SPECIAL COMMUNICATION

Does My Patient with Multiple Comorbidities Have Heart Failure with Preserved Ejection Fraction, and Does It Matter?

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Heart Failure with Preserved Ejection Fraction (HFpEF) is a common diagnosis and accounts for half or more of all cases of heart failure. Despite its high prevalence and significant morbidity, the pathophysiology of HFpEF remains incompletely understood. Patients diagnosed with HFpEF often have significant cardiac and extra-cardiac comorbidities. Given the availability of evidence-based treatments for common comorbidities, but not for HFpEF, the necessity of diagnosing HFpEF among symptomatic elderly patients with multiple comorbidities is unclear. This commentary raises the question of whether the search for the diagnosis of HFpEF should instead be refocused to the management of common comorbidities without necessitating the heart failure diagnosis. (J Am Board Fam Med 2019;32:424–427.)

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Heart failure with preserved ejection fraction (HFpEF) comprises about half of the cases of heart failure in the United States.[1] Despite its growing prevalence and significant morbidity, HFpEF remains incompletely understood and diagnosis in the community setting may be difficult. Widely used diagnostic criteria that incorporate clinical findings with laboratory values and echocardiographic parameters lack sensitivity which may result in underdiagnosis.[2] Overdiagnosis based on vague symptoms and nonspecific diagnostic parameters may likewise be problematic. The concern of over- and underdiagnosis is further compounded by the lack of evidence-based treatments for those diagnosed with HFpEF. Patients with HFpEF tend to be older, with multiple cardiac and noncardiac comordbities.[3] This begs the question of whether diagnosis of HFpEF remains critical to optimize the care of predominantly older patients with multiple comorbidities.

Defining Heart Failure with Preserved Ejection Fraction

Heart failure has been defined as the inability of the heart to generate adequate cardiac output or the ability to generate adequate cardiac output only in the setting of elevated filling pressures.[4] The standard clinical diagnostic criteria for HFpEF includes heart failure symptoms (such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea) and elevated filling pressures (predominantly Wedge pressure) at rest or with exercise.[5] Elevated filling pressures may be clinically estimated through measurement of jugular venous distention. Confirmation of elevated filling pressures, and therefore the heart failure diagnosis, can be obtained through invasive right heart catheterization. The history and physical examination-derived signs and symptoms suggestive of heart failure may be difficult to ascertain, and their correlation with invasively derived filling pressures has largely been based on studies of acutely decompensated or end-stage patients with reduced ejection fraction.[1,6] Recently, permanently implanted pulmonary artery monitors have been used to help evaluate central filling pressures as a supplement to the physical examination,[7] although

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the utility of such devices as part of the diagnostic evaluation of heart failure may be limited.

Current diagnostic criteria for HFpEF from the American College of Cardiology and American Heart Association include clinical signs or symptoms, ejection fraction ≥50%, and evidence of diastolic dysfunction.[1] Patients meeting heart failure criteria with ejection fraction of 41% to 49% can be classified as having heart failure with borderline or midrange ejection fraction, which is more clinically similar to HFpEF than to heart failure with reduced ejection fraction.[1,8] Diagnostic criteria for HFpEF from the European Society of Cardiology are similar, and include signs and symptoms, ejection fraction of ≥50%, elevated B-type natriuretic peptide values and echocardiographic evidence of structural abnormalities or diastolic dysfunction.[9]

Limitations of Diagnostic Criteria for HFpEF

While seemingly straightforward, the application of these criteria to the community setting is fraught with limitations. These diagnostic criteria have been criticized for low sensitivity,[2] and the reliance on echocardiographic evaluation of diastolic dysfunction may neither accurately evaluate cardiac relaxation abnormalities nor contain sufficient sensitivity or specificity to detect a clinical course consistent with HFpEF.[10] Although exact criteria for grading of diastolic dysfunction have changed over time,[11] diastolic abnormalities on echocardiography are common in community cohorts of patients with comorbidities such as obesity, hypertension, diabetes and coronary disease,[12] and have poor correlation with heart failure symptoms.[12,13] In addition, only minimal abnormalities in diastolic parameters (including a high prevalence of normal diastolic function, normal left atrial size, and normal wall thickness) are noted in cohorts with symptomatic HFpEF.[10] Echocardiographic diastolic parameters may primarily estimate ventricular filling pressures,[11] rather than necessarily providing an explanation for their elevation.

Clinical trials and day-to-day care of patients with HFpEF highlight the high burden of comorbidities associated with this condition. Common noncardiac comorbidities include older age, chronic kidney disease, and lung disease. Common cardiac comorbidities include diabetes, hypertension, coronary artery disease, obesity and atrial fibrillation. As dyspnea is a common symptom in patients with many of these comorbidities, and given the notable limitations of the diagnostic algorithms, how are clinicians to identify which of these patients may have HFpEF?

In light of these limitations, some have proposed scoring systems to help identify patients with HFpEF among those being evaluated for dyspnea[5]; identifying that the biggest predictors of elevated filling pressures (and therefore the HFpEF diagnosis) among patients with dyspnea are advanced age (>60 years old), obesity (Body Mass Index >30 kg/m^2) and atrial fibrillation. Other factors having a smaller association with elevated filling pressures include elevated pulmonary artery systolic pressure, treatment with multiple antihypertensive medications, and abnormal diastolic parameter of E/e'.[5] Having the 3 risk factors of advanced age, obesity, and atrial fibrillation was associated with a greater than 90% likelihood of meeting criteria for the diagnosis of HFpEF based on elevated filling pressures.[5] Importantly, elevated B-type natriuretic peptide, dilated left atrium, ventricular hypertrophy, or abnormal ventricular strain—all key parameters associated with diastolic dysfunction—had either smaller or no independent predictive ability to diagnose elevated filling pressures.

This focus on comorbidities as the key contributor to pathophysiology of HFpEF raises significant questions about our current understanding of what it means to impart onto a patient the heart failure diagnosis. Dyspnea is a ubiquitous and subjective symptom in older individuals,[14] and is particularly common in patients with comorbidities including obesity and atrial fibrillation. Dyspnea may also be multifactorial, and not primarily caused by elevation in intracardiac filling pressures.[15] Elevated filling pressures, even in the presence of dyspnea, may not always reflect heart failure, as every patient with end-stage renal disease on dialysis is not generally considered to have "heart failure" before a dialysis session.

Refocus on Patient Management

Instead of focusing on the diagnosis of HFpEF, (ie, attempting to determine whether dyspnea is cardiac in origin or whether echocardiographic abnormalities are relevant to the clinical presentation), perhaps a better approach would be to return to the diagnosis and management of key cardiac and extracardiac comorbidities[3] that are common in el-

derly patients with limitations to functional capacity. It should be acceptable to diagnose and manage conditions associated with fluid retention, such as anemia, obesity, diabetes, kidney disease, or atrial fibrillation without invoking the heart failure diagnosis. Each of these comorbidities is a significant stand-alone diagnosis, associated with its own symptoms (often dyspnea), diagnostic criteria, and evidence-based treatments.[3] Whether these comorbidities contribute to fluid retention through: their association with diastolic abnormalities, other ventricular myocardial abnormalities, their own unique pathophysiologies, or a combination of these remains unclear. Diuretics are the mainstay treatment of symptoms of volume overload regardless of etiology, and can be used to control symptoms regardless of whether the patient is diagnosed with HFpEF, is suspected as having HFpEF, or is presumed to have volume overload from a noncardiac etiology. Among patients with HFpEF, the diuretic spironolactone is primarily effective at lower ejection fractions (<50%), and the benefits among patients with higher ejection fractions are less certain.[16]

While the search for underlying pathophysiology continues, there is increasing evidence that comorbidities are the most prominent contributors to symptoms among patients labeled as having HFpEF. If symptomatic comorbidities require another name or label, perhaps a better one is "comorbidity associated heart failure" or even "comorbidity associated diuretic dependence." Employing terminology to more closely correlate with etiology based on subpopulations of HFpEF patients may simplify the diagnosis of a widely encountered clinical syndrome and help guide management in a way not currently possible with HFpEF.

May the diagnosis of HFpEF become more clinically relevant if ongoing trials of novel therapies, including sacubitril valsartan, empagliflozin, and others demonstrate improvement in clinical outcomes? The answer to that question has yet to be determined, as these medications may yield similar benefit in high risk primary prevention populations without the necessity of a HFpEF diagnosis. While diagnosing specific diseases that have previously fallen under the HFpEF umbrella such as Amyloid or Fabry's cardiomyopathy are increasingly critical as treatments become available, the benefit of diagnosing comorbidity associated HFpEF remains unclear. In addition, while diagnosing HFpEF may carry prognostic implications, the associated adverse prognosis may result more from a particularly advanced comorbidity burden rather than primary cardiac pathology or heart failure itself.

In conclusion, diagnosing HFpEF in the community may not be easy or even clinically relevant, and the answer to the question of, "does my patient with multiple comorbidities have HFpEF?" may be less important than using available treatments to improve the quality of life of symptomatic patients.

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