

Heart Failure with Mid-Range Ejection Fraction – a New Category of Heart Failure or Still a Gray Zone

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ABSTRACT

Heart failure with midrange ejection fraction (HFmrEF) is a new category of heart failure (HF), in-between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).

Previous studies were mainly conducted in HFrEF patients having a left ventricle ejection fraction (LVEF) lower than 35-40%. Later on, HFpEF captured the spot-light of the research field, and studies focused on patients with HF symptoms, but with a LVEF exceeding 50%.

Consequently, a gap of knowledge comprising the LVEF between 40 and 49% has arisen. Current studies focusing on patients with HFmrEF are arguing the same conclusions or even having contradictory findings.

HFmrEF has a prevalence of 10-20% of HF patients. HFmrEF has distinct, but intermediate clinical, structural and functional characteristics, as well as intermediate outcomes in comparison with HFrEF and HFpEF. However, there is still a large gap in evidence regarding detailed hemodynamic characteristics, long-term follow-up and optimal therapeutic options for these patients.

Extensive research was recommended in order to improve knowledge about this “gray area” of patients with HF. Therefore, we aimed to provide an over-view of the existing and lacking data regarding patients with HFmrEF.

Keywords: Heart failure, mid range ejection fraction

INTRODUCTION

HFmrEF encompasses all patients with a clear diagnosis of HF by clinical, biological and imagistic criteria that have a LVEF between 40% and 49%. This concept, though thought of many years ago, has first earned its official title in 2016, when the 2016 ESC Guidelines for the diagnosis and treatment of

acute and chronic heart failure revealed the new HF classification, based primarily on LVEF (1).

Four elements are simultaneously required for a positive diagnosis of HFmrEF: (i) symptoms with or without signs of HF, (ii) LVEF of 40-49%, (iii) elevated natriuretic peptides (BNP ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL), and (iiii) relevant structural heart disease: left ventricle hypertrophy (left ventricular mass index ≥ 115 g/m² for males and ≥ 95 g/m² for females) or left atrial en-

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largement (>34 mL/m²) or diastolic dysfunction ($E/e' \geq 13$ and a mean e' septal and lateral wall <9 cm/s) (1).

Previous ESC HF guidelines established two categories of HF: HFrEF, when the LVEF is below 50%, and HFpEF, when the LVEF exceeds 50% (2). However, many clinical trials that targeted the outcome of different therapeutic strategies in HFrEF usually included patients with a LVEF lower than 35-40%, and not all patients with LVEF lower than 50%, as some would expect in accordance with the definition (3-5). Therefore, a borderline area has arisen from patients that are neither well represented in clinical trials of HFrEF, nor have a normal LVEF that completely separates them from HFrEF. The 2012 ESC HF guideline mentioned the “gray area” of LVEF between 35-50%, due to scarce data on the prognostic of this type of patients, but still kept them included in the HFrEF category.

Consequently, the 2016 ESC HF guideline reconsidered the HF classification, and three types of HF were clearly defined: HFpEF (with a LVEF $\geq 50\%$), HFmrEF (with a LVEF 40–49%), and HFrEF (with a LVEF $<40\%$). The central element distinguishing the three types of HF is the LVEF. This has been over the years the main parameter used in clinical trials for cut-off value stratification, even though numerous limitations of the LVEF were found.

Until recently, the LVEF was mainly measured by two-dimensional echocardiography (2DE), using an assumption formula from the 2- and 4-chamber views of the LV (6). The method applies to only 2 sections of the LV (including the antero-septum, lateral, anterior and inferior LV walls), but completely ignores other LV walls (the posterior wall, from the 3-chamber view, as an example). The formula assumes a symmetric shape of the LV, and it might be inaccurate in remodeled or aneurismal LVs. Moreover, foreshortening often biases the 2-chamber view of the LV, if the user is not well trained in 2D echocardiography or in difficult chest walls.

New three-dimensional echocardiography (3DE) tools allowed a more accurate and reproducible assessment of the LVEF (7). 3DE enabled the measurements of the LVEF from the real end-diastolic and end-systolic volumes of the LV obtained from a full-volume of the LV, without geometric assumptions. LV volumes obtained with 3DE were more similar to the ones measured

with cardiac magnetic resonance than those obtained with 2DE (8).

Therefore, according to the 2015 *Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults*, the global systolic function of the LV should be routinely assessed by measuring the ejection fraction using either the 2D Simpson biplane method or 3D echocardiographic methods. A LVEF $<52\%$ for men and $<54\%$ for women is suggestive of abnormal LV systolic function, a normal LVEF being defined between 53% and 73%. Mildly abnormal LVEF in men was defined between 41-51% and in women between 41-53%, while moderately and severely abnormal LVEF was lower than 40% for both genders (9). These values are similar with the ESC HF classification, suggesting that HFmrEF is actually a state of mildly LV systolic dysfunction.

Our manuscript aims to provide a short overview on HFmrEF in terms of prevalence and etiology, echocardiographic assessment, prognostic profile, and therapeutic options and to set some future research directions for patients with HFmrEF.

Proposed prevalence and etiology of HFmrEF

The prevalence of HFmrEF is estimated to be in the range of 10-20% of all HF patients (10, 11). HFmrEF seems to have intermediate clinical characteristics and tends to have less clinical manifestations of HF when compared with HFrEF and HFpEF (12).

The background etiology is similar among the different types of HF. Patients with HFmrEF are more likely to have hypertension than patients with HFrEF and more likely to have ischemic heart disease and diabetes than patients with HFpEF. It has been hypothesized that HFmrEF is actually a subset of HFpEF that acquires coronary artery disease and is transitioning to HFrEF (10).

A recently published study (13) showed that patients with HFmrEF are older (median age, 77 years) and more likely female (49%) when compared with HFrEF (median age, 72 years; 37% women), thus resembling HFpEF (median age, 78 years; 65% women). Patients with HFmrEF also had a high comorbidity burden (diabetes in 50%, atrial fibrillation in 42%, chronic obstructive pulmonary disease in 36%, anemia in 27%, and renal insufficiency in 26%), which was high-

er than in HF_rEF, and similar to HF_pEF. Conversely, there was a high association with ischemic heart disease in patients with HF_{mr}EF, similar to HF_rEF.

Echocardiographic profile of HF_{mr}EF

In 2009, Kun-Lun He studied the ventricular structure and function of Chinese patients with HF and different subsets of LVEF (>55% versus 40-55% versus <40%) by using noninvasive pressure-volume analysis and showed pathophysiological differences between the three groups (14).

Patients with HF and a LVEF of 40-55% had increased LV diastolic stiffness, similar to those with LVEF \geq 55%, but had significant abnormalities of ventricular size and function that were more similar to patients with LVEF <40%. Despite a mildly reduced LVEF, the ventricles of these patients were markedly enlarged by eccentric remodeling, and had a significant decrease in chamber contractility (14). Diastolic dysfunction and left atrial enlargement were present in all patients with HF, with the most severe cases of diastolic dysfunction in the LVEF<40% group (14). This is consistent with the observation that HF_{mr}EF may represent an early stage of HF_rEF.

Prognostic profile of HF_{mr}EF

The outcome of patients with HF with a wide range of LVEF was studied in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program. Patients with lower LVEF tended to have higher baseline New York Heart Association class. LVEF was the best predictor of fatal or non-fatal cardiovascular events, with the highest rates of mortality and re-hospitalization in the HF_rEF subgroup. The discriminatory effect of the LVEF for prediction of adverse outcomes was, however, limited above a LVEF of 45%. Patients with an LVEF over 45% had a much lower risk of adverse cardiovascular outcomes than those with reduced systolic function (11). This suggests that, in these patients, research should be conducted for the evaluation of additional factors to predict outcome.

In the Cardiovascular Health Study the mortality rate of HF_{mr}EF was intermediate between that of HF_rEF and HF_pEF (115 deaths *per* 1000 person-years in HF_{mr}EF, compared with 154 and 87 deaths *per* 1000 person-years in HF_rEF and

HF_pEF, respectively, and 25 deaths *per* 1000 person-years in controls without HF) (15).

Among patients with HF_{mr}EF, recovered systolic function (HF that was previously HF_rEF but was partially recovered and reclassified as HF_{mr}EF) was a marker of a more favorable prognosis despite similar clinical characteristics and cardiopulmonary response to exercise. It was also showed that most of the patients with HF_{mr}EF remained with a LVEF between 40% and 55% after a median of 2.8 years of follow-up, suggesting that HF_{mr}EF is not necessarily a transition step of the progression from normal LVEF to HF_rEF or vice versa (12).

Additionally, the natural history of the LVEF in patients with HF that were subdivided in either HF_pEF or HF_rEF was studied in a cohort of 2413 patients, with a longer follow-up time (mean of 4.4 years) (16). This study showed that LVEF is, in some patients, a dynamic factor related to sex, coexisting conditions, and drug therapy. Women, patients who were adherent to β -blockers or had hypertension were more likely to transition from HF_rEF to HF_pEF. This was in contrast with patients who had a previous myocardial infarction who were more likely to transition from HF_pEF to HF_rEF. This study did not use the current ESC HF classification of reduced, midrange and preserved LVEF but it's safe to assume that the transition from HF_{mr}EF to either HF_rEF or HF_pEF is to be expected during sufficiently long follow-up interval.

Therapeutic implications

The vast majority of clinical trials that were conducted in patients with HF_rEF (LVEF<40%) provided solid evidence for the use of different therapeutic pharmacological agents and devices aiming a prognostic improvement of these patients. Since the concept of HF_pEF (LVEF>50%) was accepted as a distinct form of HF, at first termed "diastolic HF", clinical trials were conducted in these patients with the same hope of improving their prognostic. Unfortunately, the results were not as expected, and there is still no evidence-based therapy that impacts the prognosis of this category of patients.

Patients with LVEF between 40 and 50% were sometimes included in HF_pEF trials, when the cut-off point for inclusion was LVEF >45%, but they were never studied as a separate entity (17).

Therefore, specific therapeutic evidence for this group of patients is still lacking.

Because patients with HFmrEF have generally been included in trials of HFpEF, rather than in HFrEF, the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure recommended that they should be treated the same as patients with HFpEF, that is until new clear evidence demonstrating a prognostic difference between these two categories arises.

The recommendation for treatment of these patients focuses on co-morbidity control. Either cardiovascular diseases (atrial fibrillation, arterial hypertension, coronary artery disease, pulmonary hypertension) or non-cardiovascular diseases (diabetes, chronic kidney disease (CKD), anemia, iron deficiency, COPD and obesity) should be screened for and managed optimally. The aim should be symptom relief and/or prognostic improvement related to the specific co-morbidity (1).

Moreover, precipitating factors should be prevented or rapidly managed. In the Get With The Guidelines – Heart Failure (GWTG-HF) registry of patients hospitalized for HF the most common precipitants for hospitalization were pneumonia/respiratory process (28%), arrhythmia (22%), medication noncompliance (16%), worsening renal failure (15%), and uncontrolled hypertension (15%), regardless of the baseline EF group (18).

Diuretics should be used only if signs or symptoms of congestion are present; they represent the hallmark of symptom relief therapy, but have no influence on mortality. There is no specific recommendation for diuretic usage depending on LVEF, but rather a clinical judgement, depending on symptoms.

Because HFmrEF patients often have co-morbidities such as hypertension, atrial fibrillation or ischemic heart disease, they often receive beta blockers and ACE inhibitors or ARBs, and rarely MRAs, in different combinations. These are the drugs known to have prognostic impact on HFrEF, and hope in the same direction applies when

treating patients with HFmrEF. However, future prognostic studies on this sub-set of patients are needed. □

CONCLUSION

Exceeding efforts have been made to develop elaborate algorithms for diagnostic, classification and management of patients with HF. Etiology is not the only element that subdivides the heart failure syndrome, but also the type and the degree of left ventricular dysfunction, and the pathophysiological characteristics.

Although many would argue that LVEF is not the optimal parameter for the evaluation of the left ventricle systolic function, it has been widely used in the guidelines and in clinical trials as the central parameter for evaluating HF patients.

Based on the division of HF patients in accordance with their LVEF, a borderline area has progressively emerged - heart failure with midrange ejection fraction (LVEF between 40-49%), due to the lack of prognostic and descriptive studies on this subset of patients. The knowledge accumulated so far regarding pathophysiology, natural history, and prognosis of patients with HFmrEF is limited and sometimes contradictory and substantial heterogeneity may exist within patients with HFmrEF. This highlights the necessity for further research of the characteristics and therapeutic options for these patients.

LVEF measured by 2DE has not yet been rendered absolute for the classification of HF. Other diagnostic methods should be developed for the future, with better accuracy and reproducibility than the LVEF, in order to ensure a correct stratification of patients with HF and a correct means of follow-up. No studies using advanced echocardiographic methods have been conducted in patients with HFmrEF and they could be an alternative for identifying new prognostic parameters. □

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