

## ⊗ Pulmonary Hypertension in Patients with Heart Failure with Preserved Ejection Fraction

### Where to Draw the Line

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent, debilitating condition that is common in patients with parenchymal lung or pulmonary vascular disease (1). Even in the current era, HFpEF remains highly morbid without effective or patient-specific therapy. Indeed, HFpEF-associated mortality has remained largely unchanged over the past two decades despite a surge of clinical trials studying novel therapies. One major challenge in HFpEF at point of care and in clinical trial design is the vast phenotypic and pathophysiological heterogeneity of this condition (2). However, with this limitation also comes an important opportunity to optimize patient phenotypes to enhance diagnosis and, ultimately, identify effective therapeutic treatment targets.

Pulmonary hypertension (PH) is a well established and highly prevalent HFpEF subphenotype that is due to pulmonary venous and precapillary remodeling from left atrial hypertension (3–5). Data from large U.S. referral populations enriched with patients with HFpEF have demonstrated a wider continuum of clinical risk relative to mean pulmonary artery pressure (mPAP) than was previously appreciated, including hospitalization and mortality (1, 6–8). These and similar observations contributed to a recent revision of the mPAP threshold used to define PH in the setting of left heart disease, from  $\geq 25$  mm Hg to  $>20$  mm Hg (9–11). However, some critical questions remain to be addressed, including 1) is an mPAP of 20–24 mm Hg in fact an independent predictor of hard clinical events in HFpEF, and 2) is the association between mPAP  $>20$  mm Hg and poor outcomes generalizable to international HFpEF populations?

The report by Nishihara and colleagues (pp. 386–388) in this issue of the *Journal* begins to address some of these questions (12). This group studied patients who had been hospitalized for HF at a single institution in Japan and met prespecified criteria for HFpEF, including symptoms of HF, left ventricular ejection fraction  $\geq 50\%$ , B-type natriuretic peptide  $> 35$  pg/ml, and echocardiographic evidence of diastolic dysfunction ( $E/e' \geq 13$ ). Patients with any history of reduced left ventricular systolic function were excluded, as were those with radiographically severe lung disease at the time of index hospitalization. The patients underwent right heart catheterization and echocardiography after receiving standard-of-care HFpEF therapy. The authors showed that an increased risk for

future HF hospitalization was observed at mPAP  $\geq 20$  mm Hg, and this was even extended to include patients with mPAP  $\geq 15$  mm Hg. A cutoff of 17.5 mm Hg determined by receiver operating characteristic analysis was used to define the lowest mPAP threshold level for covariate adjustment. Using this criterion, a significant increase in the risk of adverse clinical outcome was maintained in several multivariate analyses.

This study confirms that patients with HFpEF and mild PH in this Japanese population have an increased clinical risk, and raises several further points to note. First, although current methods can define the HFpEF syndrome more accurately than previous ones, there is an opportunity to improve early diagnosis. Discovering PH in patients with other clinical or imaging data suggestive of HFpEF, for example, may be useful for diagnosing specific cardiomyopathies that associate with PH, such as amyloid and hypertrophic cardiomyopathy (13), which would inform disease-specific treatment plans.

Second, data from Nishihara and colleagues raise the possibility that easily accessible and clinically important biomarkers in HFpEF, such as mild PH, may be overlooked at present. This is an important potential consideration, as slight increases in PA pressure estimated by echocardiography are suitable for determining the prognosis of PH in at-risk populations (14). Viewing mild PH in a new light—as a high-risk clinical parameter in HFpEF—could pave the way for early intervention (e.g., diet modification, prescription exercise, and enhanced diabetes control) irrespective of symptom burden. In principle, such a shift may ultimately give rise to opportunities to prevent HFpEF (or PH) (15).

Third, this study brings much-needed attention to the clinical spectrum of PH due to left heart disease (World Health Organization group 2 PH), for which no therapy currently exists. Data from the current study reinforce the ubiquity of this PH subtype, as 49% of patients in this study had an mPAP  $> 20$  mm Hg (1). It may be the case that identifying key pharmacotherapeutic treatment targets in World Health Organization group 2 PH, in which initial successes have been seen (16), requires an expanded view of this disease to include its inception or early onset. To this end, at least five clinical trials (NCT03015402, NCT03629340, NCT03541603, NCT03153111, and NCT03037580) are currently focusing on novel treatments in HFpEF-PH, although the extent to which these efforts will focus on patients with mPAP  $< 25$  mm Hg is not clear (17).

The most notable limitation of the study by Nishihara and colleagues is the relatively small sample size ( $N = 183$ ). Confirmation of these data in larger, international datasets is needed. In sum, this work extends the findings of increased risk in mild PH to a prespecified Japanese population with HFpEF. It invites us to carefully consider these patients and work to develop targeted strategies to improve quality of life and clinical outcomes in this large at-risk patient population. ■

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