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EDITOR'S PAGE


Physical Function and Well-Being in HFpEF

The Constrained Mechanics and Compensatory Strategies

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The normal heart has a remarkable capacity to match ventricular filling and cardiac output to complex needs during exercise, but an inability to maintain "cardiac reserve" is often an early manifestation of cardiac dysfunction. Ventricular mechanics are dependent on interconnected myocytes that spiral in 2 counter-directional helices (1). The endocardial helix augments the longitudinal mechanics, whereas the epicardial helix intensifies the circumferential and wringing motion. The potential mechanical energy stored in the wringing motion, also referred to as "twist," is subsequently released with a rapid untwist and recoil for generating diastolic suction. Cardiac mechanical sequences are exquisitely augmented for suction and ejection during the increased demands of exercise. Consequently, in pathological states, the heart "remodels" to maintain these attributes and its cardiac reserve, a process also referred to as "cardiac compensation."

What causes the shift from a compensated to a decompensated state, especially in heart failure with preserved ejection fraction (HFpEF) is not well characterized but is crucial to decipher. Patients with HFpEF show abnormal functions in both filling and emptying. Left ventricle (LV) shortening is reduced in the longitudinal direction, even though the circumferential shortening remains normal or increased to maintain global LV EF (2). Computational models of LV myofiber mechanics highlight the role of subepicardial fibers in maintaining global LV EF in HFpEF (3). If endocardial strain is reduced with no change in epicardial strain, the LV EF remains reduced. Increased torsion could also play a role in attenuating the decline in systolic function, as seen in aging (4). A deficit in longitudinal mechanics in HFpEF is more readily identified during exertion. Exercise limitation is a major problem for patients with HFpEF and may represent many things including impaired LV systolic and diastolic reserve. Both the impaired LV untwisting (an active component of LV filling) and the E/e′ ratio (a comparatively passive component of LV filling) contribute to reduced exercise capacity, and effective therapy improves both exercise tolerance and these 2 components concurrently (5).

A study by Kosmala et al. (6) in this issue of *iJACC* used a well-characterized HFpEF cohort to comprehensively study LV mechanics during exercise and its prognostic relevance. They found that lack of systolic and diastolic reserve predicted adverse outcomes independently of and incrementally to clinical data and natriuretic peptide concentrations. Interestingly, EF and cardiac output increased during exercise despite failure to augment longitudinal mechanics. Why then did the patients experience symptoms? The answer lies in the fact that longitudinal mechanics of the LV may be directly coupled with left atrial (LA) reservoir function and, in turn, pulmonary artery-right ventricular (PA-RV) coupling. Impaired LA reservoir response to exercise appears to be a key trigger for RV-pulmonary circulation (RV-PC) uncoupling and exercise ventilatory inefficiency in HFpEF (7). RV-PC coupling influences RV contractile

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function and exercise capacity, and stratifies HFpEF phenotypes at different levels of risk (8).

Although diastolic dysfunction, as measured using echocardiography (usually at rest), was initially thought to be the main driver of symptoms in HFpEF, recent clinical studies have questioned this simplistic view. HFpEF is a mixture of many underlying conditions, where phenotypes matter in terms of risk and response to therapies (9) and evaluating multiple pathophysiologic pathways may be necessary. For example, a recent comprehensive study showed that extracellular volume (evaluating the interstitial compartment) and global longitudinal strain (evaluating contractile function) could differentiate hypertensive heart disease from HFpEF and correlated well with exercise physiology and that both parameters became worse proceeding from healthy subjects to pre-heart failure subjects to clinical HF subjects (10).

How does this complexity and the fact that HFpEF may not be one clear entity affect diagnostic imaging strategies? There are potentially many major avenues to understanding this disease. One could use more sophisticated assessment of diastolic dysfunction (11,12), perhaps with comprehensive exercise testing to tease out physiology (13). Exercise echocardiography is feasible, reflects physiology with reasonable accuracy (14) and can detect impaired LA strain response that triggers RV-to-PC uncoupling and inefficient ventilation (15). Another recent strategy has been to image different pathophysiological pathways at the same time (10) or let something more comprehensive like machine learning help unravel these complex interactions (16). Automated algorithms that take massive sets of complex information and provide simplified decision support for the busy clinician may be imminent. Indeed, a recent study evaluated the feasibility of machine learning approaches to automatically classifying exercise-related changes in cardiac longitudinal deformation for differentiating HFpEF from other causes of dyspnea (17). Such techniques can integrate clinical information to develop patient phenotypic groups with similar comorbidities and pathophysiology. Importantly, standardizing interpretations and increasing the diagnostic throughput in the face of the growing burden of HFpEF may also help address the existing work shortage in the field.

Finally, is reduced longitudinal strain a central integrated marker of all comorbidities that exist in HFpEF? Regardless of the underlying cause, most risk factors and pathophysiological processes may lead to reduction in longitudinal strain. This hypothesis could certainly reconcile the phenotypic diversity seen in HFpEF and echocardiographic evidence of reduced longitudinal strain in most of these patients. This question needs urgent answers, given that there are therapeutic strategies that can modulate contractility; for example, cardiac contractility modulation involves a device that delivers a strong electrical current in the refractory period into the septum, thus triggering molecular remodeling which is thought to improve EF and optimize symptoms (18). Its therapeutic effect seems to be more pronounced in patients with better EF. Perhaps careful selection of patients based upon documented evidence of deficit in cardiac contractility, as studied by Kosmala et al. (6), could help focus new treatment strategies to the right HFpEF patient.

In summary, HFpEF is still an enigma. The one question that needs to be asked is whether HFpEF is a single condition. Second, are the new techniques and their ability to predict long-term morbidity and mortality generalizable to the entire spectrum of patients with the diagnosis of HFpEF. Studies like those from Kosmala et al. (6) illustrate the power of LV mechanics by carefully segregating high-risk HFpEF phenotypic features. However, these studies, which are surely valuable for their insights, will only be valuable if the frontline clinician can translate them into better outcomes.

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