Pulmonary hypertension (PH) is a significant public health problem that may develop from abnormalities in the pulmonary vasculature, with left-sided heart failure (HF), high cardiac output states, or any combination of these. The commonest cause is HF (group 2 PH), although many clinicians continue to associate the term PH with the much smaller cohort of patients with isolated pulmonary vascular disease (group 1 PH). A host of efficacious therapies improve outcome in group 1 PH, and when on appropriate treatment, this subgroup enjoys the highest survival rates. In contrast, group 2 PH is associated with the worst outcomes. Although trials are underway, there is currently no established treatment for group 2 PH, and some pulmonary vasodilators may even worsen outcome in patients with HF. Thus, distinction of these entities is of paramount importance.

Groups 1 and 2 are distinguished by the pulmonary capillary wedge pressure (PCWP), which is elevated (>15 mm Hg) in the latter and normal in the former. Accurate noninvasive assessment of PCWP is difficult, but if there is a low ejection fraction (EF) or significant left-sided valve disease, the diagnosis of group 2 PH is generally rendered with confidence. The more difficult distinction is between group 1 PH and PH caused by HF with preserved EF (HFpEF). Diagnosis of HFpEF is problematic because of the difficulty in noninvasively assessing PCWP and because PCWP is often normal at rest and elevated only during physiologic stresses such as exercise or volume expansion. As such, current guidelines recommend provocative testing (exercise or saline loading) to distinguish HFpEF from group 1 PH among individuals with normal PCWP and typical HFpEF risk factors; although there has been little data to support this practice.

In this issue of Circulation: Heart Failure, Robbins et al take an important step forward to inform current practices regarding the optimal hemodynamic assessment of patients presenting with PH. The authors performed a retrospective analysis of hemodynamic and clinical data from consecutive patients with PH undergoing fluid challenge at the Vanderbilt University Medical Center from 2004 to 2011. As per local practice standards, patients in their program received a 0.5-L bolus of normal saline over 5 to 10 minutes, provided there was PH (mean PA pressure ≥25 mm Hg) and both right atrial pressure (RAP) and PCWP were ≤15 mm Hg. All pressure tracings were reviewed by 1 of 2 coauthors with experience in hemodynamic assessment—an important methodologic strength given the notorious inaccuracies of computer-based measurements. Patients were predominantly women (74%) with mean age 50 to 60 years. Individuals with significant pulmonary parenchymal disease or low EF were excluded. Roughly 6% to 7% of patients had thromboembolic disease (group 4 PH).

Of 287 patients with analyzable data, 32 were found to have group 2 PH and 207 were found to have PH with normal PCWP. However, after fluid challenge, 46 (22%) of these patients initially labeled as non–group 2 PH displayed an increase in PCWP to >15 mm Hg, which the authors reclassified as occult pulmonary venous hypertension (OPVH). Clinical, echocardiographic, and hemodynamic characteristics of the OPVH group more closely resembled those of HFpEF patients, supporting the authors’ contention that this represents a pathophysiologically distinct PH subgroup. Mean PCWP was higher in the OPVH group (12±2 versus 9±3 mm Hg; P<0.001), meaning that less of an increase was necessary to achieve PCWP >15 mm Hg, yet the mean increase in PCWP in the OPVH group was significantly greater, suggesting that their reclassification was not purely ascribable to starting from a higher baseline. The administration of fluid challenge was safe, with no episodes of pulmonary edema observed. As might be expected, typical HFpEF risk factors including systemic hypertension, higher body mass index, and older age were associated with the diagnosis of OPVH.

The potential implications of this study are staggering, because perhaps 2 of every 9 patients presenting with apparent group 1 (or group 4) PH may in fact have a significant component of left-sided HF. Given the gravity of these implications, it is important to scrutinize these findings carefully in light of previous work and to consider the varied mechanisms of PCWP elevation in patients with and without cardiovascular diseases. Mean PCWP, measured at mid-A wave during end-expiration, closely approximates left ventricular (LV) end-diastolic pressure. High LV end-diastolic pressure in patients with HFpEF is commonly considered to be caused by a leftward shift in the LV end-diastolic pressure–volume relationship, reflecting an increase in chamber stiffness (Figure, A). However, high LV end-diastolic pressure may also be caused by a parallel shift upward, with no true alteration in the slope of diastolic pressure–volume relationship (ie, no difference in LV diastolic stiffness). The latter scenario is usually associated with increased pericardial restraint and enhanced diastolic ventricular interaction, where high right heart pressures...
increase left heart pressures via parallel effects mediated across the interventricular septum.\textsuperscript{11}

Enhanced diastolic ventricular interaction is common in patients with left-sided HF and PH,\textsuperscript{1} but may also occur with isolated right ventricular pressure overload.\textsuperscript{12} Importantly, enhanced pericardial restraint can be observed even among healthy volunteers during saline loading. This was recently demonstrated by Fujimoto et al.,\textsuperscript{7} where 60% of normal individuals developed a Kussmaul sign (increase or absent fall in RAP during inspiration) after just 1 L of saline infusion. Because RAP approximates pericardial pressure, one can estimate the component of PCWP that is related to LV properties (independent of pericardial restraint) by transmural LV filling pressure, defined as PCWP minus RAP.\textsuperscript{7,13} Although Robbins et al.\textsuperscript{8} did not report transmural pressures, the greater increase in PCWP relative to RAP in the OPVH group suggests that, on average, PCWP elevation was driven more by left heart disease.\textsuperscript{8} However, it would not be surprising to find that many patients in the OPVH group displayed elevated PCWP largely in relation to right atrial hypertension and pericardial restraint rather than primary left heart disease. This is important because the pathophysiology, natural history, and treatment for this group of patients may be distinct from the others.

In light of these data,\textsuperscript{8} it is also important to consider what constitutes a normal PCWP after fluid loading. Fujimoto et al.\textsuperscript{7} observed significant increases in PCWP with volume expansion in healthy volunteers, which were greater in women than in men, particularly among older women. Although volumes infused were higher and somewhat more rapid compared with the current study, one can extrapolate what the PCWP would have been after the same 0.5-L infusion used by Robbins et al.\textsuperscript{8} As can be seen (Figure, B), 27% of normal women (8 of 30) would have been expected to display PCWP \( \geq 15 \) mm Hg after 0.5-L infusion. Data for this plot have been previously published\textsuperscript{7} and were kindly provided by Drs Naoki Fujimoto and Benjamin Levine.

Robbins et al, and it is not known how many OPVH patients met this more stringent definition. Given the possible consequences of withholding potentially lifesaving PH therapies from people who might benefit, we must carefully consider what partition values should define OPVH or group 2 PH, which might be different in men and women and in different age groups.\textsuperscript{7} As acknowledged by Robbins et al, additional prospective studies are needed to definitively answer these questions.

The rate of saline infusion is an important determinant of the magnitude of PCWP change—with slower infusions, there is likely redistribution to the interstitial spaces and large capacitance splanchnic veins; so infusion rates need to be sufficiently rapid and consistently applied in practice to provide meaningful data. There may be differences even within the 5- to 10-minute window used by Robbins et al.\textsuperscript{8} In addition to thermodilution, cardiac output was assessed by the assumed Fick method, which is associated with significant error, and outputs and RAP were not consistently assessed after saline. Curiously, Robbins et al.\textsuperscript{8} noted a reduction in pulmonary vascular resistance with saline infusion. Although one might expect some degree of flow-mediated vasodilation and pulmonary vascular recruitment in healthy subjects, it is difficult to reconcile how this would occur in patients with advanced pulmonary vascular disease, who by definition display a steep slope in the pulmonary arterial pressure–flow relationship, at least during exercise.\textsuperscript{14}

The findings reported by Robbins et al.\textsuperscript{8} raise many important questions for future study. First, how were patients with newly discovered OPVH treated? The authors state that 41% were receiving group 1 PH therapies at the time of evaluation, though it was not reported whether these medications were continued or stopped, or if additional therapies were later added (or withheld) based on the diagnosis. How did these patients fare in comparison to true group 1 PH? Should OPVH patients be managed like group 1 or group 2 patients? It is stated that nitric oxide was administered to patients with PCWP \( \leq 15 \) mm Hg before saline loading,\textsuperscript{3} yet these data were not reported. This would be important because it has been shown that unbalanced pulmonary vasodilation can markedly increase PCWP in patients with HfPEF.\textsuperscript{15} Given the intense interest in pharmacologically targeting pulmonary vascular disease in HF patients, answers to each of these questions would be well worth investigating in future studies. Finally, it
remains unclear what the optimal provocative testing should be in patients presenting with PH and suspected HFpEF. Exercise is the more physiologically relevant stressor, but is less widely available compared with saline infusion.6,7 Future studies comparing these stresses may shed important light on this question.

Robbins et al8 are to be congratulated for a valuable contribution to the literature regarding hemodynamic evaluation of PH. Left heart disease is already the dominant cause of PH, and although the current data suggest that it might be even more dominant than previously appreciated, further study is required to identify the optimal partition values to define left heart disease, the impact of right–left heart interactions and pericardial restraint with fluid loading, the benefits of saline compared with exercise stress, and the ultimate management of the large and growing population of patients with HF and PH.

Disclosures

None.

References


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Barry A. Borlaug

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