Does HFpEF Really Exist? From Mimics to Misclassification in Clinical Practice

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Dear Editor,

I read with interest the recent article by Villacorta et al.[1] addressing the distinction between "true" heart failure with preserved ejection fraction (HFpEF) and conditions that merely mimic it. Their effort to clarify this conceptual ambiguity is commendable and timely. However, I believe the issue extends further, even when HFpEF mimics such as amyloidosis, constrictive pericarditis, or severe valvular disease are carefully excluded, the clinical entity known as HFpEF often dissolves under closer scrutiny.

Over the past 18 months, I have conducted a retrospective analysis of 773 consecutive acute heart failure admissions to our cardiology department, all of whom underwent standardized echocardiographic assessment at admission by experienced operators. Among 323 patients with left ventricle ejection fraction (LVEF) >40%, systemic congestion was present in 252. Of these, 81.7% had severe valvular disease. An additional 10% had other major abnormalities (e.g., cardiomyopathies, precapillary pulmonary artery hypertension, hemodynamically relevant rhythm disorders such as ventricular sustained arrhythmias and advanced atrio-ventricular block, or stage V renal disease). Only 8% lacked any identifiable structural or extracardiac cause. These results, published in Internal and Emergency Medicine, the official journal of the Italian Society of Internal Medicine, and further discussed in the European Journal of Internal Medicine, the official journal of the European Federation of Internal Medicine, have been commented in numerous reviews and commetary published in international journals,[2-7] suggest that truly guideline defined HFpEF — defined as diastolic dysfunction and increased filling pressures, in the absence of other primary causes such as severe valvular disease or cardiomyopathy — is exceedingly rare.

This observation aligns with the historical trajectory of HFpEF research. Early trials such as CHARM-Preserved[8] enrolled patients based on preserved LVEF and nonspecific symptoms, often without comprehensive echocardiographic evaluation (structural and of fluid status) at the time of decompensation. Even more recent studies like TOPCAT,[9] PARAGON-HF,[10] DELIVER,[11] and EMPEROR-Preserved[12] attempted to refine inclusion criteria but continued to rely heavily on indirect markers like natriuretic peptides and administrative diagnoses. Importantly, echocardiography was not systematically performed at admission to confirm structural abnormalities, assess congestion, or rule out mimics. Even the authors of PARAGON-HF acknowledged that some patients may have been misclassified due to a lack of comprehensive diagnostic evaluation at baseline.[10]

Furthermore, given the limitations of imaging technology in the early 2000s, it is likely that many cases of severe valve disease were not detected. Moreover, the underuse of cardiac magnetic resonance imaging or nuclear scintigraphy limited the recognition of wild-type transthyretin amyloidosis, a condition now increasingly recognized, and contributed to the creation of the "diastolic dysfunction without significant structural abnormalities" narrative, which in turn shaped the HFpEF concept as a distinct syndrome.

In recent years, the diagnosis of HFpEF has expanded substantially, approaching epidemic proportions. Indeed in internal medicine wards, HFpEF is commonly assigned in elderly patients presenting with acute dyspnea, often in the context of pneumonia or COPD exacerbation. Not infrequently, a dual diagnosis (e.g., COPD and HFpEF) is recorded despite the absence of echocardiographic assessment at admission to support elevated filling pressures or volume overload. Inthis scenario acute haert failure diagnosis is made only ex adiuvantibus following empirical diuretic therapy in patients with acute dyspnoea.

In this context HFpEF has become a syndromic label applied too liberally in cases of diagnostic uncertainty, rather than a well-defined pathophysiologic condition.

While refining the terminology by excluding mimics is valuable, the more pressing message is that guideline-defined HFpEF represents a theoretical construct that is rarely encountered in real-world clinical practice. To ensure diagnostic accuracy and appropriate therapy, a return to a physiology-based diagnostic framework is warranted, avoiding the indiscriminate use of the HFpEF label.

Keywords

Diastolic Heart Failure; Dyspnea; Heart Valve Diseases

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Reply

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Dear Editor,

We thank the author of the letter for engaging thoughtfully with our article and for sharing insights on a complex syndrome such as HFpEF. Our paper focused only on the distinction between HFpEF and its mimics, and many aspects pointed out by the authors were not within the scope of our manuscript. However, it is important to clarify some points brought up by the authors. While we agree with some observations presented, we respectfully disagree with the conclusion that HFpEF is largely a theoretical construct.

We agree that HFpEF is frequently overdiagnosed in acute care settings, especially in the absence of robust imaging and hemodynamic assessment. The author's observation that many patients labeled as HFpEF exhibit significant structural abnormalities, such as severe valvular disease, rhythm disorders, or extracardiac contributors like COPD and renal failure, is consistent with our own position: these patients do not have HFpEF. These are cases of misdiagnosis.

However, the assertion that "pure" HFpEF is "exceedingly rare" or even an "unreal" entity demands closer scrutiny. First, the definition of HFpEF has evolved substantially over the past two decades. Contemporary guidelines now emphasize comprehensive evaluation, including evidence of diastolic dysfunction, elevated natriuretic peptides, signs of structural heart disease (e.g., left atrial enlargement, LV hypertrophy), and elevated filling pressures. So, the statement that HFpEF is defined as "acute decompensation in a structurally normal heart" is incorrect. It is quite the opposite. We need to demonstrate that the heart has been affected either using the gold-standard cardiac biomarker for the diagnosis of heart failure – natriuretic peptides – and/or the demonstration of structural alterations of the heart, as mentioned above. Please observe that the definition of HFpEF includes a normal LVEF but not a structurally normal heart. These concepts are well demonstrated in the latest universal definition of heart failure.[1]

We also caution against the definition by the authors as an "acute decompensation…". HFpEF is frequently a chronic condition with intermittent exacerbations triggered by comorbidities. Actually, most of the patients present as ambulatory cases, with a complain of exercise intolerance.

While early trials may have included patients with less stringent criteria, recent studies such as EMPEROR-Preserved,[2] DELIVER,[3] and FINEARTS-HF[4] have significantly refined patient selection. The inclusion of patients with valvular heart disease in these trials is quite unlikely since an echocardiogram was mandatory to confirm a LVEF ≥50% (or ≥40% in some studies, to include those with mildly reduced LVEF as well), which is part of the definition of HFpEF itself.

The author rightly highlights the under-recognition of conditions like transthyretin amyloidosis in the past. Nevertheless, the increasing diagnostic yield of cardiac magnetic resonance imaging, nuclear imaging, and biomarker profiling has only strengthened the distinction between HFpEF and other infiltrative or valvular diseases – not blurred it.

HFpEF encompasses a distinct pathophysiological syndrome marked by systemic inflammation, cardiac stiffening, endothelial dysfunction, chronotropic incompetence, and abnormal

ventricular-arterial coupling—often coexisting with comorbidities such as hypertension, obesity, and diabetes. These are not merely confounders, but active participants in disease manifestation. These alterations result in a stiff LV, as demonstrated by Zile et al. in 2004.[5] The stiffness of the LV leads to increased filling pressure and increased left atrial volume. Its clinical expression is heterogeneous by nature, not a flaw in the concept.

In conclusion, we welcome the call for diagnostic rigor and physiological thinking. However, rather than invalidating HFpEF, this perspective reinforces the need for precise phenotyping, careful exclusion of mimics, and ongoing refinement of diagnostic pathways. HFpEF does exist – not as a specific disease, but as a spectrum of diseases rooted in identifiable mechanisms deserving proper therapy.

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