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EDITORIAL COMMENT

Diagnosing HFpEF

On Track at Last?*

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Heart failure with preserved ejection fraction (HFpEF) accounts for almost one-half of the total heart failure burden. Based on the consistent increment of its prevalence, it seems likely that HFpEF will be the most common HF category in the near future (1). The poor prognosis conferred by HFpEF has not been improved by any previously trialed pharmacological interventions, and the gap in the specific treatment possibilities in this entity still remains a concern. Unsatisfactory results of prior large randomized drug trials in HFpEF might be attributable to a variety of reasons, including inappropriate diagnostic criteria and limited reversibility of pathologies at advanced stages of disease. In these elderly and highly symptomatic patients, the aims of therapy might be reconsidered, with priority for the alleviation of symptoms over the increase in longevity. However, perhaps the biggest problem has been the etiological and pathophysiological heterogeneity of the syndrome, which favors a subset-specific rather than a uniform therapeutic approach. Exercise intolerance in HFpEF is due to multiple mechanisms, including left ventricular (LV) diastolic and systolic dysfunction, impaired ventricular-arterial coupling, endothelial dysfunction with reduced nitric oxide availability, increased vascular stiffness, chronotropic incompetence, autonomic dysfunction, compromised skeletal muscle oxygen extraction, pulmonary hypertension, and right ventricular dysfunction (2–7). Both the phenotypic diversity and progression of pathological alterations may determine the responsiveness to treatment and the level of cardiovascular risk (8). Accordingly, the adoption of diagnostic protocols that uncover these features is essential to optimize patient management.

In this issue of *iJACC*, Mordi et al. (9) provide interesting data demonstrating that the symptomatic phase of HFpEF is characterized by abnormalities of a number of myocardial imaging markers. Among these, extracellular volume (ECV) by cardiac magnetic resonance (CMR) and global longitudinal strain (GLS) by echocardiography are the most robust metrics to delineate the pathophysiological distinctiveness of this stage. The histoanatomical spectrum described by these parameters include noncardiomyocyte and cardiomyocyte compartments. Both ECV and GLS progressively deteriorated from healthy subjects through pre-clinical cardiac impairment to overt HF. Possibly, a critical mass of the pathological substrate needs to be present to give rise to the emergence of symptoms. Importantly, both ECV and GLS were associated with acknowledged prognosticators—peak oxygen consumption and minute ventilation/carbon dioxide production slope—which further emphasizes their clinical significance in the context of effective phenotyping of HFpEF patients. This is in line with previous studies in HFpEF that demonstrated the linkage of reduced myocardial deformation and shortened T_1 times by CMR imaging with worse outcome (10,11).

Both GLS and ECV components provide novelty. The detection of reduced global circumferential deformation before the development of GLS impairment is an unexpected finding that is not consistent with some previous studies in various cardiovascular disorders, including hypertension (12–15). Indeed, further investigations are needed to better explore the role of circumferential and torsional mechanics in the natural course of cardiac pathologies, especially in the pre-clinical disease and its transition to the symptomatic state. An attractive aspect of this work is the inclusion of T_1 mapping into the diagnostic algorithm: the myocardial ECV assessed by this technique correlates with the extent of collagen deposition. The ability to quantify fibrosis is truly

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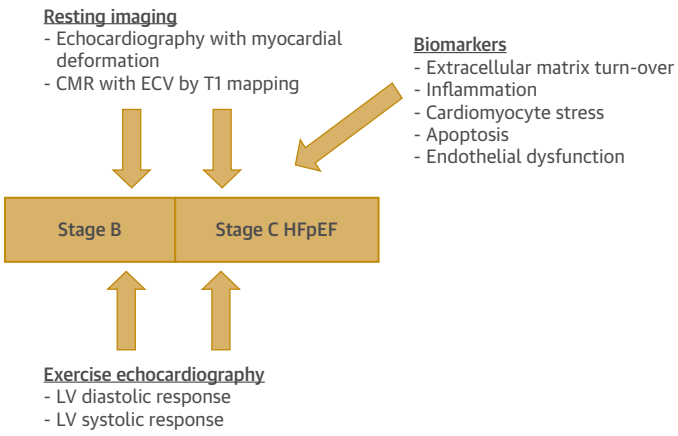
FIGURE 1 Diagnostic Algorithm for HFpEF



Application of resting and exercise imaging, and biomarkers in the diagnostic process in HFpEF. CMR = cardiac magnetic resonance; ECV = extracellular volume; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular.

incremental to what has traditionally been provided by echocardiography.

The concept of a multiparametric imaging approach proposed by Mordi et al. (9) is a very important step in exploiting the complementariness of echocardiography and CMR. However, it might be extended by addition of an assessment during exercise and some biomarkers reflecting different pathophysiological domains, such as extracellular matrix turnover, inflammation, cardiomyocyte stress, apoptosis, or endothelial dysfunction. Identification of flawed LV functional reserve is particularly relevant for patients with predominantly exertional symptoms, in whom some abnormalities may be absent at rest and appear only with stress. Exercise testing can provide important information on LV hemodynamic response to stress (which can be assessed noninvasively by echo-Doppler measurements), myocardial ischemia, chronotropic reserve, or exaggerated hypertensive response, all of which are determinants of functional capacity. Such a comprehensive strategy would allow better characterization and, possibly, more efficient diagnostic stratification of HFpEF patients (**Figure 1**). Specifically, this wide-based diagnostic framework could be helpful in differentiating HF from noncardiac dyspnea or deconditioning, especially in subjects unable to perform adequate exercise effort because of noncardiac reasons; identifying the underlying disease severity in the individual patient, which might be critical for therapeutic decision making; monitoring the disease progression/treatment effects; and defining more uniform phenotypes, representing potential target subsets for future drug trials.

The paper by Mordi et al. (9) provides support for imaging markers, especially ECV, to be used as proxy outcome measures in HFpEF clinical studies. However, some pending issues need to be resolved to give the green light. The most important, particularly for CMR, technical challenges that should be addressed in the near future are the standardization of methods and normative ranges. The cutpoints for ECV and GLS identified by the investigators require external validation to be recommended for the diagnostic and therapeutic purposes. Although resting early diastolic mitral inflow velocity to early diastolic mitral annular velocity ratio (E/e′) was not the major discriminatory marker in the current analysis, exertional measurements of this index are imperative for recognition of a very common HFpEF phenotype characterized by the induction of hemodynamically significant LV filling abnormalities with stress (2).

In summary, the data from Mordi et al. (9) convincingly support the notion that the diagnostic strategy in HFpEF should include an array of markers obtained by different imaging modalities to improve our understanding of the complex pathophysiology underlying this heterogeneous condition. This update might translate into refinements of patient phenotyping and diagnostic stratification, thus forming the base for targeted, more personalized treatment and giving a perspective for both symptomatic and prognostic benefits. Barriers to the clinical uptake of this approach are not overwhelming, and it might be expected that its practical applicability will be further validated. There is still a long way to go, but we are definitely on the right track.

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