Discerning Pulmonary Venous From Pulmonary Arterial Hypertension Without the Help of a Catheter

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Pulmonary hypertension (PH) is an increasingly recognized cause of dyspnea and effort intolerance that may develop in response to 5 broad categories of disease. After excluding patients with hypoxic pulmonary disease, thromboembolism, and other systemic disorders, the differential diagnosis narrows to group I PH (or pulmonary arterial hypertension [PAH] due to abnormalities in the pulmonary arterial vasculature) and group II PH (due to pulmonary venous hypertension from left-sided heart disease). Group II PH is straightforward to diagnose noninvasively when obvious culprits such as left ventricular (LV) systolic dysfunction or valvular heart disease are identified by echocardiography. However, half of patients with left-sided heart failure have preserved ejection fraction (HFpEF), without significant valvular disease, and it can be challenging to distinguish this group of patients from those with PAH, who similarly have a normal EF, elevated pulmonary artery (PA) pressure estimates, and diastolic dysfunction on echocardiogram. The treatments and mechanisms underlying PAH and HFpEF are quite different, so distinction of one from the other is of obvious clinical importance.

In the absence of shunts, the pulmonary and systemic circulations receive approximately the same amount of blood flow per minute, but this is where the similarities end. Pulmonary vascular resistance (PVR) is >10-fold lower than resistance in the systemic circulation, and the pressure in the venous bed draining the pulmonary arteries (pulmonary veins, left atrium) accounts for a much greater percentage of total PA pressure (40% to 60%) than the corresponding downstream venous pressure in the systemic circuit (right atrium, accounting for only ≈5% of systemic pressure). Because PA pressure is so heavily influenced by left heart filling pressures, it is not surprising that group II PH is the most common form of PH.

PH has traditionally been defined by mean PA pressure in excess of 25 mm Hg. Mean PA pressure is equal to the product of cardiac output and PVR summed with pulmonary wedge pressure (PWP). Thus, abnormalities in any 1 (or more) of these 3 components can cause PH. PAH is defined hemodynamically by elevated PVR with normal PWP. HFpEF is defined by an elevated PWP with or without PH. Just as in HF with reduced EF, patients with HFpEF may develop elevated PVR in response to chronic pulmonary venous hypertension, although the mediators and pathways underlying this process remain unclear. Fundamentally, the distinction between PH due to HFpEF and PAH is based on the PWP, but PWP is notoriously difficult to determine noninvasively, which raises the question of how we might be able to discriminate these entities on the basis of clinical grounds before (or perhaps in place of) invasive assessment. Another intriguing question is whether or how patients with HFpEF with pulmonary vascular disease (high PVR) differ from those with HFpEF with normal PVR.

These questions are the focus of an interesting study by Thenappan and colleagues in this issue of Circulation: Heart Failure. The authors report cross-sectional data from the following 3 well-characterized groups of patients who underwent invasive hemodynamic assessment: (1) patients with HFpEF without pulmonary vascular disease (HFpEF group) characterized by high PWP with normal PVR and normal transpulmonary gradient (defined as mean PA pressure minus PWP); (2) patients with HFpEF with pulmonary vascular disease (PH-HFpEF group) characterized by high PWP with high PVR, transpulmonary gradient, or both; and (3) PAH. The PH-HFpEF and PAH groups were drawn from a PH clinic referral population at the University of Chicago, whereas the HFpEF group was identified through screening of inpatient records at Northwestern University.

Compared with patients with PAH, patients with PH-HFpEF were older (mean age, 64 versus 48 years) and had greater comorbidity burden, including more prevalent hypertension, coronary disease, diabetes, and obesity. In receiver operating characteristic analysis, age alone distinguished PH-HFpEF from PAH, with an area under the curve of 0.81. Adding clinical variables to this model (comorbidities, functional class, creatinine level, and medications) increased the area under the curve to 0.92. These results confirm and extend the findings of 2 recent studies reporting similar results and are consistent with current guidelines used to identify patients more likely to have PH due to HFpEF. Concentric LV remodeling and hypertrophy are structural changes commonly observed in HFpEF, but somewhat surprisingly, LV mass and wall thickness were similar in HFpEF and PAH and did not discriminate between the groups. In contrast, the most striking echocardiographic differences were identified at the atria, with more left atrial enlargement in PH-HFpEF (64% versus 18%) and more right atrial enlargement in PAH (89% versus 68%). Despite these differences, adding echocardio-

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graphic data to the model did not significantly enhance predictive ability. A fourth model that added invasive data to clinical and echocardiographic findings resulted in modest improvement but did not provide nearly the incremental discriminatory value as age or age plus clinical data. An important implication of these findings is that most of the information required to distinguish PAH from PH-HFpEF (at least in a PH referral population) is readily available from brief review of the clinical chart and demographics.

Although the variable used to determine the presence or absence of PH is the pressure measured in the PA, use of the term pulmonary arterial hypertension is historically restricted to patients with group I PH. Moreover, the term pulmonary hypertension in and of itself often is equated with an elevated PVR rather than simply with an elevated pressure. In the current study, the authors appropriately refer to the 2 HFpEF groups as patients with or without pulmonary vascular disease, yet the terms designating the groups are a little misleading. For example, Figure 2 in their article shows that ≈50% of the patients with HFpEF “without PH” do in fact have elevated PA pressures, as defined by current criteria.1

With increasing recognition of the prevalence and importance of PH in HF and pulmonary disease, it will be important to use precise, easily understood terminology to avoid confusion in the literature and everyday practice. As the authors point out, when pulmonary venous pressures are high, it is quite difficult to not have at least mild PH simply because the high downstream venous pressure adds in series to resistive and flow-related PA pressure determinants.

Going a step further, one might then consider that PA pressure in patients with HFpEF without pulmonary vascular disease is essentially another indirect measure of PWP. This was illustrated in a recent invasive study examining patients with early stage HFpEF who did not have elevated PVR.8 It was observed that 76% of the variability in PA pressure during exercise was attributable to PWP pressures (Figure). More than 80% of patients with HFpEF have PH as estimated by echocardiography, and the presence of PH has been found to distinguish HFpEF from hypertensive heart disease better than other established echocardiographic markers of diastolic dysfunction, such as the E/e’ ratio, LV mass, and left atrial size.9 Recent studies have raised questions regarding noninvasive estimates of PWP,10,11 and as such, it would seem that the addition of echocardiography-estimated PA pressure to HFpEF diagnostic criteria is justifiable provided that other consistent HFpEF markers (older age, systemic hypertension, etc), as reported by the authors and others, are present.

Importantly, the validity of PA pressure as a surrogate for PWP will be violated in patients with pulmonary vascular disease, and it is difficult to discern noninvasively how much vascular disease is present in a given patient. Thenappan and colleagues5 report several intriguing differences when comparing patients with HFpEF with or without pulmonary vascular disease. Patients with elevated PVR had a worse functional class and were more likely to be women, yet comorbidities and most echocardiographic measures were similar. The functional class disparity is not surprising and may be due to more advanced disease in PH-HFpEF or deleterious effects of right ventricular dysfunction on exercise capacity. The sex difference is perplexing and may be partly related to the populations studied from 2 separate registries (PH referral versus inpatient screening). Setting aside these limitations, it is tempting to consider that there may in fact be fundamental sex-specific differences in the pulmonary vascular response to chronic left atrial hypertension, as has been observed in the LV response to systemic arterial hypertension.12 These questions merit further study.

There are some limitations to this study that should be considered. As the authors acknowledge, the data were drawn from 2 separate registries, which introduces bias that may have affected the results, particularly for the HFpEF versus PH-HFpEF comparisons. Data describing Doppler transmitral diastolic filling characteristics, tissue Doppler echocardiography, and pulmonary venous inflow patterns were not reported and would be of significant interest. The differences in medication use reported are difficult to interpret because they are confounded by marked differences in underlying comorbidities, and there may be further variability in prescribing behavior that make these less-reliable discriminators in other parts of the world. The analysis applied by the authors works well in their derivation cohort, but it remains to be seen whether this model would be as robust in a validation cohort, particularly one not drawn from a PH clinic referral population. The HFpEF group reported in this study did not show the characteristic LV remodeling changes noted in other studies, which raises questions regarding the applicability of the findings to other populations where concentric remodeling is more prevalent. Data regarding exercise capacity was not available in the HFpEF group without pulmonary vascular disease, and this would be an interesting comparison. Finally, there are no outcomes presented from these
cohorts, although certainly, the authors are tracking these data prospectively.

The insights reported by Thenappan and colleagues raise new questions for consideration. Does the right ventricular response to pressure overload differ in HFrEF and PAH, or is it merely a function of duration and severity of PH? Right ventricular function predicts outcome in PAH and HF with reduced EF, but the role of right heart-PA interactions at rest or during exercise in HFrEF remains largely unexplored. Is pulmonary vascular disease a therapeutic target in HFrEF? Pulmonary-specific arterial vasodilation can lead to marked elevation in PWP in patients with HFrEF, but phosphodiesterase-5 inhibitors, such as sildenafil, may not increase PWP and have been shown to improve exercise hemodynamics and aerobic capacity in HF with reduced EF.

The National Institutes of Health-sponsored RELAX (Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure) study is currently testing the effects of sildenafil on exercise capacity and cardiac structure and function in HFrEF. Does every patient with PH and normal EF need a catheterization? This larger question cannot be answered here, but certainly if pulmonary-specific vasodilator therapies are being considered, catheterization is essential. If pulmonary vascular disease emerges as a viable therapeutic target in HFrEF, then catheterization may be required to guide treatment in this group as well. Finally, how should the patient with normal EF, severe PH, and borderline elevated PWP be considered? According to established guidelines, this pattern is diagnostic of HFrEF. The data from Thenappan and colleagues tell us that if other findings such as advanced age, left atrial enlargement, and systemic hypertension are noted, we can make this diagnosis with a very high degree of confidence. However, what if the patient with this hemodynamic profile is younger with no comorbidities and normal left atrial size—are we still to conclude that the diagnosis is HFrEF? The authors’ data suggest that we should think twice in that scenario. Guidelines are necessarily binary and algorithmic, but overly rigid and slavish adherence to them may interfere with optimal diagnostic and therapeutic approaches for the individual patient. The current findings from Thenappan and colleagues provide us with a more solid foundation on which to synergize clinical and hemodynamic data in the care of patients with HF and PH.

Disclosures

None.

References


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