Diagnosis of heart failure with preserved ejection fraction. Not seeing the forest for the trees or a step to precision medicine?

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In this issue of the journal, Shono et al. [1] report on the ability of leg-positive pressure (LPP) stress echocardiography to differentiate between patients with heart failure and preserved ejection fraction (HFpEF) from physiologic aging of the myocardium. Twenty-five patients with HFpEF and 77 healthy controls, including 27 young (20–40 years), 25 middle-aged (40–65 years) and 25 elderly (> 65 years) were evaluated. The echocardiography protocol included measures of (i) the left ventricular (LV) mass-to-volume ratio, as a marker of LV remodeling, (ii) the E/é ratio, as a marker of the LV filling pressure, and (iii) forward stroke volume using pulsed-wave Doppler. Preload stress echocardiography was performed using commercially available LPP equipment in all subjects, obviating the need for physical stress testing, and allowing the calculation of the E/é ratio and stroke volumes during this maneuver. The authors found that progressive concentric LV remodeling is observed with increasing age in healthy subjects, being accompanied by increased LV stiffness. In addition, during preload LPP mediated stress, the E/é ratio remained unchanged with younger patients but increased significantly with middle-aged and elderly subjects and in patients with HFpEF. Forward stroke volume on the other hand, significantly increased in all control subjects but failed to increase in HFpEF. Using multivariable analysis, markers of LV mass-to-volume ratio, E/é ratio and LV stroke volume were independently associated with HFpEF versus physiologic myocardial aging, with accuracy rates of ~85%, ~90% and 73%, respectively for the identification of patients with HFpEF. Furthermore, LV mass index

and changes in forward stroke volume exhibited incremental value in clinical models for the differentiation between patients with HFpEF and similar aged control subjects.

The study of Shono et al. [1] makes an important step towards better understanding the underlying pathophysiology of HFpEF; however, some specific points need to be considered when interpreting the results of this study. Thus, a relatively small number of patients with HFpEF and similarly aged healthy controls was analyzed at a single time point, whereas follow-up data are not provided. In addition, the protocol did not include cardiac magnetic resonance (CMR) or laboratory markers, including light chain assays, so that some of patients classified as HFpEF may have exhibited other specific underlying disorders. Furthermore, echocardiography or CMR based strain measures were not available, which is a limitation since patients with HFpEF usually exhibit impaired myocardial strain in the presence of normal EF. Finally, therapeutic implications are currently limited in patients with HFpEF, which limits the translation of these findings into the clinical realm from a therapeutic point of view. In addition, the findings provided by Shono et al. need to be considered in the context of the current approaches for the diagnostic classification and risk stratification of patients with heart failure, giving special attention to HFpEF [2]. Thus, HFpEF currently accounts for more than half of patients with heart failure and its prevalence continuously rises relative to those with heart failure with reduced ejection fraction (HFrEF) due to ischemic or dilated cardiomyopathies [3]. In addition, the mortality rate of HFpEF patients is similar to age matched HFrEF patients. However, the mode of death in HFrEF is only in approximately two-thirds due to cardiovascular reasons [4]. Recent large-scale trials suggested that the heart is just one of the organs affected in HFpEF. Thus, this disease needs to be considered as a systemic disorder, which may also affect the pulmonary system, the neurohumoral and the renal axis. Therefore, in such patients, attention is necessary to avoid not seeing the forest for the trees. In addition,

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patients with HFpEF are predominantly female and often exhibit advanced age, obesity, arterial hypertension, renal failure, and sleep apnea [5, 6]. Such comorbidities may initiate chronic systemic inflammation, which can be detected in form of high plasma levels of inflammatory markers in patients with HFpEF [7]. This may affect myocardial remodeling and stiffness by endothelial dysfunction, infiltration of the myocardium by activated macrophages, ultimately causing increased myocardial stiffness due to interstitial fibrosis [8].

Despite advances in the diagnostic work-up of patients with heart failure, HFpEF is still considered as more or less a ‘diagnosis of exclusion’. Thus, once an ejection fraction of $> 50\%$ has been documented in the presence of heart failure symptoms, cardiac imaging techniques focus on determining, if there is objective evidence of structural or functional myocardial disorders. Using standard echocardiography, LV diastolic dysfunction, left atrial dilatation and increased pulmonary artery pressure are common findings in patients with HFpEF [9]. Traditionally, right heart catheterization used to be the gold standard for the assessment of LV filling pressures. However, this technique is invasive and not suitable for serial evaluations. Therefore, Doppler transmitral flow patterns, pulsed tissue Doppler of the mitral annulus and the left atrial volume index are currently recommended for the estimation of LV filling pressures [10]. In addition, the mitral E velocity by PW Doppler can be divided by the ϵ , derived from tissue Doppler, thus correcting for the influence of relaxation. The resultant E/ϵ ratio has been shown to be strongly associated to the mean pulmonary capillary wedge pressure, as a surrogate marker of the LV filling pressure [11]. Cardiac magnetic resonance (CMR) on the other hand, is not as widely available as echocardiography but is considered as the gold standard for measuring LV mass, volumes, and the LV concentricity index, being free of geometric assumptions made by 2D echo and unaffected by acoustic windows [12]. In addition, CMR allows for tissue characterization using late gadolinium enhancement (LGE) for the detection of focal, diffuse, or patchy ischemic or non-ischemic scar patterns, whereas native T1 mapping techniques and extracellular volume (ECV) measures aid the detection of diffuse interstitial fibrosis [13]. Importantly, CMR can provide valuable information on the differential diagnosis of specific cardiomyopathies such as hypertrophic cardiomyopathy or infiltrative cardiomyopathies, such as cardiac amyloidosis, sarcoidosis, and the Anderson Fabry disease. This is crucial since patients with these disorders may strongly benefit from specific therapeutic algorithms. In this context, recent CMR studies reported to identify new specific pathologies such as ischemic heart disease, hypertrophic cardiomyopathy, or constrictive pericarditis in 27% of patients, initially classified as HFpEF by clinical and echocardiographic assessment [14]. In the same line,

patients with cardiac amyloidosis may have been misclassified as HFpEF in several previous clinical trials, which did not include CMR, light chain assays and technetium-labeled cardiac scintigraphy by investigational protocols. Thus, the effectiveness of pharmacotherapy in HFpEF may have been underestimated in previous trials in this context [15].

The assessment of myocardial deformation using feature tracking or strain-encoded MR (SENC) has been thoroughly investigated in previous trials in patients with ischemic heart disease and heart failure [16–18]. In contrast to feature tracking, SENC allows for more reproducible and comprehensive assessment of myocardial strain both on segmental and global level [19]. In this regard, we recently demonstrated that assessment of the percentage of ‘normal’ myocardium by SENC can reclassify patients at risk for heart failure due to arterial hypertension or diabetes, i.e., at stage A based on ACC/AHA guidelines [20] to stage B, i.e., indicating sub-clinical LV dysfunction [17]. Such patients exhibit diminished myocardial strain in the absence of structural or functional abnormalities by echocardiography and in most cases have normal ejection-fraction, compatible with HFpEF. Despite preserved ejection-fraction however, the percentage of impaired normal myocardium predicted poor outcome at follow-up, which translated in increased all-cause mortality and hospitalizations due to heart failure symptoms [17]. This may bear tremendous socioeconomic implications, since the percentage of normal myocardium may aid the identification of several millions of presumable healthy individuals at risk for overt heart failure, who may profit from early risk factor control, lifestyle modifications and pharmacologic treatment.

Despite the limitations of the trial conducted by Shono et al. [1] and the absence of CMR and strain analyses, the study makes an important step to precision medicine aiding the accurate diagnosis of HFpEF by a relatively simple and practical approach. Especially LPP stress echocardiography provides the assessment of dynamic changes in terms of forward stroke volume and LV diastolic filling pressures. LPP is associated with lower time spent than exercise echocardiography and can therefore easily be integrated into daily clinical practice. In addition, although currently no specific therapy apart from symptomatic administration of diuretics has been shown to improve the clinical course of patients with HFpEF, major randomized trials are underway, which evaluate the role of Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as Dapagliflozin and Empagliflozin in HFpEF patients (clinicaltrials.gov/NCT03619213 and NCT03057951). Interestingly, recent studies have already shown that the SGLT2 inhibitor empagliflozin reversed myocardial hypertrophy and remodeling and reduced ECV, a marker of myocardial fibrosis in patients with coronary artery disease and type 2 diabetes mellitus [21]. Thus, SGLT2 inhibitors, which have recently revolutionized the

treatment of HFpEF, may also prove beneficial for the treatment of HFpEF in future studies.

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