Heart Metab. (2017) 74:8-12

Heart failure with mid-range EF (HFmrEF): a mildly reduced EF does not imply a mild disease

Carsten Tschöpe,[1,2,3] MD, PhD; Burkert Pieske,[1,2,4,5] MD, PhD
[1]Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Berlin, Germany
[2]German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany
[3]Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany
[4]Department of Cardiology, German Heart Center Berlin (DHZB), Berlin, Germany
[5]Berlin Institute of Health (BIH)

Correspondence: Prof Dr med Carsten Tschöpe, Medizinische Klinik mit Schwerpunkt Kardiologie, Charité – Universitätsmedizin Berlin, Campus Virchow Klinikum, Augustenburgerplatz 1, D-13353 Berlin, Germany
E-mail: Carsten.tschoepe@charite.de

Abstract

Chronic heart failure (HF) patients stratified by categories of left ventricular ejection fraction (EF) represent different phenotypes in terms of demographics, clinical presentation, etiology, mechanical and electrical remodeling, and pharmacotherapies. Until recently, there were two HF categories, distinguished on the basis of EF: HF with reduced EF (HFrEF; EF<40%) and HF with preserved EF (HFpEF; EF>50%). A "gray zone" remained for HF with EF values from 40% to 49%, and in clinical trials, patients within this zone were often assigned to one or the other defined groups. The new European Society of Cardiology Heart Failure 2016 guidelines have better defined this subentity as a separate group—HF with mid-range EF (HFmrEF), aiming to stimulate research into the underlying characteristics, pathophysiology, and, ultimately, treatment of HFmrEF. Some studies have already suggested that HFmrEF shows intermediate clinical characteristics falling between HFrEF and HFpEF. HFmrEF patients were often found to be younger, more likely to be male, and to have less frequent hypertension than HFpEF patients. Etiologically, HFmrEF resembles HFrEF more than HFpEF, with a higher prevalence of coronary artery disease and previous myocardial infarction or myocarditis, suggesting specific treatment strategies. HFmrEF can dynamically transition into HFpEF (recovery from disease) or HFrEF (progression of the disease); thus, subgroups of HFmrEF patients may represent a temporary state rather than an independent entity of HF. In conclusion, HF is a heterogeneous syndrome not sufficiently characterized by the measurement of EF alone. A deeper understanding of the underlying etiology and pathophysiological mechanisms, as well as the patient´s position on the disease trajectory, is mandatory to establish more precision-medicine–based therapeutic approaches. ■ *Heart Metab*. 2017;74:8-12

Keywords: diagnostic; HFmrEF; pathophysiology; treatment

Introduction

For heart failure (HF) patients with reduced ejection fraction (HFrEF; ie, HF with a left ventricular ejection fraction [LVEF] <40%), the accumulated therapeutic evidence has given rise to effective pharmacological and device therapies that have led to impressive improvements in survival.[1] HF with preserved EF (HFpEF), defined in current guidelines as HF with an EF that meets or exceeds

Abbreviations

CHARM-Preserved: Candesartan in Heart failure—Assessment of moRtality and Morbidity – Preserved [trial]; **EF:** ejection fraction; **ESC:** European Society of Cardiology; **HF:** heart failure; **HFmrEF:** heart failure with mid-range ejection fraction; **HFpEF:** heart failure with preserved ejection fraction; **HFrEF:** heart failure with reduced ejection fraction; **LVEF:** left ventricular ejection fraction; **NT-proBNP:** N-terminal pro–B-type natriuretic peptide; **NYHA:** New York Heart Association; **TOPCAT:** Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist [trial]

the cut-off value of ≥50%,[2] shows a similar reduced outcome; however, its management remains challenging, indicating that successful treatment targets differ between HFpEF and HFrEF.[3] Between those defined categories of HF, there was an undefined gap for EF values falling within a middle range of 40% to 49%; in the American College of Cardiology/American Heart Association guidelines from 2013, HF with EF values falling within this range was referred to as an "intermediate group" but for management was treated according to what was known about HFpEF.[4] Today, the recent 2016 European Society of Cardiology (ESC) guidelines refer to HF with EF values of 40% to 49% as a "gray area" to be regarded as mild systolic dysfunction but with features of diastolic dysfunction and needing further investigation; it reclassified this subentity as HF with mid-range EF (HFmrEF).[1] Previously, HF clinical trials systematically either excluded such patients or assigned them to either the HFrEF or HFpEF group. Indeed, HFmrEF may share characteristics of both HFrEF and HFpEF[5-7] to different extents; consequently, clinically, it is not clear which HF group individual HFmrEF patients belong to, what their prognosis will be, and which treatment options would be most relevant.[8,9] Therefore, by identifying HFmrEF as a separate entity, the European Society of Cardiology (ESC) guidelines aim to stimulate research into its underlying characteristics, pathophysiology, and treatment. The main question is whether differentiation of patients with HF on the basis of LVEF can effectively separate them by underlying etiologies, demographics, and comorbidities with the ultimate aim of identifying a common response to therapies.

Prevalence and clinical characteristics of heart failure with mid-range EF

A number of data are available regarding the prevalence of HFmrEF. Although designs and settings differ between studies and registries, 14% to 24% of HF patients are characterized as having HFmrEF, as observed in Western countries, as well as in Asian trials. Thus, almost one-fifth, a substantial proportion of patients with HF, have a moderately reduced LVEF that falls between the commonly used cut offs for HFrEF and HFpEF.[5-7,10-15]

Clinical characteristics of heart failure with mid-range EF

Clinical presentation, burden of comorbidities, and quality of life were often shown to be similar for HFrEF, HFmrEF, and HFpEF.[5-7,15] HFmrEF populations share some characteristics with HFpEF and some with HFrEF, but have also been found to have intermediate characteristics. Patients with HFmrEF are usually younger and more likely to be male than those with HFpEF. The HFmrEF group resembles the HFrEF group with regard to some features, including age and gender, but usually shows less left ventricular and atrial dilation. Several cardiovascular risk factors are shared among HFmrEF, HFrEF, and HFpEF, but patients with HFmrEF are more likely to have hypertension and diabetes than those with HFrEF. Most importantly, HFmrEF more closely resembles HFrEF with regard to both a higher prevalence of coronary artery disease and a greater risk of new cardiac ischemic heart disease events.[6] A recent study from Sweden[7] found that the prevalence of ischemic heart disease is similar between HFmrEF and HFrEF and that both are higher than in HFpEF (61%, 69%, and 52.4%, respectively). Among ischemic heart disease patients, previous myocardial infarction was more common in HFmrEF and in HFrEF than in HFpEF (68%, 71%, and 56%, respectively), and, consequently, patients were more often revascularized. Although ischemic heart disease is a significant prognostic factor across all HF types, it is important that coronary artery disease was found to be the principal primary cause of HFrEF and HFmrEF, whereas hypertensive heart disease was the principal etiology underlying HFpEF.[7]

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Predictors and prognosis of heart failure with mid-range EF

The prognosis of HF is poor in general. However, data for the prognoses for the three HF forms differ. Some registries describing outcome in HFmrEF show that all-cause hospitalization-free survival, overall survival, and HF hospitalization-free survival is similar to that found in HFrEF and HFpEF without significant differences in outcome.[5] However, others found that the HFmrEF mortality rate is intermediate, falling between the rates for the other two HF groups, with 1-year mortality rates being 8.8%, 7.6%, and 6.3% for HFrEF, HFmrEF, and HFpEF, respectively.[16] Age, New York Heart Association (NYHA) class III/IV status, and chronic kidney disease predicted mortality across all LVEF groups.[17] Low systolic blood pressure and high heart rate are predictors for mortality in HFrEF and HFmrEF. Although atrial fibrillation was found to be more common with increasing EF, it was associated with a similar increased risk of death, hospitalization rate, and stroke in all HF groups. However, HFmrEF resembles HFrEF rather than HFpEF with respect to ischemic heart disease as underlying cause, and HFmrEF was shown to be intermediate with regard to risk of new ischemic events.[6,7] Established ischemic heart disease has an adverse impact on a majority of outcomes in all EF categories, but this is most prominent for new ischemic heart disease events in HFmrEF and in HFrEF. This is clinically relevant and calls for a diagnostic search for an ischemic etiology in patients with HF and EF values under 50%.

Heart failure with mid-range EF—a unique entity or a transitional state of heart failure?

Although the clinical guidelines define HFmrEF as a gray zone between HFpEF and HFrEF, several discussions have arisen with respect to the role of the dynamic transition of patients toward HFrEF and HFpEF, calling into question the classification of HFmrEF as a separate entity. Registries and trials have demonstrated that transitions from HFrEF to HFpEF, as well as from HFpEF to HFrEF, are not rare. A crossing of the 50% threshold was found in about 38% of patients, either from HFrEF to HFpEF or from HFpEF to HFrEF, in the Olmsted County, Minnesota cohort; thus, they also passed through the HFmrEF zone.[9,18] Studies primarily investigating HFmrEF also found that HFmrEF patients dynamically transitioned to other categories, supporting the concept that at least some patients with HFmrEF belong to a dynamic stage between HFpEF (recovery from disease) and HFrEF (progression of the disease), indicating that the underlying pathophysiology may differ within the HFmrEF population.[6] HFmrEF is associated with a worse prognosis when transitioned to HFrEF. A number of different processes—including worsening or improving coronary heart disease, healing after myocardial infarction, cardiomyopathy, and myocarditis—can cause transition in all HF groups,[19-22] suggesting specific diagnostic approaches and treatments. However, more than 50% of HFrEF and HFpEF patients stay within their category for at least 3 years, indicating that these categories constitute separate entities.[6] The dynamic nature of this differentiation still needs further investigation in HFmrEF.

Treatment strategies for heart failure with mid-range EF

The overall finding that coronary heart disease, with a prevalence of 60%, is the most important driver in HFmrEF suggests, at least for this subgroup of patients, specific treatment strategies. Several registries and a recent individual patient-level analysis of double-blind randomized β-blocker trials have shown

	HFrEF	HFmrEF	HFpEF
ACE inhibitor	+	NA	-
ARB	+	(+)	-
BB	+	(+)	-
Ivabradine	+	NA	-
MRA	+	(+)	-
Digitalis	+	NA	-
ARNi	+	NA	NA
Diuretics	+c	+c	+c

Table I *EF-dependent pharmacological treatment responses. Data from registries or subgroup analysis show that treatments able to improve clinical outcome in HFrEF seem to also be beneficial in HFmrEF, but not in HFpEF.*
Abbreviations: *ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNi, angiotensin-receptor neprilysin inhibitor; BB, β-blocker; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist. +, positive results for mortality and/or morbidity in prospective randomized controlled trials. (+), positive results from registries, subgroup analysis, or retrospective analysis. No data from randomized controlled trials available. -, negative results for mortality and/or morbidity in prospective randomized controlled trials. NA, not analyzed/data not available. +c, recommended to relieve symptoms and signs of congestion.*

that the impact of cardiovascular medications, including the use of β-blockers, in HFmrEF is similar to that in HFrEF, but not in HFpEF (*Table I*).[6,23] These findings are of clinical importance because there has been no evidence to guide HFmrEF management, and the ESC guidelines recommend therapies for HFmrEF patients on the basis of evidence for HFpEF rather than that for HFrEF. The effectiveness of classical HF drugs, including renin-angiotensin-aldosterone antagonists and β-blockers, on reverse remodeling has not been studied specifically in HFmrEF. It was shown that a decrease in N-terminal pro–B-type natriuretic peptide (NT-proBNP) was associated with an improved prognosis in HFmrEF.[24] However, as summarized by Lam and Solomon,[9] subgroup analyses from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist)[25] and CHARM-Preserved studies (Candesartan in Heart failure—Assessment of moRtality and Morbidity – Preserved)[11,26] have shown that HFmrEF patients had a benefit in prognosis similar to those with HFrEF with the use of spironolactone or candesartan, respectively. These findings support the hypothesis that treatment should be initiated according to the underlying etiology rather than the presenting LVEF.

Conclusion

One-fifth of HF patients belong to the HFmrEF group. A "mildly reduced EF" does not imply a "mild disease": (i) clinical characteristics and prognosis of HFmrEF are intermediate between HFpEF and HFrEF; (ii) there are important LVEF transitions in HFmrEF toward HFrEF and HFpEF; (iii) HFmrEF is associated with worse prognosis when transitioned to HFrEF; and (iv) the prognostic impact of cardiovascular medications in HFmrEF resembles that in HFrEF.[5-7,15,16]

Although guidelines have reclassified HF into at least three different groups, we should not forget that HF represents a heterogeneous syndrome, rather than a specific disorder. As discussed for HFpEF, it is also becoming more and more evident that in HFmrEF, a solely EF-based HF classification is probably not going to provide a sufficiently robust foundation on which to develop differential diagnoses and treatments.[27,28] A deeper understanding of the underlying mechanisms is warranted. The establishment of a more precision-medicine–based approach, eg, the so-called phenomapping approach,[29] combining of clinical profiles, new (dynamic) imaging investigations, biomarkers, and liquid biopsies may allow an improved classification of the individual HF patient in the future. The burden of ischemic heart disease in HFmrEF has an important clinical impact and should already be considered in our daily clinical diagnostic and treatment approaches. ■

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