH group undoubtedly reflects the greater occurrence of systemic hypertension in the former group, and substantially higher TPG in the PAH group reflects the severe PH and normal PCWP that is typical in cohorts of these patients. The pulmonary vascular resistance in the PAH group was also much higher than in the PH-HFpEF group, related to the much higher TPG and lower cardiac output, although the latter difference probably would have been eliminated had cardiac indices been calculated (in view of the much higher occurrence of obesity in the PH-HFpEF than the PAH group). This supposition is supported by the fact that PA oxygen saturations were similar.

The hemodynamic variables also highlight another weakness of the study: the imprecision of the definitions for the different hemodynamic subsets. These definitions are based on expert opinion: PCWP of ≤15 mm Hg for PAH and >15 mm Hg for PH-HFpEF and TPG of ≤12 mm Hg for HFpEF and >12 mm Hg for PH-HFpEF. The authors acknowledge this problem, and the potential difficulty of accurately measuring PCWP or even LV end-diastolic pressure especially in the face of large, rapid swings in intrathoracic pressure as often occurs in dyspneic and/or obese patients. Also, actual pressure measurements may vary between patients and within patients over time, depending on specific conditions. For example, some patients with PH-HFpEF have a PCWP <15 mm Hg when they undergo catheterization after aggressive diuresis. Other patients with idiopathic PAH may have a PCWP >15 because they have massive RV enlargement that impinges on the LV and interferes with filling due to ventricular interdependence. Likewise, the definition of a “normal” TPG has not been established empirically and ranges for this value in the literature range from 10 to 15 mm Hg. This uncertainty adds variability to the distinctions between the groups and can make differentiation of patient subsets very challenging.

Nonetheless, Thenappan et al have been able to draw sharp distinctions between the groups despite the uncertainties in the definitions. In fact, the phenotypic differences could be useful when clinicians are attempting to classify patients with borderline hemodynamic variables. For example, based on the study’s findings, an elderly obese patient with systemic hypertension and a PCWP of 14 mm Hg who has undergone recent diuresis is more likely to have PH-HFpEF than PAH despite the wedge pressure <15 mm Hg. This inference is supported by the multivariable analysis and receiver operating characteristic curves generated in the Thenappan study. The receiver operating characteristic curve that incorporates age, other clinical characteristics, and echocardiographic and hemodynamic variables achieved an impressive 0.97 area under the curve in differentiating between PH-HFpEF and PAH.

Despite the fidelity of the variables in differentiating between the groups, they are still likely to be quite heterogeneous in other respects. The PAH group is undoubtedly highly heterogeneous, comprising not only idiopathic PAH but also PAH associated with connective tissue disease, congenital heart disease, and others. Similarly, the PH-HFpEF group is likely to contain patients with differing characteristics. For example, patients with the metabolic syndrome would appear to differ phenotypically from elderly asthenic patients with longstanding systemic hypertension. As more is learned about the pathogenesis of these diseases, multiple additional phenotypes may reveal themselves.

What can we glean about the pathogenesis of PH-HFpEF from the findings of the Thenappan study? The female preponderance, as previously mentioned, suggests a potential genetic or hormonal predisposition, and, as more is learned about the connection between the metabolic syndrome and inflammatory signaling pathways, the association between the metabolic syndrome and PH suggests a possible inflammatory component. Studies investigating the genomic differences of PH-HFpEF and HFpEF as well as inflammatory mediators may be revealing.

The present study did not examine responses to therapy among the 3 hemodynamic subsets, and use of specific PAH...
therapies was surprisingly infrequent, especially in the PAH group, with usage rates of $\leq$6%, even in the PAH subgroup. This probably reflects the fact that the registry at the University of Chicago had enrolled many patients during the 1980s and 1990s, before most of the currently available therapies became available. Still, use of endothelin receptor antagonists (6%) and phosphodiesterase inhibitors (4%) was the same in the PAH and PH-HFpEF groups. Prostacyclins were used in 3% of the PAH patients but in none of the PH-HFpEF patients, perhaps because of an earlier randomized, controlled trial that showed a trend toward greater mortality in patients with LV systolic dysfunction treated with intravenous epoprostenol, leading to early termination of the trial and a contraindication against using the drug in patients with LV ejection fraction $<30\%$. Subsequent randomized, controlled trials on endothelin receptor antagonists have failed to show significant benefit in patients with LV failure.

Despite preliminary findings suggesting that phosphodiesterase 5 inhibitors may be beneficial in LV failure, their use in PH-HFpEF and HFpEF cannot be endorsed pending completion of further studies such as the 24-week randomized, controlled trial currently ongoing that examines the effect of sildenafil on maximal oxygen uptake in patients with HFrEF regardless of PA pressure (RELAX trial). Pending these results, the therapy of PH-HFpEF and HFpEF should aim to optimize systemic blood pressure and fluid volume, attempting to normalize left heart filling pressure. Studies conducted after correction of mitral valve stenosis or insertion of LV assist devices indicate that there can be reversal of PH-HFpEF after normalization of the PCWP.

By carefully analyzing their relatively large registries of PH and HFpEF patients and providing statistical models of differentiating characteristics, Thenappan et al present the differentiating characteristics, Thenappan et al present the differentiating characteristics of PH-HFpEF after normalization of the PCWP. This probably reflects the fact that the registry at the University of Chicago had enrolled many patients during the 1980s and 1990s, before most of the currently available therapies became available. Still, use of endothelin receptor antagonists (6%) and phosphodiesterase inhibitors (4%) was the same in the PAH and PH-HFpEF groups. Prostacyclins were used in 3% of the PAH patients but in none of the PH-HFpEF patients, perhaps because of an earlier randomized, controlled trial that showed a trend toward greater mortality in patients with LV systolic dysfunction treated with intravenous epoprostenol, leading to early termination of the trial and a contraindication against using the drug in patients with LV ejection fraction $<30\%$. Subsequent randomized, controlled trials on endothelin receptor antagonists have failed to show significant benefit in patients with LV failure.

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