Editorial

All for One or One for All?

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Heart failure with preserved ejection fraction (HFpEF) is a growing segment of cardiovascular medicine that causes significant morbidity and mortality, as well as rising healthcare costs.[1] Our ability to reduce adverse outcomes suffers from the challenge in identification of diagnostic criteria and mechanisms of disease. Furthermore, clinical heterogeneity has made it difficult to implement evidence-based therapies.[2,3]

Pulmonary hypertension (PH), defined as mean pulmonary artery pressure >25 mmHg, is a growing area of interest and study in HFpEF. The importance of morbidity of PH is readily apparent. With limited data, PH has been shown to predict increased morbidity and mortality in HFpEF.[4] Unfortunately, mechanistic explanations have been postulated but not yet verified.

Vascular stiffness, previously associated with aging and cardiovascular risk factors such as diabetes, hypertension, obesity, and chronic kidney disease, has been recognized as a mechanistic cause of HFpEF. Ventricular stiffening occurs in response to vascular stiffness and acts as a compensatory response to preserve adequate ventricular-arterial coupling.[5] The impact of the associated peripheral artery stiffness and the adverse prognostic sign of pulmonary vascular resistance (PVR) in isolation and in tandem on HFpEF outcomes remains uncharacterized. In addition, the links between large artery stiffness and pulmonary hypertension remains incompletely characterized.[6]

Brachial-ankle pulse wave velocity (baPWV), a non-invasive method of analyzing arterial rigidity, has been used to diagnose arterial stiffness in population studies. In this issue of *Journal of Cardiac Failure*, Nakamura et al analyzed the association between PVR and baPWV in order to understand its prognostic value in patients with HFpEF and to find a mechanistic link between systemic and pulmonary arterial stiffness. The study enrolled 204 patients diagnosed with HFpEF based on the following criteria: 1) clinical congestive heart failure defined by the Framingham criteria with disease history of at least 3 months; 2) stable heart failure with NYHA class I-II after standard medications before discharge; and 3) left ventricular (LV) ejection fraction >50% demonstrated by echocardiography. All patients underwent right heart catheterization (RHC) prior to discharge in order to characterize pulmonary vascular pressures. baPWV was measured after stabilization of HF symptoms to characterize large artery stiffness in the stable state. The patients were then evaluated prospectively every 3 years for 96 months or were censored after reaching an adverse clinical outcome.

The authors report that pre-capillary PH is associated with increased baPWV. This link between PVR and baPWV suggests that patients with HFpEF suffer from systemic vascular dysfunction. Although as noted PH negatively impacts clinical outcomes in patients with HFpEF, the authors now suggest that large artery stiffness is associated with the development of pre-capillary PH. Interestingly, the impact of baPWV no longer maintained statistical significance after adjustment for confounders including PH in multivariable analysis. As a consequence, more data will be required before baPWV can be considered a predictive metric for clinical outcomes in HFpEF.

Whether pulmonary and systemic vascular diseases are a single disorder or linked through effects on the heart remains unclear. Aortic stiffness has been directly correlated with the diffusing capacity of the lungs for carbon monoxide (DL_{CO}) and distance covered in a 6-minute walk test in patients with pulmonary hypertension.[7] Interestingly, although participants with PH demonstrated endothelial dysfunction, brachial artery flow-mediated, endothelium-dependent vasodilation did not correlate with functional parameters. It is interesting to note previous work showing nitric oxide's beneficial impact on arterial stiffness within the pulmonary vascular bed making clear that we do not yet understand the mechanistic role of endothelium-derived nitric oxide.[8] Similarly, more recent data has shown efficacy in the use of inhaled nitrites to reduce pulmonary pressures and prevent right ventricular hypertrophy.[9] Nitrites lower both left and right sided filling pressures as well as pulmonary artery compliance for patients with HFpEF. These data highlight opportunities for further study to both better understand the importance of the different parameters

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of vascular homeostasis and health on HFpEF and pulmonary hypertension.

Causes of HFpEF are not only challenging to identify, but also have varying impact on outcomes. Myocardial stiffness seen in HFpEF may be a result of myocardial fibrosis that is associated with the inflammatory states such as diabetes mellitus, or due enhanced renin-angiotensin activation. Dysfunction may also result from microvascular-induced ischemia, which prevents LV unloading and worsens symptoms of HF.[10] Diabetes, a common comorbidity in HFpEF, places patients at significant risk in the setting on PH.[11] As each of these processes are linked,[12–14] it becomes hard to delineate a specific etiology. Conversely it suggests that HFpEF is a late-stage consequence of a variety of disorders. The work by Nakamura et al adds to the idea that it is the interplay of highly morbid chronic diseases that lead to development and worsening of outcomes in HFpEF and PH.

Despite the limitations of this study, the investigators provide an important analysis, by showing a correlation between PVR and baPWV. This finding provides evidence that vascular stiffness may be a systemic problem without single cause or therapeutic target. Although the study does not offer a causative relationship, additional research is needed to explore the relationship between systemic and pulmonary vascular stiffness and the influence of both, separate and together, on the development and progression of HFpEF. In addition, although right heart catheterization remains the gold standard for diagnosis, the authors have demonstrated a novel tool to raise the possibility of PH in patients with HFpEF.

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