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Heart Failure with Presereved Ejection Fraction: A Heterogenous Disorder with Multi-Factorial Pathophysiology

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Heart failure with preserved ejection fraction (HFpEF) is the most common form of HF in the population.[1] Among elderly women living in the community, HFpEF comprises nearly 90% of incident HF cases.[2] Furthermore, HFpEF is increasing out of proportion to HF with reduced EF (HFrEF), and its prognosis is worsening while that of HFrEF is improving.[3] The health and economic impact of HFpEF is at least as great as that of HFrEF, with similar severity of chronic exercise intolerance,[4] acute hospitalization rates[3,5] and substantial mortality.[3]

Despite the importance of HFpEF, our understanding of its pathophysiology is incomplete and optimal treatment remains largely undefined. Originally thought to be purely due to LV diastolic dysfunction (hence the now-discarded misnomer ‘diastolic HF’) it is now obvious that HFpEF is much more complex. Findings to date indicate important contributions from aging,[6,7] neuroendocrine dysfunction,[4,8] inflammation,[9,10] LV systolic dysfunction,[11,12] RV dysfunction,[13] chronotropic incompetence,[14] autonomic dysfunction,[15] vascular dysfunction,[15–17] pulmonary and renal dysfunction,[1,2,18] skeletal muscle dysfunction,[19–21] and multiple comorbidities,[22] including obesity, hypertension, atrial fibrillation, and anemia. Although this complexity presents challenges, it also presents opportunities for advancing our understanding and provides potentially novel therapeutic targets. Such should be welcomed since the agents tested in trials to date, which were based upon our previous, simplistic assumptions, have not been positive.

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Potential Conflicts of Interest:
Dr. Kitzman is a consultant for Relypsa Inc., Boston Scientific., Abbot, Servier, AbbVie, Icon, and GlaxoSmithKline, has received grant support from Novartis, and owns stock in Gilead, Sciences.
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The results of the exemplary study by Kraigher-Krainer and colleagues reported in this issue of the Journal provide additional strong support for the concepts of phenotypic heterogeneity and multi-factorial contributions in the HFpEF syndrome.[12] Their well-designed, well-conducted ancillary study utilized a standardized protocol with state-of-the art, detailed echo-Doppler measures of cardiac structure and function, formal training of sonographers at 65 field sites, and expert, blinded quantitative image analysis, all orchestrated by a highly experienced echocardiographic core laboratory.[12] Systolic function was assessed as longitudinal and circumferential strain by deformation analysis using 2-dimensional digital echo speckle-tracking. This method has advantages over tissue Doppler strain methods and is more amenable to multi-site trials involving multiple ultrasound instrument vendors. The investigators further enhanced the study by including two age-matched control groups – normals and patients with hypertension.

Despite relatively preserved ejection fraction, both longitudinal and circumferential strain were significantly reduced in HFpEF patients compared to both control groups.[12] Longitudinal strain was the most abnormal. Reduced longitudinal strain was most common in the HFpEF patients within the lower EF range (45–54%) but was present in 50% of patients within the normal EF range. Reduced strain was present even after excluding patients with ischemic heart disease. Reduced strain was associated with acute hospitalization and higher NT-proBNP levels.

These data indicate that systolic dysfunction is common in HFpEF and likely contributes to its pathophysiology and poor outcomes. Kraigher-Krainer and colleagues performed measurements only at rest and in stable outpatients. Previous studies of exercise intolerance[23,24] and acute pulmonary edema,[25] the two key manifestations of HFpEF, have not found contributions from traditional measures of systolic dysfunction. However, Henein found that failure to increase longitudinal strain during exercise contributes to exercise intolerance.[26]

These findings should not be surprising. LV relaxation and contraction are intimately related; both are dependent upon availability of ATP and modulated by adrenergic stimulation. Studies in HFrEF established long ago that systolic dysfunction is rarely present without concomitant diastolic dysfunction. The present study further promotes the concept of generalized cardiac dysfunction in HF, even when EF is apparently preserved.

The therapeutic implications are confounded by trial experience in HFrEF patients, in whom inotropes improve systolic function and exercise capacity but increase mortality. Beta-blockers, which are negative inotropes (and negative lusitropes), paradoxically reduce mortality. Manipulating LV systolic and diastolic function to improve outcomes in HF patients has proved more challenging than anticipated.

The present study[12] had several other important findings: only 8% of patients had LV hypertrophy; only 15% had concentric remodeling; Doppler tissue diastolic velocities were only mildly lower than normals and similar to hypertensives; end-diastolic volume was larger than both normal and hypertension controls; systolic and diastolic blood pressure were controlled; and left atrial pressure was frankly increased in <50% of patients.[12] These

findings occurred despite stringent inclusion criteria, including severely increased NT-proBNP. Other studies, including population-based studies less influenced by trial selection criteria, have had similar findings.[18,24,27] Thus, in stark contrast to earlier paradigms, many stable outpatients with HFpEF, in some cases the majority, do not have LV hypertrophy, concentric remodeling, uncontrolled hypertension, elevated left atrial pressure, or abnormal diastolic filling, and do have LV dilation, reduced systolic function, and a variety of non-cardiovascular abnormalities.

The presence of phenotypic heterogeneity, multi-factorial pathophysiology, and multiorgan involvement in HFpEF should not be surprising. These features are also seen in HFrEF, and reflect HF as a systemic disorder. They are also typical of other disorders common in the elderly. HFpEF is strongly influenced by aging, a systemic process affecting all organ systems.[6,7] The impact of multiple co-morbidities typical of older HFpEF patients further ensures phenotypic heterogeneity and multi-factorial pathophysiology.[22]

A broader, systemic view of HFpEF also helps explain observations that nearly two-thirds of subsequent hospitalizations are non-HF related and approximately 50% are non-cardiac,[5] the majority of HFpEF patients die from non-cardiovascular causes,[28] and that the large HFpEF pharmacological trials to date, which were based on earlier simplistic paradigms, haven't been positive.

Progress in HFpEF will be made by incorporating these concepts of heterogeneity and multi-factorial contributions, and searching for the common threads and links with other debilitating disorders common among the elderly. For example, recent parabiosis studies show that signaling factors in the circulation can reverse or accelerate key features of cardiovascular aging related to HFpEF.[29] Key findings such as this further support that HF in the elderly is a systemic process, and could increase understanding of the fundamental pathophysiology of HFpEF and lead to development of novel strategies for its prevention and treatment.

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