Heart failure with preserved ejection fraction: a forest of a variety of trees

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This editorial refers to ‘Right heart dysfunction in heart failure with preserved ejection fraction’, by V. Melenovsky et al., on page 3452.

In heart failure (HF) with reduced ejection fraction (HFrEF), the magnitude of left ventricular (LV) contractile dysfunction which defines this group has proven an important prognostic marker and effective target for therapy. Measures of right ventricular (RV) contraction are not commonly quantified, but when they are they provide additional prognostic information. It is now well recognized that up to half of HF patients have more preserved contractile function as measured by LVEF (HFpEF), demonstrate rates of HF re-hospitalization and functional decline similar to HFrEF, and have a higher risk of death compared with age-matched controls. While abnormal cardiac performance is implied in the HF diagnosis, the mechanisms underlying HFpEF are clearly multifactorial, with contributions of age, arterial stiffening, renal dysfunction, atrial fibrillation, and obesity, among others. Even within the heart, while LV diastolic dysfunction is an important underlying cardiac perturbation, additional abnormalities of cardiac function may contribute, including subtle abnormalities of LV systolic function, dysynchronous ventricular contraction and/or relaxation, impaired left atrial (LA) function, pulmonary vascular dysfunction, chronotropic incompetence, and impaired peripheral oxygen extraction. In addition to aetiological cardiac phenotype, phenotypic heterogeneity and the prominent contribution of comorbidities make understanding this syndrome particularly challenging. Melenovsky et al. now appropriately call our attention to the importance of RV dysfunction as a contributing mechanism.

Operating in parallel with the left ventricle, the right ventricle is also intimately coupled to the left ventricle via the interventricular septum and pericardium. The right ventricle normally ejection into the low impedance, highly distensible pulmonary vascular bed, and demonstrates heightened afterload sensitivity relative to the left ventricle. RV dysfunction may therefore result from afterload mismatch, as commonly seen in pulmonary arterial hypertension (PAH), and/or as a result of an intrinsic cardiomyopathic process. Melenovsky et al. explore the prevalence, correlates, and prognostic relevance of RV dysfunction in a single-centre retrospective study of 96 selected patients with clinical HF, LVEF ≥50%, and an elevated pulmonary artery wedge pressure, all of whom underwent right heart catheterization and echocardiography within 48 h of each other. RV dysfunction, defined as an RV fractional area change (FAC) <35%, was present in 31% of their cohort. The major finding of this study was that RV dysfunction was a powerful univariate predictor of mortality over a median follow-up of 1.4 years. By combining invasive hemodynamic data with functional data from echo, the authors also interrogated the complex mechanisms mediating RV dysfunction in HFpEF. While associated with pulmonary artery (PA) pressure, RV dysfunction remained significantly associated with mortality after adjusting for PA pressure. In addition, the relationship between higher PA pressure and lower RV FAC was steeper in HFpEF compared with a sample of ‘controls’, suggesting greater afterload sensitivity in HFpEF.

This study’s finding of the prognostic value of RV dysfunction in HFpEF is an important, additional step in understanding the contribution of the right ventricle to this syndrome. Indeed, the importance of RV dysfunction in HFpEF is not surprising, as RV dysfunction has previously been described in HFpEF and is a recognized risk factor for adverse outcomes in patients with HF with reduced EF (HFrEF) and (LV) systolic dysfunction following myocardial infarction. It is unfortunate that the association of RV dysfunction with morbidity was not assessed in this analysis, particularly given the burden of HF hospitalization in HFpEF and the association between RV function and functional capacity in HFrEF. In addition, patients with RV dysfunction differed from those without RV dysfunction in several clinical characteristics, including gender, atrial fibrillation, coronary disease, estimated glomerular filtration rate (eGFR), and LVEF, although there were too few events in this study to perform multivariable analysis. The incremental value of RV function for predicting adverse outcomes in HFpEF beyond clinical and other echocardiographic risk factors therefore also remains to be determined.

The limited generalizability of this study also highlights a common challenge that patient heterogeneity presents to our understanding of HFpEF. Accrual of the 96 consecutive HFpEF patients in this
The annual mortality rate of this selected cohort, at \( \sim 22\% \), was substantially higher compared with rates previously reported in the authors’ Olmsted County HFpEF population as well as in large HFpEF clinical trials. \(^{11,12}\) PA systolic pressure in this invasively studied group was also higher than among HFpEF patients from epidemiological cohorts, registries, or clinical trials (Figure 2).\(^{11,13–18}\) In addition, the prevalence of RV dysfunction by RV FAC in the study of Melenovsky et al. (33\%) is higher than observed in either the TOPCAT echocardiography study (4\% of 673 patients)\(^{18}\) or in the Northwestern HFpEF registry (14\% of 419 patients).\(^{13}\) These findings strongly suggest that the patients in the study of Melenovsky et al., all of whom were referred for invasive haemodynamic testing, represent a particularly high-risk subset of the broader spectrum of HFpEF patients.

What is clear from Melenovsky et al. is that RV dysfunction is present in at least some patients with HFpEF, and is a potent risk marker for reduced survival. Not surprisingly, RV dysfunction appears at least partially related to pulmonary hypertension and elevated pulmonary vascular resistance (PVR). One intriguing implication of the current work is the potential utility of pharmacotherapy targeting the pulmonary vasculature in HFpEF. Several phase II clinical trials have already evaluated medications with demonstrated efficacy in PAH, including phosphodiesterase-5 inhibitors and endothelin receptor antagonists, with mixed results.\(^{17,19}\) Perhaps targeting such therapies more narrowly at the type of HFpEF patients represented in the study of Melenovsky et al.—who had greater PA pressure, PVR, and RV dysfunction relative to other HFpEF cohorts—would be more efficacious. However, several steps beyond this study are...
required to evaluate this approach further, including: (i) adequately powered prospective studies to assess the independent and incremental prognostic value of RF function in a more generalizable HFrEF population; (ii) studies assessing the relationship between change in RF function and subsequent outcomes; and (iii) adequately powered randomized trials in appropriately selected patients to assess impact on outcomes. Ultimately, the major utility of phenotyping HFrEF patients in ever greater detail may be to better identify pathophysiologically relevant patient subgroups in whom more targeted therapies may be beneficial. The study of Melenovsky et al. provides an important reminder that the forest of HFrEF consists of many different types of trees.20

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References