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Review Article

Heart failure with preserved ejection fraction in the elderly: scope of the problem

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure (HF) in older adults, particularly women, and is increasing in prevalence as the population ages. With morbidity and mortality on par with HF with reduced ejection fraction, it remains a most challenging clinical syndrome for the practicing clinician and basic research scientist. Originally considered to be predominantly caused by diastolic dysfunction, more recent insights indicate that HFpEF in older persons is typified by a broad range of cardiac and non-cardiac abnormalities and reduced reserve capacity in multiple organ systems. The globally reduced reserve capacity is driven by: 1) inherent age-related changes; 2) multiple, concomitant co-morbidities; 3) HFpEF itself, which is likely a systemic disorder. These insights help explain why: 1) co-morbidities are among the strongest predictors of outcomes; 2) approximately 50% of clinical events in HFpEF patients are non-cardiovascular; 3) clinical drug trials in HFpEF have been negative on their primary outcomes. Embracing HFpEF as a true geriatric syndrome, with complex, multi-factorial pathophysiology and clinical heterogeneity could provide new mechanistic insights and opportunities for progress in management. This article is part of a Special Issue entitled CV Aging.

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1. Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is nearly exclusively found in older persons, particularly older women, in whom 90% of new HF cases are HFpEF [1]. The prevalence of HFpEF is rising, with morbidity, mortality, and healthcare costs now equal to HF with reduced ejection fraction (HFrEF) [2–5]. Outcomes following hospitalization for decompensated HFpEF are poor, with about 1/3 of patients rehospitalized or dead within 90 days of discharge [6]. Its pathophysiology is poorly understood, and no medication trials have had positive effect on their primary end-points. Consequently, there are no class A guideline recommendations for improving clinical outcomes in patients with HFpEF [7]. This syndrome has proven challenging partly due to its association with many common co-morbidities and marked heterogeneity in presentation. The co-morbidities including diabetes mellitus (DM), atherosclerosis, renal dysfunction, chronic obstructive lung disease(COPD), anemia, sarcopenia, obesity, etc., significantly influence cardiovascular structure and function and global organ system reserve as well as long-term prognosis.

In this review, we address translational and clinical research into HFpEF, providing an overview of HFpEF for both the clinical and basic research scientist, including epidemiology and pathophysiology. We discuss potential mechanisms involving the heart and other organs, including left ventricular systolic, diastolic and chronotropic reserve, stiffening of the ventricles and vasculature, low nitric oxide bioavailability and protein kinase G (PKG) activity, altered myocardial energetics, neurohormonal activation and autonomic imbalance, arterial vasodilatory dysfunction, and abnormal skeletal muscle mass, quality, composition, and function. A review of current and potential novel treatments is discussed in relation to evolving key concepts.

2. Definition of HFpEF

The controversy surrounding HFpEF has, in part, been attributable to varying definitions employed to define the syndrome. This syndrome was historically considered to be caused exclusively by left ventricular (LV) diastolic dysfunction. In 2000, the Framingham study suggested specific criteria for definite, probable, and possible diastolic HF [8]. All 3 categories required definitive evidence of HF and a normal LVEF. Objective evidence of diastolic dysfunction (ie, abnormal LV relaxation, filling, or distensibility indexes measured during cardiac catheterization) was recommended for the diagnosis of definite but not for the diagnosis of probable or possible diastolic HF [8]. This classification was criticized for a lack of sensitivity due to the requirement of determination of EF within 72 h of presentation and invasive demonstration of LV diastolic dysfunction—a situation which can be challenging to achieve clinically. Further, Gandhi and colleagues reported stable EF upon immediate echo assessment of acutely decompensated HFpEF patients, refuting the suggestion that transient systolic dysfunction or ischemia mediates symptoms [9]. In 2001, data from Zile et al., supported the idea that almost all patients with HFpEF have Doppler evidence of diastolic dysfunction making these parameters unnecessary because of lack of specificity and sensitivity for identifying HFpEF and they concluded that objective evidence of abnormal LV relaxation, filling, or distensibility is not necessary to make the diagnosis of diastolic HF [10]. The need for invasive demonstration of LV diastolic abnormalities was also questioned, because these were shown to be uniformly present in patients with clinical HF and a normal EF [11].

Importantly, most measures used to assess diastolic function (echocardiographic or radionuclide techniques or invasive measurements) do not assess the key passive component of diastole, have significant variability, and have considerable overlap with normal aging, hypertension, and other comorbidities common in HFpEF and thus lack specificity for HFpEF. Furthermore, using direct invasive measurements, Kawaguchi et al show that during exercise, patients with HFpEF were able to increase preload volume with little if any effect on the ventricular end-diastolic pressure-volume relation, despite a substantial prolongation of time constant of relaxation [12]. Such a finding is supported by data from multiple sources indicating that even in well-characterized, symptomatic HFpEF, many patients do not have echo-Doppler indexes of diastolic dysfunction that differ greatly from that expected based on age and comorbidities [13,14]. These findings suggested that abnormalities of intrinsic diastolic function may not always be present during or completely explain the occurrence of HFpEF [15].

In acknowledgement of these considerations, as well as data supporting a broader paradigm for HFpEF pathophysiology and outcomes, diagnostic criteria for HFpEF have evolved and the most recent U.S. guideline has not included the requirement for 'diastolic dysfunction' or any specific cardiac parameter, such as LV hypertrophy or left atrial (LA) dilation, significantly elevated B-type natriuretic peptide (BNP). Instead, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) HF management guideline takes a practical, phenomenological approach to HFpEF. It states that the diagnosis of HFpEF is based on: 1) typical symptoms and signs of HF; 2) normal or near normal LVEF; 3) no other obvious factors to account for the apparent HF symptoms, including significant valvular abnormalities [16]. In contrast, the older proposed European Society of Cardiology (ESC) recommendations suggested also requiring the presence of LV diastolic dysfunction and/or increased BNP for the diagnosis of HFpEF, along with symptoms and signs of HF and normal or mildly abnormal LV function [17]. However in support of the more recent 2013 ACC/AHA guideline, studies of patients with all the clinical hallmarks of HF and an EF > 50% showed that many patients have modest diastolic dysfunction under resting conditions [18,19]. Furthermore, similar changes can be seen in elderly patients with hypertensive heart disease with no clinical HF, and diastolic dysfunction in HFpEF patients may not be greater than age-matched sedentary controls and has not prevent a fruitful target for intervention [10,15,20–22]. Overall, these newer guidelines may facilitate progress in understanding the pathogenesis and optimal therapy of the large population of elderly patients in the community who have HF symptoms and preserved EF in that they do not assume a specific mechanism of their disorder, and thereby allow for a phenomenological, iterative approach based on actual observations in humans rather than theory. However, objective evidence of cardiac dysfunction including diastolic dysfunction, elevated natriuretic peptides, and structural evidence of cardiovascular abnormalities including LV hypertrophy

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