Heart Failure With a Better Ejection Fraction
Why Should We Care?

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Consider the following clinical scenarios: (1) a 67-year-old man presents for follow-up of recent coronary bypass surgery. He had presented 6 months ago with heart failure, severe 3-vessel coronary disease, and a left ventricular ejection fraction (LVEF) of 30%. He has done well and remains asymptomatic on metoprolol succinate, lisinopril, eplerenone, and occasional furosemide. Repeat echocardiography notes his LVEF is now 55%. He wants to know how long he needs to continue these medications. (2) A 45-year-old woman with an idiopathic dilated cardiomyopathy is seen for routine evaluation. Since her diagnosis, 8 months ago, she has done well on carvedilol, losartan, and spironolactone; she does not require other diuretics. Repeat echocardiography documents an improvement in LVEF from 15% to 60%. She wants to know what her prognosis is. What do you tell them?

See Article by Florea et al

Although the primacy of patient-relevant outcomes in the study of heart failure should not be displaced, it is virtually impossible to not be obsessed with the ejection fraction. Yet, it has well-known limitations: it changes over time, its measurement in clinical practice is not precise, and what is considered normal continues to evolve. However, for patients and providers, it is simple and intuitive; it integrates the relationship between more complex concepts of myocardial contractility, cardiac structure, and ventricular-arterial coupling. The LVEF determines how heart failure is categorized, which treatments are indicated, and what the prognosis may be. However, it is important to recognize that the prognostic power of LVEF lies in its physiological determinants; for example, it is ventricular-arterial coupling, LV size, and V0 that affect outcomes and not intrinsic contractility (eg, Ees) per se that is associated with outcomes.

As a composite measurement, an improvement in LVEF generally indicates left ventricular reverse remodeling (LVRR), whether as a signature of disease remission or recovery. LVRR has been associated with better clinical outcomes and is often used as a surrogate end point in heart failure clinical trials. Undoubtedly, an improvement in ejection fraction brings with it a sense of satisfaction and relief for both provider and patient.

Although LVRR has been under investigation for decades, interest in this process has been recently accelerated by the clinical observation that severe chronic left ventricular dysfunction can be reversed with left ventricular assist devices. Consequently, new pathways and strategies for novel pharmacological and hemodynamic targets to promote LVRR are being elucidated and imagined.

For the practicing clinician, the above scenarios have become more common, particularly the phenomenon of the super-responder, when there is dramatic improvement in the LVEF. The data on this population is limited, but certain insights are coming to light. First and foremost, these patients should be distinguished from those with heart failure and preserved EF (HFpEF). Punnoose et al described these patients as having heart failure with recovered EF, herein referred to as heart failure and improved ejection fraction, or HFiEF. They were the first to compare these patients to the traditional HFpEF and heart failure and reduced EF (HFrEF) population in a cross-sectional manner. They also noted that these patients had milder symptoms, fewer hospitalizations, younger age, and more nonischemic pathogenesis than HFrEF, but less comorbidity than HFpEF. However, it remained unclear whether these patients were indeed distinct from other patients with HFrEF.

In the Penn Heart Study, the biochemical profile and the long-term prognosis of similar patients with HFiEF suggested that they were distinct from other patients with HFrEF. Interestingly, although biochemical evidence for neurohormonal activation and myocardial stress/injury were more favorable compared with the other HF groups, the biomarker levels were not normal. This observation provided evidence of persistent neurohormonal activation, increased oxidative stress, and myocyte stress and injury despite the super-response of the LVEF. Most importantly, this persistence of disease activity translated into clinical outcomes. Although these patients seemed to have a better mortality than HFpEF and HFrEF, the prevalence of cardiac hospitalizations was similar to the patients with HFpEF.

Other groups have shown that despite evidence of LVRR (often reflected in an improved LVEF), patients continue to be at risk for cardiovascular events or subsequent decline in LVEF. For example, cardiac resynchronization therapy super-responders do experience appropriate implantable cardioverter-defibrillator shocks. In one cohort, although patients with LVRR did better than persistent HFrEF patients, those who recovered to an EF of 40% to 55% showed similar risk...
of death and combined end point of LVAD, transplant or death when compared with HFpEF. These findings suggest that some patients who exhibit LVRR have persistent HF; whereas others do not. To differentiate these 2 possible outcomes of LVRR, the terms myocardial remission and myocardial recovery have been used; the former referring to patients who are at risk for disease recurrence or progression (and associated clinical events) and the latter referring to patients with a functional cure. Therefore, greater clarity in understanding HFiEF would not only help to inform management decisions (eg, continue/wean/stop medications or replace/not replace implantable cardioverter-defibrillators at end of life) and better define prognosis for such patients but also potentially provide insights into innovative approaches to inducing remission or getting to the holy grail of sustained recovery, for example, cure.

It is in this context that the investigators in this study have strengthened the concept that patients with HF and an improved EF are clinically distinct from patients with HF with persistently reduced EF (HFrEF). In this issue of Circulation: Heart Failure, Florea et al used data from the Valsartan Heart Failure Trial (Val-HeFT) to identify a subset of patients who entered the study with a reduced LVEF of <35% but went onto improve their ejection fraction (HFiEF) to >40% after 12 months of follow-up. They specifically sought to better characterize this improved LVEF population, determine independent predictors of improvement, and compare prognosis to patients who did not improve.

The patients with HFiEF represented 9.1% of the cohort, although they acknowledge that this estimate likely underestimates the prevalence. Interestingly, this prevalence of 9% is similar to other data sets. When compared with the HFrEF group, the HFiEF group seemed to be younger, more likely to be female, more likely to have a nonischemic pathogenesis of HF, and have a higher blood pressure. They also found no difference in patient symptomatology, in contrast to other previous reports. In total, these findings are generally noteworthy in that the observations are gleaned from a data set that included well-characterized patients, adjudicated outcomes, and rigorous methodology for LVEF assessment.

Importantly, patients with HFiEF were also more likely to have been on β-blockers at study onset, which would be consistent with known treatment effects of β-blockade and emphasizes the importance of guideline-directed HF therapy. Moreover, treatment with valsartan was also associated with an improved LVEF, suggesting that either more aggressive treatment of hypertension or greater neurohormonal blockade led to more LVRR.

Finally, the investigators also confirm previous observations that patients with a significant improvement in LVEF experience an important improvement in survival when compared with those patients with persistent HFiEF. Collectively, these findings are generally noteworthy in that the observations are gleaned from a data set that included well-characterized patients, adjudicated outcomes, and rigorous methodology for LVEF assessment.

A particular strength of this study was the availability of a comprehensive set of biomarkers. The authors furthered their description of this population with HFiEF using this information. They found that HFiEF had less neurohormonal activation based on norepinephrine, plasma renin activity, endothelin I, big endothelin, and brain natriuretic peptide/n-terminal pro-brain natriuretic peptide levels. There was less evidence of myocyte injury and hypertrophy as growth differentiating factor-15, ST2, and troponin levels were all lower. Although it is tempting to consider this biomarker profile as a characteristic of an HFiEF cohort, it could reflect a less ill cohort, shorter duration of disease, or the impact of greater β-blocker use.

Not surprisingly, although there was less neurohormonal activation and myocyte injury/stress, the values for these biomarkers in this HFiEF cohort were not entirely normal. These abnormalities suggest that although the HFiEF cohort demonstrates LVRR, there are a significant number of patients in this group who have evidence of persistent disease, for example, are in disease remission. It would have been of interest to know whether those patients with truly normal biomarker levels were LVEF super-responders and whether such a biomarker profile could have been used as a potential signature of true myocardial recovery.

Could HFiEF be predicted? Being in the valsartan treatment arm, the use of β-blockers at study baseline, female sex, higher blood pressure, nonischemic origin, lower indexed LV diastolic diameter, an undetectable troponin T, and a lower body mass index all improved odds of being in the HFiEF group at 12 months. Disappointingly, combining these 8 variables into a logistic regression provided only a modest predictive ability for an EF increase of at least 5% (median probability 15% in the HFiEF group versus 6% in the HFrEF group); in fact, only 3 subjects had a >50% likelihood of HFiEF using these criteria. It should also be noted that the biomarkers entered into the logistic regression were limited to 7 of the 12 biomarkers measured in a large subset of patients. In general, these findings were consistent with previous reports and highlight the difficulty in predicting a specific patient’s response to HF therapy.

The authors do acknowledge important limitations to their analysis, including the post hoc nature of the analysis, generalizability, and the difficulties in developing prediction models. Another concern includes the use of >40% as the threshold for significant LVEF improvement; it would have been more interesting to explore >50% as the threshold for improvement as other investigators have chosen. Using this substantially greater LVEF, the notion of super-responder could have been examined in greater depth.

The spectrum of other clinical events would have been of interest. For example, who was hospitalized for HF in the follow-up period or who required diuretics in the HFiEF group after improvement in LVEF could distinguish those who were experiencing a remission, rather than recovery from heart failure. Additional baseline data, such as LA size or the presence of LBBB, may have improved a predictive algorithm and could represent another opportunity to track disease severity or risk of recurrence after LV improvement. The relationship of serial changes in a multibiomarker profile to improvements in LVEF could lead to important insights into how LVEF improves. Finally, a patient-level analysis would also be illuminating. For example, an individual patient with an LVEF of 35% improving to 40% is likely distinct from a
pathophysiological point of view from a patient with an LVEF of 10% improving to 60%.

In the end, should we find these observations surprising? Is it not intuitive that being less ill and having more neurohormonal antagonism is associated with a greater LVEF improvement and greater survival? It should be recognized that a meaningful improvement in LVEF is associated with better outcomes has been well established by several previous studies; however, what may be less appreciated that the cup is still half empty rather than half full, for example, clinical events do accrue and disease activity can be demonstrated. Moreover, why there is such a spectrum of LVEF responses remains largely unknown.

The mechanisms of how and why LVRR in chronic heart failure (eg, >6 months of HF therapy) diverges to either remission or recovery is as yet unclear. Current clinical evidence is incomplete. Data from Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) suggest that despite a high prevalence of LVRR in patients with VAD, only ≈1% or less of patients are explanted because of recovery. Currently, recovery practices and protocols are not uniform nor ubiquitous across centers; when consistent approaches are used, recovery may be more common. Recent data show that despite an improvement from pre-LVAD levels, contemporary LVAD patients show persistently elevated biomarkers of myocardial stress and injury, fibrosis, inflammation, and neurohormonal activation. This would suggest a persistent HF phenotype, despite optimization of loading conditions with mechanical support. It builds a strong argument for continued HF pharmacotherapy post-LVAD implantation.

Patients who improve their LVEF, such as the 2 scenarios above, represent a significant portion of our patients that will grow. Although an improvement in LVEF has become a ubiquitous goal for patients and providers, we still know little about the patients who do improve; terminology and criteria for these patients have only recently been addressed. The term HF-Better EF has been proposed because it acknowledges the current HF classification schema (LVEF based), whereas it also recognizes that improving or recovering LVEF does not equate to a recovery or cure from the HF disease. Although population studies are a key first step in describing disease patterns and characteristics, they should lead to mechanistic investigations that are disease specific. For instance, molecular insights into the causes of dilated cardiomyopathy could now be reconciled with clinical responses to medical therapy.

Have the authors convinced us that HFiEF is clinically distinct? And if so, why should we care? This study does further reinforce the idea that there is a phenotype associated with a greater LVEF response to standard HF therapy. Why we should care lies in why such a broad spectrum of responses even exists. In an era of precision medicine, a routinely treatment approach for all patients with HFiEF seems dated. Perhaps 1 day, the routine evaluation of HFiEF will include a myocardial biopsy, sophisticated biomarker profiles, and structural and functional imaging that will direct therapy along more specific mechanistic pathways and provide a signature for those patients who are truly cured. Until then, we should acknowledge that HF with an improved EF is still HF, regardless of EF.

Disclosures

None.

References


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