HFrEF: Cardiovascular Abnormalities
Not Just Comorbidities

William C. Little, MD; Michael R. Zile, MD

Twenty-five years ago, the understanding of heart failure (HF) was straightforward. HF was a clinical syndrome due to left ventricular (LV) systolic dysfunction apparent as a reduced ejection fraction (EF). Based on this understanding, large randomized trials were conducted using an EF<0.30 or 0.35 as a key entry criterion. These studies demonstrated that the use of angiotensin-converting enzyme inhibitors, β-adrenergic blockers, aldosterone blockers, and cardiac resynchronization improved morbidity and mortality in patients with HF and a reduced EF (HFrEF). The benefit of these interventions (except for aldosterone blockade) was associated with reversal of the LV dilation (eccentric remodeling) present in HFrEF. In contrast, the use of positive inotropic agents to improve systolic function was either of no benefit or actually detrimental in HFrEF. This suggested that there was more to HF than just systolic dysfunction.

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The concept that all HF was due to systolic dysfunction apparent as a reduced EF was further challenged by the subsequent recognition that HF occurs in patients with the entire range of EFs, including EF>0.50, an EF that is in the normal or near-normal range (ie, preserved EF). Many features of the HF syndrome are similar across the EF spectrum including elevated left atrial pressure, abnormal LV filling dynamics, neurohormonal activation, dyspnea, impaired exercise tolerance, frequent hospitalization, and reduced survival.

There are also clear clinical differences between HF with a preserved EF (HFpEF) and HFrEF. Patients with HFpEF are older, more likely to be women, less likely to have ischemia, and there is a very strong association with systolic hypertension. In addition, there are differences in cardiac structure and function. In HFrEF, the LV is dilated with eccentric remodeling. In contrast, the LV end-diastolic volume is not increased relative to the stroke volume in HFpEF, and concentric remodeling (with or without LV hypertrophy) is present in many patients. In addition, in HFrEF, LV systolic elastance is reduced and arterial elastance is elevated so that there is impaired ventricular–vascular coupling. In contrast, both LV and arterial elastance are increased in HFpEF so that the coupling between them is preserved. In fact, the presence of a normal EF indicates that the coupling of the LV and arterial system is nearly optimal to convert the energy of contraction into the stroke work. Thus, arterial vasodilation improves LV systolic performance in HFrEF, but not in HFpEF.

Patients with both HFpEF and HFrEF frequently have important comorbidities. However, the presence and contribution of the comorbidities to the HF clinical syndrome have received more attention in HFpEF. In addition, there are clear differences in the response to treatment. The therapies proven to improve outcome in HFrEF, which are associated with reversal of LV dilation, have not been demonstrated to be effective in patients with HFpEF. In retrospect, this should not have been so unexpected because patients with HFpEF do not have LV dilation.

The observed differences and similarities between patients with HFrEF and HFpEF have produced a number of controversies including the following: 1) What is the role of cardiovascular dysfunction in producing HFpEF? 2) Does HFpEF represent true HF or just a collection of comorbidities? 3) Are HFpEF and HFrEF two separate syndromes or merely the extremes of a single continuum? Two recent articles from the Mayo Clinic published in this issue of Circulation: Heart Failure provide important information to help answer these questions.

Mohammed et al examined the role of co-comorbidities in 386 patients with HFpEF living in Rochester, Minnesota, by comparing them with age- and sex-matched healthy controls (without HF, hypertension, diabetes, or vascular or valvular disease) and with hypertensive controls (with hypertension, but without HF). Hypertension, obesity, diabetes, anemia, and renal dysfunction were present in many of the patients with HFpEF. However, even after accounting for age, sex, body size, and comorbidities, patients with HFpEF as a group had larger LV mass, greater systolic and diastolic dysfunction, more left atrial enlargement, and increased arterial stiffness.

Mohammed et al found that each of the common comorbidities seemed to contribute to the cardiovascular abnormalities in slightly different ways. For example, obesity was associated with greater concentric remodeling, but better systolic function and less arterial stiffening. Interestingly, anemia and renal dysfunction were associated with worse survival in HFpEF, whereas obesity was associated with better survival. Thus, the obesity survival paradox present in HFrEF is also present in HFpEF.

The observations of Mohammed et al indicate that the comorbidities contribute to the development of cardiovascular
abnormalities of HFpEF, but the abnormalities are more than expected with these conditions. In addition, other recent observations indicated that the prognosis of HFpEF is much worse than expected with the comorbidities alone. Thus, treating the comorbidities (especially hypertension) can be expected to delay or prevent the development of HFpEF but may not be adequate therapy for HFpEF once it develops.

In a second study performed at the Mayo Clinic, Dunlay et al evaluated 1233 patients with HF who had serial echocardiograms to determine the time course of changes in the LV EF during a 5-year period of observation. Consistent with previous observations, the distribution of the initial EFs shows a clear bimodality. This supports the concept that HFpEF and HFrEF are separate syndromes, not the extremes of a single continuum. In patients with HFpEF, Dunlay et al found that on average the LV EF decreased by about 0.06 during the 5 years, whereas it increased by nearly 0.07 in the HFrEF patients. In other words, the changes in both directions are about 0.01 per year. This variation in the EF resulted in nearly 40% of both the HFpEF and HFrEF patients having an EF that put them in the other classification at some point in their follow-up. The interpretation of these important observations is complicated.

The measurement of EF is subject to substantial variability, especially when it is done clinically using a variety of methods and analyzed in a retrospective review. There is a greater chance that this variability in the measurement will result in a decrease of a subsequent measure of the EF in those with the highest initial EF and an increase in those with the lowest EF (regression to the mean). This may contribute to the increase in EF found in the patients with HFrEF. In addition, HFpEF and HFrEF were divided based on an EF value of 0.50. This is an arbitrary cutoff. Clearly, patients with EFs of 0.51 and 0.49 are not different and likely to cross back and forth across the threshold.

Although these concerns are real, their detailed sensitivity analysis shows that there is clearly more to the observations by Dunlay et al. The patients with HFrEF who received evidence-based therapy had a greater increase in EF, providing another demonstration of their benefits. Consistent with clinical trials to date, these therapies were not associated with protection against a decline in EF in the patients with HFpEF. As expected, there were greater increases in EF in HFrEF patients who were women, younger, and did not have coronary disease. Similarly, there were greater decreases in EF in HFpEF patients who were older and had coronary artery disease. However, there was not a uniform deterioration in EF in patients with HFpEF. Some had no fall in EF, and the majority (>60%) did not have a decline in EF below 0.50. Another prospective study of 343 subjects with concentric LV remodeling found that during the 7-year period, only 7% developed eccentric remodeling with LV dilation and a fall in EF. However, it is apparent that having HFpEF does not protect a patient from subsequently having a drop in EF. Although few patients had documented myocardial infarctions in the study by Dunlay et al, ischemic heart disease may have contributed to the observed small decrease in EF. What is not clear is whether a progressive deterioration in EF is part of the natural history of HFpEF. This will require the prospective serial evaluation of patients with HFpEF. A more detailed analysis of LV structure and function in addition to EF would be valuable.

In conclusion, the landmark studies of Mohammed et al and Dunlay et al provide important information that advances our understanding of HFpEF. They provide additional evidence that HFpEF is real HF due to cardiovascular abnormalities. Although comorbidities are frequent and important, HFpEF is more than a collection of comorbidities. The confirmation of a clear bimodal distribution of EF’s in HF supports the concept of HFpEF and HFrEF as separate syndromes. In contrast, the finding of a progressive drop in EF in some patients with HFpEF can be interpreted as indicating that HFpEF and HFrEF may, in some instances, be extremes of a single disease. Whether progressive myocardial dysfunction is part of the natural history of patient with HFpEF or alternatively a fall in EF in a HFpEF is due to superimposed myocardial damage from infarction, ischemia, or other insults will require prospective longitudinal studies of HFpEF as proposed by Dunlay et al.

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References


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