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Review

Heart failure with preserved ejection fraction: Refocusing on diastole

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ABSTRACT

Heart failure (HF) with preserved ejection fraction (HFpEF) is a clinical syndrome of exercise intolerance and/or congestion, in the presence of a left ventricular (LV) ejection fraction within the normal limits (i.e. LVEF > 50%). Determining the presence of impaired LV relaxation and/or filling (diastolic dysfunction) in HFpEF is needed to pragmatically to distinguish it from other cardiac and non-cardiac conditions where symptoms are not due to HF. There are multiple mechanisms for diastolic dysfunction ranging from structural abnormalities to functional derangements in HFpEF yet tailored therapies are lacking. Treatments proven effective in HF with systolic dysfunction have failed to show significant benefit in patients with HFpEF, which prognosis remains poor. This review will discuss the challenges inherent to the use of diagnostic criteria for HFpEF, differential diagnosis, prognostic evaluation, and treatment, highlighting the need for more research in this field.

1. Introduction

Despite clear improvements in the treatment of cardiovascular disease over the past several decades, the incidence and prevalence of heart failure (HF) have not decreased, survival has marginally improved, and morbidity remains unacceptably high [1,2]. One of the challenges and barriers in treating HF is the heterogeneity of the clinical syndrome. Heart failure is a syndrome of impaired cardiac function leading to symptoms of exercise intolerance and/or congestion, and is the final common pathway of abnormalities in the myocardium, coronary arteries, valvular structures and/or electrical impulse generation and conduction [3]. In nearly half of the patients with HF the syndrome is driven by impaired cardiac systolic function measured by reduced left ventricular ejection fraction (LVEF), systolic HF or HF with reduced EF (HFrEF) (Table 1). The remaining half of patients with preserved LVEF represents a heterogeneous group where multiple concomitant factors lead to HF. The abnormality most commonly seen in patients with preserved LVEF is an impaired diastolic function, which however is only present in approximately 70% of these patients. Concomitant abnormalities in the heart, vasculature, lung, and skeletal muscle are often present.

A recent consensus from the European Society of Cardiology [4] suggested refocusing on the impairment in diastolic function (LV relaxation and/or filling) as the *conditio sine qua non* for the definition of the syndrome of HF with preserved EF (HFpEF) (Fig. 1). While this provides a pragmatic opportunity for a defining description of the syndrome that is based not on a negative attribute (i.e. not having reduced EF) and allows to positively identify patients with HF excluding those with symptoms not due to HF, this definition also excludes a number of patients in whom other cardiac abnormalities cause HF symptoms despite apparently 'normal' systolic and diastolic functions.

This review will discuss the definition(s), clinical manifestation, proposed pathophysiology, diagnostic and therapeutic approaches, and prognosis of HFpEF in order to address what is known and what is not known about this complex clinical condition.

2. Methods

This review is based on an updated and comprehensive MEDLINE/PubMed search, updated on September 1, 2014.

3. Definition of HFpEF

The choice of selecting the term or characteristics to define the syndrome has been long-debated. While HFpEF has now become the preferred term, several different names have been used such as '*heart*

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Table 1
Differences and similarities between HFpEF and HFrEF.

Characteristics	HFpEF	HFrEF
Age (years)	40–50 and 70–80	50–70
Gender (prevalence)	Female	Male
Comorbidities (more frequent)	HTN, Afib, obesity	CAD
LV function and structure		
• Systolic function	Preserved	Reduced
• Volumes	Normal or reduced	Increased
• End-diastolic pressure	Increased	Increased
• Relaxation time	Increased	Increased
• Relative wall thickness	Increased	Decreased
• Hypertrophy	Concentric	Eccentric
Prognosis		
• 5-Year mortality	20–40%	30–50%
Survival benefit with treatment (*)		
• ACE-inhibitors (or ARB)	Not affected	Improved
• Beta-adrenergic blockers	Not tested in RCT	Improved
• Aldosterone antagonists	Not affected	Improved
• Hydralazine/isosorbide	Not tested in RCT	Improved
• Statins	Improved (+/−)	Not affected (+/−)
• CRT/AICD	Not tested in RCT	Improved
• MCS or heart transplant	Not tested in RCT	Improved

Abbreviations: ACE = angiotensin-converting enzyme; Afib = atrial fibrillation; AICD = automated implantable cardioverter-defibrillator; ARB = angiotensin receptor blocker; CAD = coronary artery disease; HTN = arterial hypertension; MCS = mechanical circulatory support; RCT = randomized controlled trials. (*) in selected patients.

failure with normal ejection fraction' or '*diastolic heart failure*'. The term '*diastolic heart failure*' refers to the common finding of one or more abnormalities in LV diastolic function or indirect evidence of diastolic dysfunction (i.e. left ventricular hypertrophy or left atrial enlargement) in these patients, which, according to the ESC consensus statement and practice guidelines [4,5], is now a mandatory requirement. Nevertheless, the current definition of HFpEF by the American Heart Association and American College of Cardiology [6] continues to rely on the negative connotation of *not having* a reduced LVEF rather than specifying one or more positive characteristics that define HFpEF, and it is thus at odds with the ESC consensus statement. Without the defining criteria of diastolic dysfunction the diagnosis of HFpEF would become mainly a diagnosis of exclusion of all other conditions that cause HF, primarily structural abnormalities

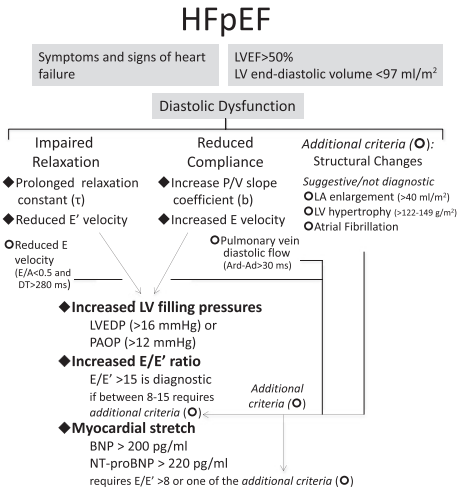

Fig. 1. Diagnostic criteria for HFpEF according to the European Society of Cardiology criteria. The diagnosis of HFpEF is based on the presence of symptoms and signs of heart failure, in the absence of left ventricular (LV) systolic dysfunction or dilatation, and also on the presence of diastolic dysfunction. The definition of diastolic dysfunction requires one major criterion (♦) or at least two additional criteria (**o**), one of which is an abnormal E/E′ ratio (>8). Abbreviations: BNP = brain natriuretic peptide; DT = deceleration time; HFpEF = heart failure with preserved EF; LA = left atrium; LV = left ventricular; LVEF = LV ejection fraction; LVEDP = LV end-diastolic pressure; NT = N-terminal; PAOP = pulmonary artery occluding pressure; P/V = pressure–volume.

that may lead to impaired LV filling such as valvular heart disease, restrictive myocardial disease, constrictive pericardial disease, pressure overload of the right ventricle with left-ward shift of the interventricular septum, or presence of intracardiac obstruction or shunting. Moreover, a long list of pulmonary, musculoskeletal, hematologic, and systemic diseases, that cause symptoms that are difficult to differentiate from HF, have to be excluded (as they would be managed in an altogether different fashion than patients with HFpEF are being managed).

Another challenge regarding the definition of HFpEF is the choice of the threshold used to define a preserved LVEF (>50%, >45% or >40%). The seminal clinical trials used different definitions [7]. The aforementioned consensus statement from the European Society of Cardiology suggests the use of a LVEF greater of equal to 50% [4]. It is, also, not clear how to categorize those patients who have an initial LVEF<40% and have an improvement in LVEF with therapy: HF with recovered EF [8]. These uncertainties in defining HFpEF have likely impacted numerous observational and interventional clinical trials in which the patient population displayed a wide variability of clinical characteristics across the different studies [7,9–13]. Following the attempt to standardize the diagnosis of HFpEF by the ESC [4], those criteria have been frequently cited and used for inclusion criteria in the more contemporary studies of HFpEF [11–13]. These criteria rely heavily on the concept of diastolic dysfunction of the LV, which is now considered the cornerstone of the diagnosis of HFpEF, at least in Europe [4,5]. The criteria include direct and indirect evidence of diastolic dysfunction and range from clinical, to structural (i.e. LV hypertrophy, left atrial enlargement), to functional (i.e. impaired relaxation), to biomarkers (i.e. elevated B-type natriuretic peptide [BNP]). Likely the greatest value of such criteria is their ability to comprehensively detect and gauge variable degrees, manifestations, and causes of impaired LV diastolic function. All of these manifestations, however, may not reflect the same mechanism of disease nor carry equal prognostic value (see subsequent section for further discussion). A number of patients will have symptoms of HF but not meet the criteria illustrated in Fig. 1, and many patients included in the seminal studies such as CHARM Preserved [9] and iPRESERVE [10] would have been excluded using the current criteria. Even in those trials, however, the presence of abnormal diastolic function (present in approximately 2/3 of patients) strongly predicted adverse outcome related to HF [14,15]. This finding supports the concept that the patients with diastolic dysfunction truly represent patients with HFpEF whereas the remaining patients may have had a milder form of cardiac dysfunction, possibly associated with comorbidities leading to symptoms that may have been confused with HF.

It still remains unclear how to define, and accordingly treat, the patients with symptoms consistent with HF but lacking the objective evidence of systolic or diastolic dysfunction. Moreover, the ESC criteria [4] do not consider those patients with "latent" diastolic dysfunction where the abnormalities become apparent only during physical exertion.

4. Clinical characteristics

While the actual signs and symptoms of HFpEF are very similar to those of HFrEF, there are many characteristics that are unique to HFpEF (Table 1). First and foremost, HFpEF is more prevalent in women and is more common with aging, with a peak prevalence in women at approximately 70 years of age [16,17], although recent studies have identified a high prevalence of HFpEF also in obese middle-aged women [18,19]. Large cohort studies and clinical interventional studies show that patients with HFpEF have more comorbidities than those with HFrEF and while they are less likely to have obstructive coronary artery disease, they are more likely to have arterial hypertension, obesity, and metabolic syndrome/diabetes [16–21].

Exertional dyspnea and exercise intolerance are the functional hallmarks of HF, irrespective of the underlying mechanism. The diagnosis of HFpEF may be delayed by the presence of comorbidities that present with similar exertional symptoms (i.e. chronic obstructive pulmonary