Pulmonary hypertension (PH) is an increasingly recognized cause of dyspnea and effort intolerance that may develop in response to 5 broad categories of disease.1 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.2 However, half of patients with left-sided heart failure have preserved ejection fraction (HFpEF),3 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.2

PH has traditionally been defined by mean PA pressure in excess of 25 mm Hg.1 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.4 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 colleagues5 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 results6,7 and are consistent with current guidelines used to identify patients more likely to have PH due to HFpEF.2 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 echocardiographic...
Recent studies have raised questions regarding noninvasive 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 echocardiography-estimated PA pressure to HFrEF diagnostic criteria is justifiable provided that other consistent HFrEF 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 colleagues9 report several intriguing differences when comparing patients with HFrEF 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-HFrEF 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 HFrEF versus PH-HFrEF 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 HFrEF 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 HFrEF 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\(^5\) raise new questions for consideration. Does the right ventricular response to pressure overload differ in HFpEF and PAH, or is it merely a function of duration and severity of PH? Right ventricular function predicts outcome in PAH\(^{13}\) and HF with reduced EF,\(^{14}\) but the role of right heart-PA interactions at rest or during exercise in HFpEF remains largely unexplored. Is pulmonary vascular disease a therapeutic target in HFpEF? Pulmonary-specific arterial vasodilation can lead to marked elevation in PWP in patients with HFpEF,\(^{15}\) 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.\(^{16}\)

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 HFpEF. 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 HFpEF, 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 HFpEF. 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 HFpEF? 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**


**Key Words:** Editorsials | catheterization | diastolic dysfunction | heart failure | hemodynamics | hypertension pulmonary
Discerning Pulmonary Venous From Pulmonary Arterial Hypertension Without the Help of a Catheter
Barry A. Borlaug

Circ Heart Fail. 2011;4:235-237
doi: 10.1161/CIRCHEARTFAILURE.111.962209
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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