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Heart Failure with Preserved Ejection Fraction: Diagnosis and Management

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a prevalent condition with substantial individual and societal burden. In this article, we review the current status of understanding of HFpEF, focusing on the challenges and uncertainties regarding diagnosis and treatment. We then propose a scientific roadmap to facilitate research that may translate into improved clinical outcomes.

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THE SCOPE OF THE PROBLEM

Heart failure with preserved ejection fraction (HFpEF) is a major global public health issue. Its prevalence is between 1.1% and 5.5%, accounting for a staggering 40%-70% of heart failure cases.[1,2] Of all patients with heart failure, the proportion of those with HFpEF continues to rise (at about 1% per year).[3,4] If current trends persist, HFpEF may become the predominant phenotype of heart failure within the next decade. The alarming rate of growth in HFpEF diagnoses is most likely a reflection of the increasing frequency of hypertension, obesity, and atrial fibrillation—conditions that drive endothelial inflammation and diastolic dysfunction. Increased life expectancy and improved recognition of HFpEF also explain the higher overall prevalence. Those epidemiological shifts are critical to comprehend, particularly given the considerable impact of HFpEF on patients' quality of life and its associated morbidity and mortality, which are comparable with those of HFrEF (heart failure with reduced ejection fraction).[4] Yet, despite the well-documented individual and health care costs attributed to HFpEF, its physiologic and molecular underpinnings remain poorly understood and the therapeutic armamentarium to effectively treat HFpEF remains limited. Some professional societies avoid issuing specific clinical recommendations given the scarcity of evidence-based data, and some even disregard HFpEF as a form of heart failure altogether.[4] Most authorities, however, do recognize the novel morphologic-hemodynamic patterns of HFpEF as well as the gaps in response to treatment, and favor a 2-subset model for heart failure (HFpEF vs HFrEF).[5]

PATHOPHYSIOLOGICAL BASIS

At its core, HFpEF represents severe dysfunction of the diastolic phase of the cardiac cycle that results in elevated ventricular pressures. Impairment of myocardial relaxation and stiffness of the ventricle culminate in reduced left ventricular filling, elevated diastolic pressures, and heart failure symptoms (**Figure 1**).[6] Invasive hemodynamic measurements demonstrate a prolonged isovolumic-pressure decline as well as upward-leftward shift in the pressure-volume loop, consistent with aberrant myocardial relaxation.[7] Indices of passive stiffness are characteristically high in those patients (**Figure 2**).

Many factors contribute to the increases in left ventricular diastolic pressure. Sodium retention, increased venous tone, and activation of neurohormonal pathways are thought to play a role (**Figure 1**). However, it is the accelerated left ventricular stiffness that leads to marked elevations in diastolic pressures, pulmonary hypertension, and pulmonary edema.[8] The noncompliance (low elastance) of the ventricle results in extreme elevations in diastolic

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pressure with very small changes in volume. High atrial pressures are maintained in an effort to increase cardiac output, yet the stiff ventricle limits optimal diastolic filling. This leads to rising ventricular diastolic pressures, pulmonary venous congestion, and exertional dyspnea.

Recently, several novel mechanisms have been implicated in causing diastolic dysfunction, including limited vasodilator capacity, pulmonary hypertension, and impaired ventricular-arterial coupling.[9-12] Among the emerging paradigms is one integrating the underlying metabolic milieu, endothelial inflammation, and cardiomyocyte function.[13,14] Following this theory, various proinflammatory conditions (ie, obesity, diabetes mellitus, hypertension) provoke microvascular inflammation at the endothelial level. The resultant cytokine storm leads to nitric oxide scavenging with insufficient supply of vasodilator molecules (cyclic guanosine monophosphate content, protein kinase G). Low nitric oxide bioavailability leads to tissue-level oxidative stress, interstitial fibrosis, and cardiomyocyte tension. Stiffness of the myocardium ensues, with the accompanying heart failure symptoms.

CLINICAL SIGNIFICANCE

- Heart failure with preserved ejection fraction (HFpEF) accounts for one-half of heart failure cases.
- Diagnosis requires 3 levels of evidence (clinical congestive heart failure, normal ejection fraction, diastolic dysfunction).
- No treatment to date has been proven effective in reducing the morbidity and mortality of HFpEF.
- Most HFpEF studies suffer from significant methodological pitfalls.
- A uniform definition of heart failure is paramount to improve the yield of clinical trials.

As tempting as these discoveries might be, studies have shown that HFpEF is a very heterogenous disease. Although patients with HFpEF may have an almost-indistinguishable constellation of symptoms, the cellular mechanisms and clinical behavior of their disease may be starkly different. Subgrouping of patients based on underlying comorbidities may help define the clinically important phenotypes of HFpEF, offering pathway-specific management.[13] One such phenotype is "obesity-HFpEF," which was first described in overweight African-American women with hypertension. Increased visceral adiposity—both independently and through its association with elevated systolic blood pressure and nocturnal hypoxemia—leads to left ventricular hypertrophy and arterial stiffness.[15] HFpEF patients with coronary artery disease represent another clinical subtype. These patients have more significant worsening of left ventricular function and are at greater risk of myocardial infarction, stroke, and death compared with HFpEF patients who do not have coronary artery disease. More granular definition of these phenotypes may prove useful in the treatment of HFpEF.

Diagnostic Considerations

Various criteria have been suggested for the diagnosis of HFpEF. Those presented in **Figure 3** serve as an important milestone in our approach to HFpEF.[14,16] To make a definite diagnosis of HFpEF, the simultaneous presence of the following 3 clinical/echocardiographic/hemodynamic abnormalities is required: 1) Evidence of congestive heart failure (typical signs and symptoms, ancillary tests, and response to diuretic treatment); 2) Normal left ventricular systolic function (left ventricular ejection fraction >50%; measured within 3 days of heart failure presentation); and 3) Evidence of left ventricular diastolic dysfunction (impaired left ventricular relaxation/filling/distensibility). The diagnostic challenge is threefold. First, defining congestive heart failure may not always be straightforward. Most signs and symptoms of heart failure (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema) are nonspecific and, not infrequently, may be explained by an alternative noncardiac condition.[17] Secondly, the echocardiographic parameters previously thought to be pathognomonic for heart failure are not entirely flawless. Left ventricular ejection function, even when measured by radionuclide ventriculography, has significant limitations. The ejection fraction is not easily reproducible, hasn't been formally standardized (with different trials setting distinct thresholds for systolic dysfunction), and is highly sensitive to therapeutic intervention (may be pseudonormal after effective diuresis).[18] Of no less significance, the ejection fraction cannot help predict diastolic function. Which leads to the third obstacle of the presented criteria: the relative paucity of absolute markers of diastolic dysfunction. In addition to these obstacles, clinicians also have to exclude a number of cardiovascular conditions—restrictive cardiomyopathy, pericardial disease, and ischemic heart disease, among others—when considering HFpEF.

To make a diagnosis of HFpEF while avoiding the low specificity of relying on clinical manifestations alone, accurate indicators of diastolic dysfunction are needed. Left ventricular hypertrophy, left atrial enlargement, and natriuretic peptides elevation have been suggested. Yet, they are all indirect markers of ventricular stiffness. Their correlation with diastolic dysfunction has never been validated in large-scale studies and they represent reasonable but unproven determinants of diastolic impairment. The question remains: is it necessary to commit every patient suspected of having HFpEF to invasive hemodynamic monitoring? Alternatively, are specific clinical presentations in appropriate settings satisfactory in order to avoid cardiac catheterization? The jury is still out regarding that question, yet the expert consensus is that particular