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Editorial commentary: Pulmonary hypertension in left heart disease: Definitions, data sources, and the road ahead☆,☆☆

Richa Gupta, MD, MPH, Evan L. Brittain, MD, MSc*

Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN and Vanderbilt Translational and Clinical Cardiovascular Research Center, 2525 West End Ave. Suite 300, Nashville, TN 37203, United States

Over half of the 6.5 million Americans with heart failure (HF) have HF with preserved ejection fraction (HFpEF) and the prevalence continues to increase [1]. Pulmonary hypertension (PH) is a common, highly morbid complication of HFpEF. Levine et al. present an important new synthesis of clinical features and outcomes in patients with HFpEF and PH (PH-HFpEF) [2]. The authors estimate that the prevalence of PH in HFpEF is approximately 35%; based on the above statistics, over 1 million Americans are affected by PH-HFpEF, which is the most common cause of PH in the US and around the world [3]. Despite this high prevalence, little is known about the mechanisms and pathobiology of HFpEF-PH, and there are no specific therapies available in clinical practice.

HFpEF-PH is subclassified into isolated pre-capillary PH (Ipc-PH) and combined pre- and post-capillary PH (Cpc-PH) in whom there is hemodynamic evidence of pulmonary vascular remodeling. This discrimination is important because Cpc-PH is associated with worse outcomes and, theoretically, may be responsive to pulmonary vasodilator therapy [4,5]. Current definitions are controversial and may underestimate the prevalence of Cpc-PH. This can be explained by reliance on the diastolic pulmonary gradient (DPG) in the definition and the sporadic use of provocative maneuvers in clinical practice. The current consensus definitions recommend using a DPG $>$ 7 mmHg to discriminate Ipc-PH and Cpc-PH in patients with PH and an elevated pulmonary capillary wedge pressure. In several cohorts, significantly more patients are classified as Cpc-PH based on TPG (transpulmonary gradient) or PVR (pulmonary vascular resistance) alone compared with the proportion of patients classified by DPG, and thus, classification by DPG rather than by TPG or PVR may underestimate the prevalence of Cpc-PH [6–8]. As a result, clinicians may underappreciate the scope of this sub-phenotype of HFpEF-PH. The DPG does not incorporate a measure of right ventricular (RV) stroke volume. This may explain why, unlike TPG and PVR, the DPG is not consistently associated with mortality and may be less sensitive for the presence of pulmonary vascular disease [9]. The prevalence of Ipc-PH is also underestimated by the lack of routine use of provocative maneuvers at the time of right heart catheterization. Fluid challenge and exercise reclassify up to a quarter of subjects with Ipc-PH who would have been classified as pre-capillary PH based on resting measurements alone [10–12]. Using these maneuvers routinely is important because the management of pulmonary arterial hypertension and HFpEF-PH are markedly different and misclassification may put patients at risk. The authors present a nuanced discussion surrounding the controversy of these hemodynamic definitions. The 6th World Symposium on Pulmonary Hypertension was held earlier this year and included discussion of the clinical and hemodynamic classification of these phenotypes. We await publication of revised consensus definitions, which is expected later this year.

Cpc-PH and Ipc-PH share similar comorbidity profiles, making discrimination based on clinical features alone challenging. As a result, clinicians often assume that Cpc-PH is simply a sequela of long-standing severe left-heart disease and that the chronic pulmonary vascular congestion of Ipc-PH is sufficient to cause vascular remodeling seen in Cpc-PH. As aptly summarized by this review, recent literature suggests that Cpc-PH and Ipc-PH may represent two distinct disease states. For example, patients with Cpc-PH are younger on average than patients with Ipc-PH despite a similar LV filling pressure and remodeling [5]. One inference from these observations is that patients with Cpc-PH may harbor a molecular predisposition to developing pulmonary vascular disease when exposed to elevated left atrial pressure. Unfortunately, molecular data in this population are extremely limited. A recent exploratory genetic analysis suggested that Cpc-PH may share genetic architecture with pulmonary arterial hypertension but the limited sample size prevents any definitive conclusions [13]. Meoli et al. showed that Cpc-PH is characterized by elevated PA wedge ET-1 levels compared with Ipc-PH, suggesting that pulmonary microvascular production of ET-1 contributes to vasoconstriction in Cpc-PH [14]. These findings suggest a “two-hit” mechanism for Cpc-PH in which exposure to elevated left atrial pressure triggers vasoconstriction and vascular remodeling in genetically predisposed individuals. The field badly needs further molecular profiling studies, which may permit identification of individuals at high risk, reveal underlying mechanisms, and guide treatment. Forthcoming results from the NHLBI-funded Pulmonary Vascular Disease Phenomics Program may help address some of these pressing knowledge gaps.

Many of the recent findings discussed by Levine et al. were derived from electronic health record (EHR) cohorts. EHR cohorts

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* Corresponding author.
E-mail address: evan.brittain@vumc.org (E.L. Brittain).

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are an efficient and cost-effective means of studying pulmonary hypertension epidemiology compared with prospective enrollment and data collection. Recent evidence suggests that the prevalence and incidence of PH due to left heart disease are increasing; however, these data were based on ICD codes and other administrative data that have poor sensitivity and specificity for PH etiology [15]. The ability to extract raw data from diagnostic tests (e.g. echocardiography and right heart catheterization) is an important advantage over using ICD codes because it allows etiology ascertainment based on guideline-recommended measurements. EHR cohorts also have an advantage over registries (e.g. the Registry to Evaluate Early and Long-term PAH Disease Management) which tend to enroll patients with specific PH etiologies and no healthy or at-risk subjects. Inclusion of subjects without PH in EHR cohorts is important because it permits investigators to identify risk factors for disease. Finally, EHR cohorts contain longitudinal data in many patients which allows investigation of the natural history of pulmonary hemodynamics [16]. Despite these strengths, EHRs have important limitations that must be considered when interpreting results including missing data, referral bias, confounding by indication, and loss of follow-up, among others.

Emerging efforts to link EHR data with corresponding biospecimens will be an important strategy to understanding disease pathophysiology. Ongoing EHR-linked repositories include the Million Veterans Program, the eMERGE consortium, and Vanderbilt's BioVU program, though focus on HFpEF-PH has been limited. Direct correlation of phenotype to molecular profile including genetic variants and protein biomarkers can allow us to better understand genetic predisposition and predictors of pathology like RV failure, which may lend themselves to the development and testing of additional targeted therapeutics.

Most trials targeting patients with PH due to left heart disease have failed to improve clinical outcomes. As a result, evidence-based recommendations for the management of PH-HFpEF is lacking in comparison with HFrEF. While discouraging, these failures highlight the need for molecular profiling of patients with HFpEF-PH to identify both the correct target and appropriate subpopulations who might be responsive to a specific therapy. For instance, despite data implicating elevated wedge ET-1 in the development of Cpc-PH, trials of endothelin receptor antagonist therapies for patients with PH-HFpEF have proven unsuccessful [17,18]. Despite a negative outcome for the cohort as a whole, it is likely that some subjects had clinical improvement. Future and on-going trials in this population should consider responder analyses to identify molecular features associated with a favorable response.

In summary, this review provides an important update on our evolving understanding of the epidemiology and pathogenesis of HFpEF-PH. Variation and disagreement on the diagnostic criteria for Cpc-PH remains a major challenge to designing clinical trials. Future efforts to improve outcomes in patients with HFpEF-PH should focus on molecular phenotyping to develop a mechanistic understanding of disease risk, progression, and response to treatment. Linking EHR cohorts to biorepositories may allow investigators to efficiently examine the natural history of HF-PH and identify molecular markers associated with disease progression and risk.

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