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"Frailty, Thy Name Is Woman" Syndrome of Women With Heart Failure With Preserved Ejection Fraction

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Heart failure (HF) is the most common cause for hospitalization among patients aged ≥65 years, affecting ≈6 million Americans; at 40 years, American men and women have a 1 in 5 lifetime risk of developing HF.[1] There are 2 distinct HF phenotypes: a syndrome with normal or near-normal left ventricular ejection fraction (LVEF) referred to as HF with preserved EF (HFpEF)[2] and the phenotype associated with poor cardiac contractility or HF with reduced EF (HFrEF). HFrEF is frequently caused by coronary artery disease with a male predominance; evidence-based strategies have been established for more than a decade. In contrast, the precise clinical criteria for HFpEF are not universally agreed on, the syndrome disproportionally affects women in 2:1 ratio, and there are no proven treatments.[3–5] There are some commonalities between HFrEF and HFpEF in addition to the classic symptoms of breathlessness, edema, and fatigue: older age, diabetes mellitus, and a history of valvular disease are risk factors that are predictive of both clinical phenotypes.[6] Risk factors associated with HFpEF include female sex, especially women with diabetes mellitus,[7] higher body mass index, smoking, hypertension, concentric LV hypertrophy (LVH), and atrial fibrillation (AF).[6,8,9] Risk factors associated with HFrEF include male sex, higher total cholesterol and heart rate, eccentric LVH, coronary artery disease, and left bundle-branch block.[6,9]

Evolution of the HFpEF Definition

A remarkable lack of consensus exists with respect to the phenotypic characteristics of HFpEF, as evidenced by the divergent definitions of the European Study Group on Diastolic Heart Failure,[10] the Framingham Group,[11] and the European Society of Cardiology,[12] to name just a few (Table).[13] All include symptoms or signs but vary in specificity and a requirement for objective data. The definition of preserved LVEF is also inconsistent but typically defined as >50%.[13] The most important consequence of this variability is that the inclusion criteria for large, clinical HFpEF trials are likewise inconsistent and contribute to the heterogeneity of the results.[13] Several important recent HFpEF trials underscore the above inconsistencies: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), Candesartan in Heart Failure Assessment of Reduction

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Disclosures

None.

in Mortality and Morbidity (CHARM-Preserved), and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). TOPCAT included patients aged ≥50 years with HFpEF, diagnosed by signs and symptoms in conjunction with previous hospital admission or elevated brain natriuretic peptide level with an LVEF of >45%. This study showed no improvement with spironolactone on a composite of cardiovascular mortality, cardiac arrest, or hospitalization for HF.[14] CHARM-Preserved included patients with New York Heart Association II–IV HF and LVEF >40%; the results showed no significant benefit of candesartan on cardiovascular death or hospital admission for HF.[15] I-PRESERVE included patients with New York Heart Association II–IV and an LVEF of ≥45% and a hospitalization for HF in the previous 6 months. Again, there was no significant improvement with irbesartan on a composite outcome of death from any cause or hospitalization for a cardiovascular cause.[16]

Accordingly, there has been growing interest in the development of criteria for specific subsets of HFpEF, a syndromal disease where multiple cardiac and vascular abnormalities exist. HFpEF is associated with ventricular dysfunction (impaired relaxation and impaired filling), atrial enlargement and dysfunction, autonomic dysregulation and chronotropic incompetence affecting exercise tolerance, vascular reactivity and stiffening, and dynamic mitral regurgitation. Patients with HFpEF are typically hypertensive, diabetic, obese, older, and deconditioned.[13] Moreover, when important morbidities of the elderly coexist in patients with HFpEF, such as renal insufficiency, [17] iron deficiency or anemia,[18] and chronic obstructive lung disease,[19] poor outcomes become even worse. Given the confounding effect of a complex set of risk factors and comorbidities, matching treatment interventions to a specific patient's phenotype in HFpEF is a promising approach and may increase the chance of showing clinical benefit with targeted therapies. The question arises as how to best group patients.

One approach is to implement phenomapping, identifying phenotypically distinct HFpEF categories and developing a classification system to group together pathophysiologically similar individuals who may respond in a more homogeneous, predictable way to intervention. A recent study by Shah et al[20] identified 3 clinical phenogroups from a HFpEF cohort with shared diagnostic features: group 1, younger patients with moderate diastolic dysfunction who had relatively normal brain natriuretic peptide; group 2, obese and diabetic patients with a high prevalence of obstructive sleep apnea and ventricular relaxation abnormalities; and group 3, older patients with significant chronic kidney disease, electric (longest QRS duration and largest QRS-T angle) and myocardial remodeling (highest relative wall thickness, LV mass index, and highest E/e′ ratio), pulmonary hypertension, and right ventricular dysfunction. Perhaps not surprisingly, these groupings were an independent predictor of differential outcomes.[20] Other studies have examined geographic variation in outcomes observed in HFpEF trials highlighting not only the differences in hospitalization criteria in different regions but also the possibility of racial, ethnic, or even environmental determinants on health end points.[21,22] Still, other investigations have developed cohorts stratified by specific comorbidities, including renal function,[23] right heart function,[24] and diabetes mellitus.[25] Lindman et al[25] asked whether diabetic patients with HFpEF had distinctive characteristics and outcomes from those of nondiabetic patients. As might be predicted, diabetic patients with HFpEF had a more severe disease phenotype with higher

comorbidities, increased LVH, and elevated serum markers for vasoconstriction, oxidative stress, inflammation, and fibrosis. Diabetic patients comprise ≈30% to 40% of the HFpEF population; this phenotype subgroup seems appropriate. But it only serves to further confuse the diagnostic criteria for HFpEF. What components of the diabetes mellitus syndrome contribute to the cardiac disorder and should be classified: duration of diabetes mellitus, extent of diabetic control, age at onset, etc? If age proves to be an important criterion for grouping, are we certain years of age are not a surrogate for some physiological marker of severity? More importantly, this form of phenotyping may not serve to identify the mechanisms responsible for the actual pathophysiology of the HFpEF syndrome.

Can Phenotypes of HFpEF Provide Pathophysiological Insights?

Another option would be to focus on a known physiological difference that might shed light on pathological mechanisms, for example, sex. Women are disproportionately affected with HFpEF; it has long been recognized that at puberty, even normal hearts are different between the sexes. Distinctions in cardiac structure between men and women include LV chamber size and mass that are 15% to 40% lower in women, even after adjustment for smaller body type.[26,27] There are fundamental differences in structural remodeling in response to chronic load, either from aortic stenosis or from hypertension. Men are more likely to develop eccentric LVH, whereas women develop concentric LVH. Interestingly, regression of LVH is more pronounced in women after aortic valve replacement, suggesting that women have a greater sensitivity to pressure overload.[28,29] Importantly, the greater reversibility of LVH in women suggests that pressure reduction may be a useful intervention in women. Female LV chambers under increased load do not dilate compared with their male counterparts, which leads to higher estimated filling pressures, characteristic of HFpEF.[30] Although hypertension causes increased chamber stiffness in both men and women, it is persistently higher in women at any age.[31] Noteworthy too is that younger women, aged 20 to 40 years, have enhanced diastolic function compared with men; this is reversed once women become >60 years of age.[32,33] Finally, differences in vascular biology determine increased arterial stiffing in women comparatively. [3] Even the lower range of LVEF for HFpEF is usually defined as an EF of >50%, but a normal LVEF is typically higher in women, averaging 75% in women aged 30 to 65 years.[26] Perhaps a LVEF of 50% may, in fact, represent systolic dysfunction in women.[26,34] The specific implications of these important sex differences for finding more definitive therapies for HFpEF are not clear. Nevertheless, in this era of phenomapping, the important phenotype of being woman should not be ignored.

The intersect between HF and AF is a collision of 2 epidemics. [6,35,36] AF is consistently associated with HFpEF, whereas ≤65% of patients with HFpEF have AF.[35] Interestingly, although AF typically displays a male preponderance, women with HFpEF are equally affected by AF.[35,37] Diastolic dysfunction has also been shown to be an independent predictor of AF. The pathophysiological and clinical implication of left atrial (LA) remodeling is significant in the HFpEF population. Effects of atrial abnormalities are atrial endocrine function, including natriuretic peptides; LA mechanoreceptor function in vasopressin production, water, and electrolyte balance; LA remodeling and increased collagen synthesis and fibrosis, thereby decreasing LA compliance; and the loss of atrial contraction, possibly influencing the reduced exercise tolerance in HFpEF.[38] Furthermore,

those with diastolic dysfunction undergoing AF ablation have a higher risk of AF recurrence.[39] Intriguingly, a recent clinical trial showed patients with HFpEF and dilated LA benefited more from carvedilol than patients without a dilated LA. The authors suggested that disease in the atria might be a target, as well as factor, in patient selection for HFpEF therapies.[40]

A third important phenotype in a HFpEF cohort is obesity. Obesity, particularly central adiposity, influences LV geometry substantially more in women than in men.[26] In addition, adipose mass is greater in women compared with men.[34] A new HFpEF paradigm has proposed that frequently associated comorbidities, most significant being obesity, trigger a systemic inflammatory response that leads to increased oxidative stress in the coronary microvascular endothelium. The result is stiffer and more hypertrophied cardiomyoctes.[41] Increased oxidative stress might also lead to increased myocardial fibrosis, both in the atria and the ventricles, a pathway linking obesity, HFpEF, and AF.

There are other pathophysiologically based pathways currently being investigated, including the degree of fibrosis and coronary microvascular rarefaction (loss of vessels either from destruction or lack of regeneration), both possibly related to oxidative stress in the coronary microvascular endothelium as discussed above.[42] Although several possible new areas for exploration have been discussed, there are currently many promising areas being explored and the overlap of all these pathways will likely be the key.

Case to Begin Simply

Phenomapping and genomic typing are technologies that may introduce new paths of discovery; they are costly and not currently suitable for classifying patients in a large trial. The easily ascertained phenotypes of sex, obesity, and AF have been and are available now; sex is binary, whereas obesity and AF can be further divided into discrete subsets. These 3 clinical phenotypes (obesity, sex, and AF) are characterized by abnormal fibrosis and inflammatory responses that have been shown to be pathophysiologically related to patients diagnosed clinically with HFpEF. Thus, the first step must be to show that these 3 clinical phenotypes, separately and together, result in different outcomes for patients with HFpEF. Future mechanistic investigations about HFpEF should be focused on the overlap, instead of differences, with sex at the epicenter (Figure) Thus, extent of myocardial fibrosis could be examined in HFpEF women with and without AF or with various degrees of obesity. The physiological abnormalities delineated could then be linked, once again, to clinical outcomes. The power of applying our knowledge of sex differences in cardiac remodeling, vascular biology, and cardiac arrhythmias to the larger dilemma of the HFpEF syndrome is one that should not be overlooked. The phenotype of the frail woman with HFpEF may still be a powerful tool in understanding this vexing syndrome.

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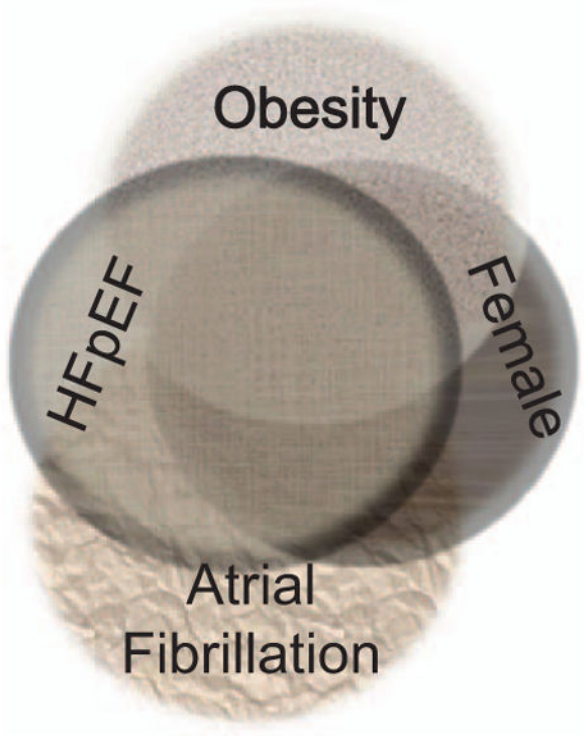

Figure.
The overlap of heart failure with preserved ejection fraction (HFpEF) phenotypes for sex, obesity, and atrial fibrillation.

Table

HFpEF Classification

European Study Group on Diastolic Heart Failure[10]	Framingham[11]	ESC Guidelines[12]
Lung crepitation, pulmonary edema, ankle swelling, dyspnea on exertion, and fatigue	Clinical signs and symptoms, supportive laboratory tests (chest x-ray), and typical response to treatment with diuretics	Symptoms: breathlessness, ankle swelling, and fatigue; Signs: elevated jugular venous pressure, pulmonary crackles, and displaced apex beat
Objectively reduced peak V_{O_2} (<25 mL/kg/min) or 6-min walk test (<300 m)	LVEF >50% within 72 h of HF	Normal LVEF with LV not dilated
LVEF >50%	Diastolic assessment not required	Relevant structural heart disease (LVH/LA enlargement) and diastolic dysfunction
Evidence of abnormal LV relaxation, filling, and diastolic distensibility	…	…

ESC indicates European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; and LVH, left ventricular hypertrophy.