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REPLY: Heart Failure With Preserved Ejection Fraction: Types 1 and 2?

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We appreciate the thoughtful comments by Drs. Goldsmith and Simegn. We agree that a clearer understanding of various heart failure with preserved ejection (HFpEF) phenotypes, such as the 5 phenotypes proposed by Shah et al. (1) can facilitate advances in understanding and treating this important, highly prevalent disorder. Goldsmith and Simegn propose that HFpEF be divided into 2 categories, depending on whether the disorder is derived predominantly from a “cardiac” or a “noncardiac” cause. Although this approach is appealing due to its simplicity, such a categorization could pose a number of challenges. First, it is exceedingly difficult to determine, within an individual patient, the degree of cardiac versus noncardiac contributions. Second, both cardiac and noncardiac factors nearly always contribute and are closely intertwined. Third, the current view of HFpEF is conceived of as a systemic syndrome that involves multiple organ systems; rarely is there solely cardiac involvement (1). For instance, obese HFpEF, the most common phenotype in the United States, is likely initiated by circulating factors, such as inflammatory cytokines that originate from excess intra-abdominal adipose tissue and cause widespread loss of capillarity and mitochondrial function, particularly in critical organs such as cardiac and skeletal muscle (2). Thus, attempting to categorize individual patients with HFpEF by predominantly cardiac versus noncardiac origin seems unrealistic and incompatible with our current understanding of the disorder.

Although it is appealing to envision dividing patients with HFpEF into narrow categories with specific causes and direct management and treatment from there, HFpEF is inherently a complex, multi-factorial, heterogeneous syndrome with significant contributions from noncardiac factors, including the multiple chronic comorbidities that tend to drive the clinical events and adverse outcomes in HFpEF (3). The 5-phenotype concept described by Shah et al. (1) recognizes this and also accounts for the fact that most phenotypes have both cardiac and noncardiac contributions. However, even that scheme is imperfect, as some patients with HFpEF do not fit well into any category, and some have features of multiple categories. Furthermore, there are important gaps in our understanding of the

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pathophysiology of all the phenotypes, and it is uncertain whether the various phenotypes respond differently to specific therapies.

We believe that progress in HFpEF management can be facilitated by embracing and seeking to understand this complex pathophysiology and leveraging this knowledge for the development of novel, patient-specific, therapeutic alternatives; cardiac or noncardiac. We strongly agree with Goldsmith and Simegn, and several lines of evidence support the fact that the noncardiac factors that are usually part of the HFpEF syndrome not only present opportunities for novel treatments but can be more modifiable than cardiac factors (3). Indeed, the negative results from completed HFpEF pharmacological trials, nearly all of which focused predominantly on cardiac factors, also suggest that a broader approach may be fruitful (3).

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