Echocardiographic characterization of heart failure

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Chapter 3

What have we learned about HFmrEF one year after its introduction?

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Abstract

The 2016 ESC heart failure guidelines introduced the term ‘Heart Failure with mid-range Ejection Fraction’ (HFmrEF) to refer to patients with HF and a mildly reduced ejection fraction of 40-49%. About 20% of heart failure patients fall in this category. One of the main reasons for the introduction of this category was to stimulate research into this grey area. This review aims to highlight the key findings that have been published so far. Firstly, HFmrEF more closely resembles HFrEF than HFpEF with regards to ischemic etiology, which is more frequent in both HFmrEF and HFrEF compared to HFpEF. Secondly, changes in ejection fraction over time are common, and seem to be more important than baseline ejection fraction alone. Patients who progress from HFmrEF to HFrEF have a worse prognosis than those who remain stable or transition to HFpEF. Lastly, and perhaps most importantly, retrospective analyses from a randomised trial suggest that patients with HFmrEF seem to benefit from therapies that have shown to improve outcome in HFrEF, whereas no such benefit was seen in patients with HFpEF.

Introduction

In May 2016, the new ESC heart failure guidelines were presented and published.[1] The task force decided that patients with heart failure with a left ventricular ejection fraction (LVEF) between 40-49% were to be newly categorised as having Heart Failure with mid-range Ejection Fraction (HFmrEF). This new category was not created from the identification of a new group of patients, but rather provided formal nomenclature and acknowledgement of a group of patients formerly referred to as a "grey area" in the 2012 ESC Heart Failure Guidelines.[2] Similarly, the 2013 ACC/AHA Guidelines stated that "patients with an EF in the range of 40% to 50% represent an intermediate group", but did not give this category of patients a name.[3] About 20% of patients have an ejection fraction between 40-50%. Reasons to formally identify HFmrEF as a separate group include evidence suggesting that patients with HFmrEF respond differently to treatment compared to patients with HFpEF as well as to stimulate research into the underlying characteristics, pathophysiology and treatment of this group of patients as stated in the 2016 ESC guidelines. One year after its introduction, we have to conclude that this statement has become reality, as many papers on patients with HFmrEF have since been published, and many are currently under review or in preparation. This review is a one year summary of the knowledge we have collected on this new category, and will summarise the main conclusions that we can draw from these papers.

Population characteristics

Even before the introduction of HFmrEF as a separate category, it was questioned whether HFrEF and HFpEF are two entirely different syndromes or just two ends of the same disease spectrum, or whether HFpEF is merely a manifestation of ageing and age-related co-morbidities.[4] The introduction of the HFmrEF category enhances the contrasts between HFrEF and HFpEF. From a pathophysiological point of view there are marked differences between HFpEF and HFrEF.[5] With the introduction of HFmrEF, it is questioned whether HFmrEF looks more like HFpEF or more like HFrEF. In the last year, a multitude of studies have provided us with population characteristics to help us answer this question.

Etiology

A striking and consistent finding is that patients with HFmrEF seem to be similar to HFrEF with regards to ischemic etiology. Patients with HFrEF and HFmrEF show higher percentages of ischemic heart disease and idiopathic dilated cardiomyopathy, while hypertensive heart disease and valvular heart disease are the more common etiologies in HFpEF. In the Swedish Heart Failure registry of 42,987 patients, percentages of ischemic heart disease were 60% for HFrEF, 61% for HFmrEF and 52% for HFpEF[6]. Chioncel et al. report on 9134 patients in the ESC Heart Failure Long-Term Registry.[7] Etiology was ischemic for 48.6% of HFrEF patients, 41.8% of HFmrEF patients, but only in 23.7% of HFpEF patients. Rickenbacher et al. performed an extensive post-hoc analysis of the TIME-CHF trial that included 622 elderly patients with symptomatic heart failure.[8] Ischemic etiology was 58.2%, 56.5% and 31.3% for HFrEF, HFmrEF and HFpEF respectively. Therefore, in terms of etiology, HFmrEF patients are more like HFrEF than HFpEF (*Figure 1*).

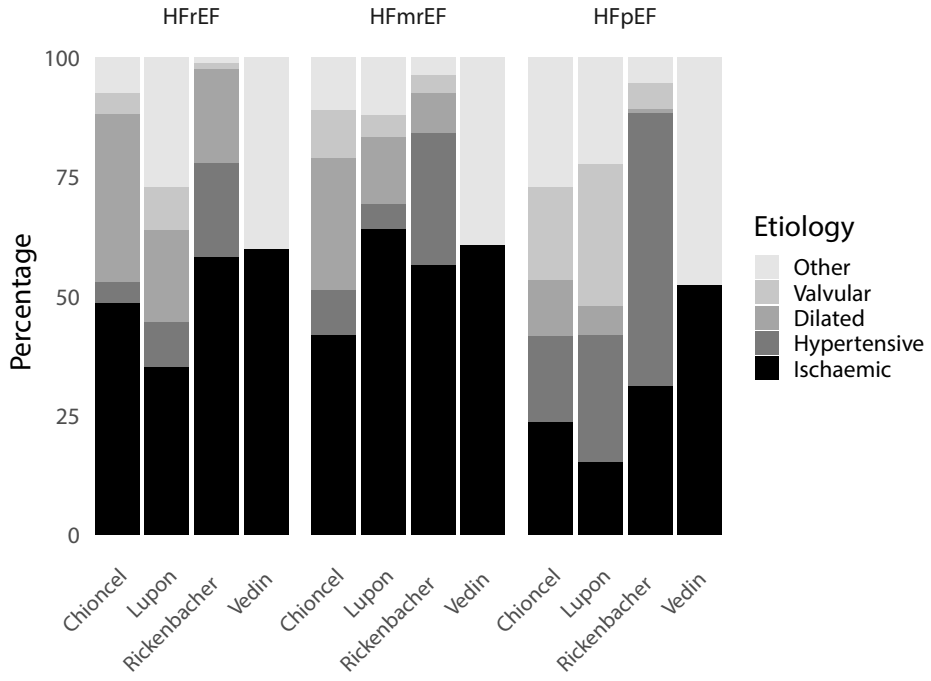

Figure 1. Hypertensive and ischaemic etiologies for HFrEF, HFmrEF and HFpEF in three recent studies.

Comorbidities

With regard to both noncardiac and cardiac comorbidities, the findings are less consistent. Chioncel et al. show that COPD, liver function abnormalities and chronic renal disease are more common in HFrEF[7], but in Rickenbacher's study the three EF strata have a comparably high burden of comorbidities.[8] Löfman et al. studied the relationship of CKD along the EF spectrum in the Swedish Heart Failure registry and found that CKD was associated with similar covariates regardless of EF.[9] The prevalence of atrial fibrillation in the Swedish Heart Failure registry was 65%, 60%, and 53% in HFpEF, HFmrEF, and HFrEF, respectively.[10]

Medication use

The ESC Heart Failure Long-Term Registry gives us insight in current practice with regard to heart failure medication. Use of beta-blockers and ACE inhibitors was around 90% in both HFrEF and HFmrEF, compared to approximately 75% in patients with HFpEF. Percentages in the Swedish Heart Failure registry were comparable. Use of MRAs was high in the ESC HF registry: around 70% in HFrEF, 55% in HFmrEF, and 35% in HFpEF. For comparison, MRA use in the Swedish Heart Failure registry was around 32-33%, 23-24% and 25-28% for HFrEF, HFmrEF and HFpEF. Ivabradine was prescribed to around 10% of HFrEF and HFmrEF patients, and only 5% of HFpEF patients.

Biomarker profile

Three recent papers provided information on the biomarker profile of patients with HFmrEF. Data from 1096 in- and outpatients from the Singapore Heart Failure Outcomes and Phenotypes (SHOP) cohort showed that troponin levels in HFmrEF fell between those observed in HFrEF and HFpEF.[11] Savarese et al. confirmed that decreases in NT-proBNP levels over time are associated with better survival.[12] Tromp et al. analysed 37 biomarkers in HFrEF, HFmrEF and HFpEF.[13] Using network analysis, biomarkers of cardiac stretch were central in HFrEF. Biomarkers of inflammation were more important in HFpEF. Patients with HFmrEF displayed an intermediate profile with biomarker interactions that were both related to inflammation and cardiac stretch.

Prognosis

In general, most studies have indicated that the prognosis of HFpEF is slightly better than for patients with HFrEF, especially when corrected for the difference in age. Now several studies have compared the difference in prognosis between patients with HFrEF, HFmrEF, and HFpEF.

1. Kapoor et al. found an in-hospital mortality of 3.2% for HFrEF, 2.6% for HFmrEF, and 3.0% for HFpEF in the 99,825 patients of the Get With The Guidelines Registry, which included adults hospitalised for new or worsening heart failure.[14]

2. In the ESC Heart Failure Long-Term Registry one year all-cause mortality was 8.8% for HFrEF, 7.6% in HFmrEF, and 6.4% in HFpEF.[7] The mean age was 64 years in HFrEF and HFmrEF, and 69 in HFpEF.

3. In the TIME-CHF trial, the mean age was higher: 75 years in HFrEF and 80 years in HFpEF. Overall mortality was high as well: 39.7% after 2.2 years, with no significant difference between HFrEF, HFmrEF and HFpEF.

4. In the Swedish Heart Failure registry, prognosis of HFmrEF and HFpEF were similar after adjustment for age and other confounders, and slightly better than HFrEF.[15] When only patients with CAD were considered, prognosis was worse for the HFmrEF group compared to HFpEF. HFrEF had the worst prognosis.

Currently available studies report different on outcomes in HFmrEF. Overall, medium term outcomes appear intermediate, while in the long term, HFmrEF might be similar in prognosis to HFpEF.

Temporal changes in ejection fraction

Ejection fraction often changes over time.[16,17] It seems that there are important differences in outcome when these changes occur. For this review, we focus on three groups: from HFmrEF to HFrEF (deterioration), stable HFmrEF, and from HFmrEF to HFpEF (recovery) (*Figure 2*). Tsuji et al. studied 3480 stable heart failure patients in the CHART-2 study.[18] They found, after a median follow-up of 3 years, that 21% of HFmrEF patients transitioned to HFrEF and 45% to HFpEF. Mann et al. found that 17% had a 'deteriorated' EF (prior >50%), 73% had a 'recovered' EF (prior <40%) and 10% remained stable in HFmrEF

in their registry study of 1091 patients.[19] Vedin et al. found 36.5% of HFmrEF patients deteriorated, and 23.6% improved after a variable follow-up time of up to 14 years. Patients with ischemic heart disease were more likely to experience worsening EF. Lupon et al. prospectively studied 1057 ambulatory patients. After 1 year 25% of those patients had a 'recovered' ejection fraction.[20]

Figure 2. Illustration of possible temporal changes in ejection fraction.

Prognostic impact of changes in ejection fraction

Tsuji et al. report hazard ratios relative to 'stable HFpEF' patients. The prognosis for HFrEF patients that 'recover' to HFmrEF is more favourable than that of patients that have an unchanged ejection fraction and remain 'stable HFrEF' or 'stable HFmrEF'. Nadruz et al. find similar results in their study of heart failure patients referred for cardiopulmonary exercise testing.[21] HFpEF patients that deteriorate to HFmrEF have higher risk for all-cause death compared to 'stable HFmrEF' patients in Tsuji's study, but this difference is not statistically significant. Mann et al. find similar results. Taken together, improvement of ejection fraction from HFrEF to HFmrEF correlates with a significantly better prognosis than patients who remain in 'stable HFmrEF'. Patients who deteriorate from HFpEF to HFmrEF seem to have a prognosis that is slightly worse than 'stable HFmrEF'. Testing bias might be introduced when the serial echocardiograms were not systematically performed, but their timing was dictated by the clinical status of the patient. The studies of Tsuji and Lupon had echos that were required by protocol at fixed times, whereas the studies of Mann and Vedin let the indication for echo at the discretion of the treating physician.

Treatment response

In the past years, several pharmaceutical interventions that showed to be beneficial in HFrEF patients have shown neutral effects in trials specifically targeting HFpEF: PEP-CHF for perindopril, CHARM-Preserved for candesartan, I-PRESERVE for irbesartan and TOPCAT and ALDO-DHF for spironolactone.

Interestingly, several retrospective analyses that have now been published suggest that patients with mid-range ejection fraction might benefit from these drugs including ARBs, beta-blockers and MRAs:

1. Lund et al. analysed the data from the CHARM programme and assessed the effect of candesartan across the EF spectrum.[22] With continuous spline modeling, candesartan showed a positive treatment effect for LVEFs of up to 50%. Hazard ratios for the primary outcome of time to cardiovascular death and heart failure hospitalization were 0.82 (0.75-0.91) and 0.76 (0.61-0.96) in the HFrEF and HFmrEF categories respectively, versus 0.95 (0.79-1.14) in the HFpEF category.

2. A large propensity-score matched analysis was performed with data from the Swedish Heart Failure registry. It was suggested that ACE inhibitors and ARBs were overall associated with reduced all-cause mortality in HFpEF.[23] Although the interaction did not reach significance (p=0.12), there was a strong signal toward a stronger association in HFmrEF (HR 0.85 [0.76-0.95]) than in HFpEF (0.95 [0.87-1.04]).

3. Tsuji et al. looked at the prognostic impact of beta-blockers in the CHART-2 study, a multicentre observational study with 10,219 stable heart failure patients enrolled in multiple centres in Japan. Use of beta-blockers was associated with improved survival in HFrEF and HFmrEF, but not in HFpEF.

4. The association between beta-blocker use and mortality was also extensively studied in the Swedish Heart Failure registry.[15] The authors stratified patients by ejection fraction and by the presence or absence of coronary artery disease. All HFrEF patients had lower hazard ratios when treated with beta-blockers. For HFmrEF, only the patients with CAD benefitted from a beta-blocker (hazard ratio for mortality 0.74 versus 0.99). For HFpEF however; this relationship was inversed: beta-blockers were only associated with reduced 1-year mortality in the absence of CAD. Of note, the three-way interaction between CAD, ejection fraction and beta-blocker use was significant (p=0.023).

5. The Beta-blockers in Heart Failure Collaborative Group recently performed an individual patient level meta-analysis on the effect of beta-blockers across the spectrum of ejection fraction in 18,637 patients

that participated in 11 different randomized trials.[24,25] Beta-blockers improved mortality in sinus rhythm in all ejection fraction categories up to and including 40-49% (HFmrEF), but not in ≥50%.

6. The TOPCAT trial showed an overall neutral effect of spironolactone on outcome in patients with HFpEF.[26] Solomon et al. studied the relationship between ejection fraction and treatment effect in TOPCAT. Patients with an ejection fraction between 45-55% showed an estimated benefit from spironolactone treatment which disappeared in patients with ejection fractions higher than 55%.[27]

So, interestingly, several papers have now shown that treatments that improve clinical outcome in patients with HFrEF also seem to benefit patients with HFmrEF. This is in contrast to patients with HFpEF who did not seem to derive such benefits from these therapies.

We have learned, but more insight is needed

The introduction of HFmrEF as a separate category has achieved its aim of stimulating research into this group of patients, and has yielded several interesting insights. The general assumption is that HFmrEF patients are considered to be the “middle child”. However, HFmrEF seems to be more similar to HFrEF, in terms of (ischemic) etiology, biomarker profile and in response to treatment.

What else do we need to learn about HFmrEF? Firstly, we need more insight in the underlying pathophysiology. With limited data, the current perspective is that HFrEF is considered as primarily a disease of the myocardial cells, while in HFpEF endothelial dysfunction and various inflammatory processes play a central role.[5] We need to find out whether HFmrEF is pathophysiologically more related to HFrEF or to HFpEF, for instance using a proteomics/genomics approach.

Secondly, there is a need to more precisely define heart failure endotypes. Even though ejection fraction is one of the cornerstones of the diagnosis of heart failure, it might not be the perfect tool to guide treatment decisions.[28] In addition, echocardiographic measurement of LVEF is not very precise, and it has been suggested that the variability in LVEF measurements might be larger than the sub-category of HFmrEF. Further research is warranted in different approaches

to help in phenotyping heart failure patients more precisely, for instance using biomarker profiles. Additional echocardiographic techniques, such as global longitudinal strain, can might be useful as well.[29]

Thirdly, and perhaps most importantly, the suggestion of a positive response to treatment in HFmrEF needs to be validated in adequately designed prospective studies. Studies in HFmrEF alone might be difficult to conduct, as only around 20% of patients are in the HFmrEF category. Therefore, novel studies might include both HFrEF and HFmrEF (i.e. all ejection fractions <50%) so that treatment effects can be analysed across the EF spectrum.

In summary, although heavily debated, the introduction of HFmrEF has resulted in a considerable number of important studies. These studies, and many others that are currently in development, will contribute to our understanding of heart failure, which will undoubtedly lead to better diagnosis and treatment which is the ultimate goal of all heart failure guidelines.

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