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EDITORIAL COMMENT

HFpEF

Is Splitting Into Distinct Phenotypes by Comorbidities the Pathway Forward?*

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Among the numerous comorbidities that can confound the diagnosis of heart failure with a preserved ejection fraction (HFpEF), diabetes is among the most prevalent. Approximately one-third of patients with HFpEF have diabetes (1,2), and as many as half of patients hospitalized with HFpEF are diabetic (3). Not only is diabetes associated with worse outcomes patients with HFpEF (4), but it is an independent predictor of incident heart failure (5). Given the lack of efficacy of pharmacological therapy for HFpEF, there is a growing focus on the role of comorbidities in the genesis of this heterogeneous clinical syndrome (6) with an emerging hypothesis that comorbidities drive phenotypic expression (7). Characterization of HFpEF stratified by subgroups may identify relevant cohorts for investigation and targetable pathophysiological mechanisms.

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In this issue of the *Journal*, the RELAX (Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure) investigators report on their analysis of clinical features, exercise capacity, and outcomes in patients with HFpEF with or without diabetes (8). RELAX, a multicenter, randomized trial of sildenafil versus placebo in HFpEF, enrolled a small but well-characterized cohort of older adults with HFpEF using functional, biomarker, echocardiographic, and cardiac magnetic resonance measures. The rigorous entry criteria focused on reduced exercise capacity as determined by cardiopulmonary exercise testing and elevated pulmonary capillary wedge pressures or natriuretic peptides. RELAX was a negative trial (9), and diabetes had no effect on the primary endpoint of exercise capacity or the effect of study drug on hospitalizations.

In this substudy (8), HFpEF with diabetes was characterized by a younger, more frequently male and obese cohort with multimorbidity (e.g., more hypertension, renal dysfunction). Biomarkers showed evidence of chronic inflammation, increased fibrosis, and higher endothelin-1 levels. Diabetic patients with HFpEF had more ventricular hypertrophy, but ventricular function did not differ between cohorts. Peak oxygen uptake and 6-min walk distance were lower in diabetic patients after controlling for relevant confounders (age, sex, body mass index, hemoglobin, and chronotropic incompetence), whereas hospitalization for renal and cardiac causes was 4 times more likely.

These differences suggest that diabetic patients with HFpEF may differ significantly from those without diabetes, but several limitations of the study should be noted. First, the diagnosis of diabetes was not based on any formal criteria and not adjudicated centrally. There were no measures of diabetic severity or duration, which did not allow exploration of the relationship between diabetic control and/or severity with phenotypic expression. Another limitation is the small sample size, which limits the power to detect significant differences between cohorts with a strong potential for a type II error. Further evaluation of differences between HFpEF patients with and without diabetes in larger trials could provide important confirmation, clarification, or revision of these findings. In fact, the relatively selective nature of the RELAX population could minimize important differences with regard to concomitant renal dysfunction and anemia.

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Finally, the absence of hemodynamic characterization during exercise is a limitation because the cause of exercise intolerance (e.g., central vs. peripheral factors) in HFpEF patients with diabetes is unknown.

There are multiple mechanisms by which diabetes could contribute to the phenotypic expression of HFpEF. Previous studies demonstrated expanded plasma volumes in patients with HFpEF (10), which is influenced by comorbidities of diabetes, anemia, renal dysfunction, and obesity. This results in altered pressure volume relations with shifts in noninvasive estimates of the end-diastolic pressure volume relations downward and rightward (e.g., increased capacitance) (11), which is consistent with a phenotype of a high-output state (1) and eccentric remodeling. Additionally, comorbidities induce a systemic proinflammatory state (7), causing microvascular endothelial inflammation, which can contribute to altered cardiomyocyte biology, interstitial fibrosis, hypertrophy, and altered ventricular vascular coupling. Indeed, endothelial dysfunction has been shown to have independent prognostic significance in HFpEF (12). Chronotropic incompetence is an important mechanism of exercise intolerance (8). Altered autonomic control is a known complication of diabetes, which affects baroreflex-mediated control of sympathovagal balance. Altered baroreflex control has been shown in animals to contribute to intolerance of volume loading in the absence of left ventricular dysfunction and may be important in the genesis of acute pulmonary edema (13) and impaired cardiac output response and blood flow to exercising muscles. Finally, diabetes is strongly linked to obesity, specifically a phenotypic of sarcopenic obesity, which can contribute to the reduced exercise performance in patients with HFpEF (14).

Peripheral mechanisms also may be key mediators of the reduced exercise capacity in HFpEF with diabetes. Prolonged hyperglycemia, hypo- or hyperinsulinemia, and hyperlipidemia with elevations in triglycerides and nonesterified fatty acids can contribute to skeletal muscle dysfunction. Additionally, inflammatory mediators produced by adipose tissue might alter myocardial, vascular (both arterial and venous), and skeletal muscle mass, quality, and perfusion.

Given the high event rate among diabetic patients with HFpEF, it would appear that this cohort is worthy of targeted investigation. Nonpharmacological interventions such as cardiac rehabilitation (15) may address the emerging extracardiac targets in HFpEF. Dietary interventions, such as the DASH-DHF (Effects of the Dietary Approaches to Stop Hypertension Sodium-Restricted Diet in Diastolic Heart Failure) (16), are methods to address the metabolic abnormalities that lead to a salt-sensitive state and phenotypic expression of HFpEF. Novel pharmacological therapies including endothelial nitric oxide synthase activators, matrix metalloproteinase 9 inhibitors, nitroxyl donors, and LCZ696, a combination drug of angiotensin II receptor blocker and neprilysin inhibitor, could be beneficial. Each of these has attractive properties, including antifibrotic, antihypertrophic, and antiadrenergic actions that oppose adverse cardiac remodeling.

The main objective of phenotypic characterization of the heterogeneous cohort that comprises HFpEF is to identify a pathway forward for management of older adult patients with HFpEF. Our hope is that such lines of investigation provides more than proving the obvious, namely, that diabetes and HFpEF are bad diseases and worse in combination. However, only after future carefully conducted investigations in targeted populations will we know whether the splitting into distinct phenotypes will be a fruitful pathway forward.

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