Review article

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MID-RANGE HEART FAILURE: A NEW KID ON THE BLOCK?

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Heart failure may be defined as a clinical syndrome with a great range of left ventricle abnormalities, in its function and/or its structure. In 2016, with reference to the ejection fraction, the European Society of Cardiology guidelines, for the first time, introduced a separate clinical entity, called heart failure with mid-range ejection fraction (HFmrEF). The introduction of the mid-range heart failure into the clinical practice and its involvement into the current ESC guidelines led to the inclusion of these patients into great clinical trials as a separate cohort of patients. The biomarker panel, the exact pathophysiological mechanism and the most effective therapy approach are yet to be determined and most probably depend on the underlying etiology of the heart failure. Identification of the proper pathophysiological mechanism of mid-range heart failure will probably answer the current question about whether this type of heart failure is a transitional form between reduced and preserved ejection fraction or represents a distinct and a brand new clinical entity.

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Introduction

Heart failure (HF) may be defined as a clinical syndrome with a great range of left ventricle abnormalities, with regard to its function and/or its structure. However, the dimensions of the left ventricle (LV) may vary, from the normal size, presented with the preserved ejection fraction (EF), up to significant LV chamber dilatation, presented with the reduced EF (1). Ever since it was introduced into the clinical practice, left ventricular EF has been considered an important clinical parameter with respect to the classification of heart failure patients, regarding their demographics, response to therapies and general outcomes (2).

According to the measuring EF, current American heart failure guidelines divide patients into two main cohorts: heart failure patients with reduced ejection fraction - (EF < 40%) and those with preserved EF - (EF > 50%) (3). However, this kind of patient division poses a very important question how to define and how to categorize patients with EF in between (4). This so-alled grey area, or borderline ejection fraction, involves patients with ejection fraction that ranges from 40%-49% and may be considered pathophysiologically, biochemically and clinically as a completely distinct group of patients. At the beginning, these borderline patients were classified as heart failure with preserved ejection fraction (HFpEF) patients who had isolated diastolic dysfunction, with the declined LVEF secondary to the systolic dysfunction development (5). However, the knowledge that heart failure with reduced ejection fraction (HFrEF) patients may recover after medical or device therapy (6) implies that these patients in the gray zone may represent a separate and heterogeneous group of patients, sharing similar pathophysiological and biochemical features. Understanding that the prevalence of these borderline patients is increasing, with no current guidelines referring to this particular group, the European Society of Cardiology (ESC) recognized the need to create a new subgroup of patients with heart failure (7). Therefore, the 2016 ESC HF guidelines created a separate clinical entity for patients who were previously in the borderline zone, called heart failure with mid-range ejection fraction (HFmrEF).

This new division will raise the opportunity for the research to be conducted, aiming to better understand their underlying pathophysiology, possible biomarkers and management strategies (8).

Epidemiological consideration

There is not much data regarding the exact prevalence of HFmrEF, since most of the trials are stratifying patients into EF below or above 50% (4). Some of the studies reported that heart failure with mid-range EF constitutes at least 10%-20% of all heart failure patients (4) and that it may be more prevalent in less selective cohorts. The others (9-11) reported that their portion stands between 13% and 24%, implying that in United States approximately 1.6 million people have heart failure with EF between 40% and 50%. Nevertheless, many researchers agreed that patients with HFmrEF may make up one-quarter of all patients with HF (12-15) and about 10% of newly diagnosed heart failure patients (12). However, after the analysis of the trends, the portion of HFmrEF was reported to be pretty steady, remaining between 13% and 15%, while the portion of HFrEF was decreasing (from 52% to 47%) and HFpEF was increasing (33% to 39%) (16). Similarly, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study reported that 17% of included patients had EF between 43%-52% (17), the same percentage seen in Cardiovascular Heart Study (18) and Chinese Study (19). Given that 10%-20% of any heart failure cohort represents patients with mid-range EF, this group should not be easily neglected.

Pathophysiological and biochemical consideration

The current knowledge on the exact pathophysiological mechanism of the HFmrEF is very limited. Patients' signs and symptoms may vary, from the ones seen in HFrEF to those presented in patients with preserved EF (4, 8). However, it is most likely that the major underlying feature is ischemia, presented in more than 40% of HFmrEF (9, 20). This high percentage is more similar to those with reduced EF and much higher compared to HFpEF. Ischemia was the most probable cause, twice as likely, for HF admission in HFmrEF and HFrEF than in HFpEF (9), as well as new and prior ischemic events (21). Pathophysiologically speaking, it may be that patients with mid-range HF represent a subgroup of patients with preserved EF who have a coronary artery disease and are therefore in an early stage of HF with reduced EF. Thus, the pool of potential HFmrEF patients may consist of all who had limited or re-vascularized myocardial infarction, cardiac remodeling, myocarditis or cardiomyopathy, partially recovered or in the early stages (4).

The assessment of functional capacity, measured on CPET by peak VO2 and Ve/VCO2, turned out to be similar in HFmrEF and HFpEF and is much better compared to HFrEF (22). This was the first study that documented the heterogeneity of patients with mid-range heart failure, coming to the conclusion that the patients who recovered from HFrEF had a more favorable phenotype.

If we consider mid-range heart failure as an overlapping phenotype of systolic and diastolic dysfunction (23), it may be hypothesized that generalized endothelial dysfunction represents the base for abnormal diastolic properties of the heart (24), while initial cardiac disease is responsible for impaired systolic yet diastolic properties of the heart (25). It was proposed that comorbidities may be a key factor accelerating general inflammation that then leads to diastolic dysfunction of the heart. However, systemic inflammation involves microvascular endothelial dysfunction, therefore myocyte hypertrophy, increasing resting tension and fibrosis (26). Accordingly, endothelial dysfunction and inflammation may have a crucial role in the pathogenesis of HFmrEF, so their targeting may be beneficial for the general outcome.

There is not much evidence about biomarker profiling in HFmrEF. By measuring different biomarkers, according to the known pathophysiology of heart failure (myocardial stretch, inflammation or oxidative stress), it was demonstrated that patients with HFmrEF had an intermediate biomarker profile interacting between cardiac stretch and inflammation (27). Furthermore, biomarkers related to inflammation and cardiac remodeling had predictive value for HFmrEF and HFpEF, but not for HFrEF. However, natriuretic peptides, cystatin C and high sensitivity troponin were all good predictors for HFmrEF among the patients who were followed for a median of 12 years (28). Natriuretic peptides were stronger predictors of HFrEF compared to HFmrEF and did not differ in their association with incident HFmrEF and HFpEF. Moreover, lower levels of NT-proBNP during the monitoring of patients with HFmrEF were positively associated with reduced risk of HF hospitalization or death of any cause (29).

Many different pathophysiological mechanisms may account for the development of the HFmrEF, suggesting that this type of heart failure is very diverse and that the underlying etiology may be crucial for the future outcome.

Clinical consideration and risk factors

European Society of Cardiology guidelines define this group as patients with EF between 40% and 49%, positive natriuretic peptides levels and structural heart disease or diastolic dysfunction (7). According to the literature, their demographic characteristics stand in between those with HFrEF and HFpEF, but are more similar to HFpEF. Furthermore, mid-range heart failure patients are more likely to be females, having a hypertensive disease or a history of atrial flutter/fibrillation (13, 30-32). However, some researchers confirmed that HFmrEF was more prevalent in males and younger patients compared to those with HFpEF (33). The likeliness of having a coronary artery disease was documented to be much higher compared to those with preserved ejection fraction (34). Mid-range heart failure patients also had a greater risk of a new ischemic heart disease

(34). Nevertheless, prior myocardial infarc-tion and revascularization were more likely to be present in patients with HFmrEF and HFrEF than in those with preserved EF (21,35). The atrial fibrillation prevalence seen in HFmrEF (60%) was estimated to be somewhere between HFpEF (65%) and HFrEF (53%) (36), while dilatation of both left ventricle and atrium was significantly lower in patients with mid-range EF compared to those with reduced EF (12). After comparison of HFmrEF patients with atrial fibrillation (AF) and those who had sinus rhythm, it was noted that those with AF were older, more hypertensive, had different cerebrovascular events or longer history of heart failure, but the prevalence of ischemic heart disease was lower (36). The analysis of risk factors for hospitalization in HF patients revealed that HFmrEF stood in between HFrEF and HFpEF, and the most significant factors were: medication incompliance, lung infections, arrhythmias and myocardial ischemia (9, 21). The assessment of comorbidities demonstrated that renal disease, diabetes mellitus, hypertension and anemia had similar prevalence in HFmrEF and HFpEF, which was higher than in those with reduced EF (33).

The usage of beta blockers has been observed in a few studies and was similar in all three groups of heart failure patients. It should be noted that those with reduced EF were using more digoxin and agents that block renin–angiotensin–aldosterone system, while calcum-chanel blockers were more used as therapy in patients with preserved EF (11, 37, 38).

Outcome consideration

However, studies have shown that the outcomes for HFmrEF were different when compared to those with reduced or preserved EF. Cardiovascular Health Study (18) demonstrated that the mortality rate for HFmrEF was between those with reduced and preserved EF and that the all-cause mortality rate in HFmrEF was higher compared to the control group. It should also be noted that an inverse relationship between EF and risk of events was documented, es-pecially when EF was between 40% and 45% (17). Therefore, in patients with EF below 45% the hazard ratio for all-cause mortality was by 39% higher for every 10% reduction of the ejection fraction (17). However, when ejection fraction over 45% was as-sessed, all-cause mortality and all respective elements of cardiovascular events were steady (17). These facts may lead to the conclusion that when analyzing the outcomes, the stable form of chronic HFmrEF corresponds to HFpEF. Still, in terms of outcomes, these findings cannot be applied in acute heart failure hospitalization nor the therapies that should be used (4).

The Acute Heart Failure Global Registry of Standard Treatment (ALARM-HF) demonstrated that HFmrEF patients had hazard ratio of all-cause in-hospital mortality or 30 days mortality lower than that of HFrEF, but close to that of HFpEF (39). The Get With The Guidelines-HF (GWTG-HF) Registry documented similar five-year mortality in all patients with HF (37), whereas HFmrEF had a statistically significant re-admission rate compared to the other groups of heart failure. Furthermore, in the Rica registry, one-year mortality was highest for HFrEF, while it was similar for HFmrEF and HFpEF with no differences in the 30-day or one-year re-admission rate (40). Network for the Study of Heart Failure (REDINSCOR I) and the Muerte Súbita en Insuficiencia Cardíaca (MUSIC) (41) assessed all-cause mortality during the 41-month follow-up and found out that it was higher for HFrEF than for HFmrEF and HFpEF, where the rate was very similar. However, the likeliness of cardiovascular death or sudden cardiac death was higher for patients with HFmrEF compared to HFpEF. In the other, similarly designed study, REDINSCOR II registry, in over one-year prospective follow-up no statistical significance in all-cause mortality, cause of death or HF re-admission was demonstrated in the analyzed groups (42). The most frequent cause of death among all the groups was refractory HF. All-cause mortality after 30 days, one-year and three-year follow-up in all three groups was assessed in the Swedish Heart Failure Registry (14) with a statistically higher rate in favor of HFrEF compared to HFpEF and HFmrEF, where it was similar and without significance. However, the existence of coronary artery disease raised the three-year mortality rate in HFmrEF compared to HFpEF. This study also confirmed that chronic kidney disease was a risk factor for mortality of patients with mid-range heart failure and HFrEF, but not in HFpEF (14). Heart failure with mid-range EF, chronic obstructive pulmonary disease and having an age over 85 years all positively correlated with higher mortality in the first year after hospital discharge, compared to the other groups of heart failure (12, 21). The ESC Heart Failure Long-Term Registry (12) observed a one-year follow-up in ambulatory patients with heart failure and demonstrated that mortality rate of HFmrEF was intermediate between HFrEF and HFpEF, but with no statistical significance. Non-cardiovascular mortality also did not differ between evaluated groups. However, the proportion of patients who underwent hospitalization was higher in the group with reduced EF compared to HFmrEF or HFpEF.

The post hoc analysis in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) (17) documented that the primary end point of the study (mortality due to cardiovascular death) was reduced, but only in patients with preserved ejection fraction who had EF 45%-49%.

The Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study (10) assessed patients with mid-range heart failure according to whether they improved or deteriorated from HFrEF (16%) or HFpEF (44%) during one year. The mortality rate of patients with mid-range heart failure was similar to those with HFpEF, but it significantly increased if they transitioned to HFrEF. Similar results were documented at Washington University Heart Failure Registry (1) where 73% of patients improved their EF from below 40%; 17%

deteriorated from EF that was over 50%, while 10% kept their EF between 40%-50%, remaining within HFmrEF. Accordingly, patients with improved HFmrEF had statistically significant cardiovascular clinical outcomes compared to those who deteriorated or those who remained mid-range (1). The most recent data from the CHARM study mostly confirmed the previous findings. That post hoc analysis confirmed that the incidence rates for different cardiovascular events, including cardiovascular death and all-cause death were both similar and lower in patients with HFmrEF and HFpEF, after comparison with HFrEF, indicating that HFmrEF may be a milder form of HFrEF (43).

All of the data indicate that in the context of HfmrEF, it is worth noting whether patients experienced worsening or improving of their EF during the follow-up period. It is documented that patients with ischemic heart disease or with an acute ischemic episode will be more prone to a deterioration of EF instead of an improvement (21). Therefore, patients who transitioned from reduced to mid-range ejection fraction had better outcomes in general, compared to patients who had stable HFmrEF. However, patients who impaired their EF, from preserved to mid-range, had a worse prognosis when compared to the ones with stable HFmrEF. So far, no conclusions can be drawn from the data about whether HFmrEF is a transitional form of heart failure or an independent clinical entity.

The treatment considerations

The current European Society of Cardiology guidelines on Heart Failure (7) suggest that treatment of HFmrEF should be equal to HFpEF rather than HFrEF, but so far no therapies have conclusively been shown to improve outcomes in HFmrEF (1, 3, 7). The analysis of data from different clinical registries (11, 14, 37, 40-42) indicate that the most prescribed agents are angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA). Accordingly, diuretics are recommended when signs of congestion are present (7). The CHART-2 study assessed the prognostic characteristics of agents commonly prescribed in heart failure patients (10). It was found that therapy with beta blockers positively correlated with improved mortality in patients with reduced or mid-range heart failure, contrary to those with HFpEF (10). However, the use of diuretics was a negative prognostic factor in mid-range and reduced EF, but not in patients with preserved EF (10), while the usage of lipid lowering therapy demonstrated reduced mortality only in HFpEF (10). In general, the outcomes when traditional heart failure disease-modifying agents were prescribed differed in HFmrEF compared to HFpEF patients (10). The prognosis, however, was likely to be equal to those with HFrEF. Moreover, the therapy with beta blockers was found to be very effective in improving mortality when patients presented with sinus rhythm, but not with atrial fibrillation, in all those with EF below 50% (44).

The results from the Swedish Heart Failure Registry (14) also documented the beneficial effects of beta-blocker therapy in decreasing mortality in a one-year follow up, but only in HFmrEF patients who had coronary artery disease. However, the therapy with ACEI and ARB was proven to be beneficial in reducing mortality, whether patients had coronary artery disease or not. Moreover, the use of diuretics in HFmrEF had negative impact on their prognosis. The CHARM study found that candesartan may be beneficial for HFmrEF in the same way for HFrEF, since it was proven to reduce cardiovascular and heart failure events to the same extent (43).

When arguing about the most potential therapy approach in patients with mid-range heart failure, it should be worth mentioning that the treatment of coronary artery disease, as a possible underlying factor of HFmrEF, may be a key factor for improving prognosis in this group of patients. The management of risk factors and cardiovascular and non-cardiovascular comorbidities is also highly recommended.

Conclusion

It can be observed that the introduction of the mid-range heart failure into the clinical practice and its involvement into the current ESC guidelines has gained sufficient attention for them to be included in the clinical trials as a separate cohort of patients. Briefly, they are likely to be older and females, clinically resembling patients with heart failure with preserved ejection fraction. However, regarding the presence of coronary artery disease they are more similar to those with heart failure with reduced ejection fraction. The biomarker panel and the most effective therapy approach are yet to be determined and most probably depend on the underlying etiology of the heart failure. Identification of the proper pathophysiological mechanism of mid-range heart failure will probably answer the current question about whether this type of heart failure is a transitional form between reduced and preserved ejection fraction or represents a distinct and a brand new clinical entity.

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SRČANA SLABOST SA GRANIČNOM EJEKCIONOM FRAKCIJOM – TRANZITORNA ZONA ILI ZASEBAN KLINIČKI ENTITET

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Srčana insuficijencija može se definisati kao klinički sindrom sa različitim spektrom abnormalnosti leve komore, njene funkcije i/ili strukture. Evropsko udruženje za kardiologiju je 2016. godine, u vodiču za lečenje srčane slabosti, po prvi put, kao posebnu kategoriju uvelo srčanu slabost sa graničnom ejekcionom frakcijom, EF 40% - 49%. Uključivanje u evropski vodič, a samim tim i prepoznavanje bolesnika sa graničnom srčanom slabošću, u kliničkoj praksi dovelo je do toga da oni budu uključeni u velike kliničke studije kao zasebna grupa bolesnika. Biomarkerski profil, tačan patofiziološki mehanizam i najefektniju terapiju za grupu bolesnika sa ejekcionom frakcijom 40% - 49% tek treba utvrditi i najverovatnije zavise od same etiologije srčane slabosti. Identifikacija pravog patofiziološkog mehanizma srčane slabosti sa graničnom ejekcionom frakcijom najverovatnije će odgovoriti na aktuelno pitanje da li je ovaj tip srčane slabosti tranzitna forma između srčane slabosti sa redukovanom i očuvanom ejekcionom frakcijom ili predstavlja poseban klinički entitet.

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Ključne reči: *srčana slabost, ejekciona frakcija, granična ejekiona frakcija, očuvana ejekciona frakcija*