VIEWPOINT

Redefining Heart Failure With a Reduced Ejection Fraction

Javed Butler, MD, MPH, MBA
Department of Medicine, University of Mississippi Medical Center, Jackson.

Stefan D. Anker, MD
Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany; and Department of Cardiology, German Center for Cardiovascular Research at Berlin, Charite Universitatsmedizin Berlin, Berlin, Germany.

Milton Packer, MD
Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas; and Imperial College, London, United Kingdom.

Corresponding Author: Milton Packer, MD, Baylor Heart and Vascular Institute, 621 N Hall St, Dallas, TX 75226 (milton.packer@baylorhealth.edu).

The current management of patients with chronic heart failure depends on the noninvasive measurement of left ventricular ejection fraction (LVEF). In patients with an LVEF of 40% or lower, large-scale randomized clinical trials have demonstrated the benefits of inhibitors of the renin-angiotensin system, sympathetic nervous system, aldosterone, and neprilysin in reducing the risk of cardiovascular death and hospitalization for heart failure. Because these trials only enrolled patients with an LVEF of 40% or lower, a value of 40% has been used to define patients with heart failure and a reduced ejection fraction (HFrEF) for the past 30 years. Current guidelines strongly recommend the use of combination treatment with neurohormonal antagonists for patients with HFrEF.[1] By contrast, there are no evidence-based recommendations concerning the treatment of patients with LVEF greater than 40%, who have been conventionally referred to as having heart failure with a preserved ejection fraction (HFpEF). This lack of guidance is a concern because such patients now represent a majority of those with heart failure in the general community, particularly among women.[2]

How Should Patients With Impaired Systolic Function Be Identified?

Despite its historical use, a value for LVEF of 40% does not distinguish patients with heart failure who have normal LVEF from those who have abnormally low LVEF values. Like many measurements in medicine, LVEF is a continuous variable, and the identification of normal values is dependent on various variables including sex and age. Guidelines indicate that the low end of normal for LVEF is 52% in men and 54% in women[3]; an LVEF of 41% to 51% in men and 41% to 53% in women is regarded as mildly reduced. However, despite having meaningful systolic dysfunction, these patients were not enrolled in trials of HFrEF because those studies were designed to have high event rates to make their sample sizes financially feasible.

Because an LVEF of 40% or lower was used as a criterion for enrollment in studies of HFrEF, when trials of patients with HFpEF were first conducted, they focused on patients who had been excluded from trials of HFrEF, ie, they required patients to have an LVEF higher than 40%.[4] Early investigators deemed such patients to have preserved ejection fraction because they understood that the group included patients with a subnormal LVEF (<50%-55%) as well as patients with an LVEF in the normal range (>50%-55%). In 2013, the ACCF/AHA (American College of Cardiology Foundation/American Heart Association) guidelines classified patients with heart failure who had an LVEF of 41% through 49% as having "HFpEF, borderline" and considered them to be distinct from those with HFrEF.[1] More recently, the 2016 ESC guideline classified patients with an LVEF of 40% through 49% as having "heart failure with a mid-range ejection fraction."[5] The authors formulated this category to encourage further study of this intermediate group. However, this intent was widely misunderstood, and many physicians considered this mid-range group to represent a new distinct clinical entity.

Any classification of heart failure that relies on LVEF has inherent limitations. First, the measurement of LVEF is highly dependent on the method used for imaging, and even when the same method is used, there is considerable intraobserver and interobserver variability. Repeat measurements of LVEF in the same patients using the same methods by experts in echocardiography routinely vary by 7%; the variability is greater in clinical practice. When the echocardiograms of patients enrolled in clinical trials are reviewed using standardized criteria, differences between the values obtained by site investigators and the core laboratory routinely vary as much as 15% when reading the same images. Furthermore, the quality of images is highly operator-dependent, and the values for LVEF depend on loading conditions, ie, volume status and blood pressure. Hence, it is likely that a meaningful proportion of patients with an LVEF of 40% to 50% would be reclassified as having an LVEF of lower than 40% or higher than 50% if the measurement were repeated.

Perhaps more important, when assessed using biomarkers that reflect potential disease mechanisms, patients with HFrEF typically show evidence of increased circulating levels of proteins that reflect the occurrence of cardiomyocyte injury, loss, and stretch. In contrast, patients who have heart failure and an LVEF higher than 50% typically show biomarkers that reflect systemic inflammation and evidence of endothelial injury and myocardial fibrosis. It is therefore noteworthy that, in these studies, patients with an LVEF of 40% to 50% exhibit a pathophysiological profile that closely resembles patients with an LVEF lower than 40%, but manifest a profile that differs from patients with heart failure and an LVEF higher than 50%.[6]

Benefit of Neurohormonal Antagonists in Patients With an LVEF of 40%-50%

The concept that patients with heart failure and an LVEF of 40% to 50% have similar clinical features as those with an LVEF lower than 40% is strongly supported by the results of several large-scale randomized trials that enrolled patients with preserved ejection fraction. Each trial enrolled patients who had chronic mild to severe symptoms of heart failure, including those with and without underlying coronary artery disease or hypertension.

The CHARM-Preserved trial[4] evaluated the effects of the angiotensin receptor blocker candesartan in 3023 patients with heart failure and LVEF higher than 40%. Compared with placebo, candesartan reduced the risk of cardiovascular death or hospitalization for heart failure in 1322 patients with LVEF of 40% through 49% (hazard ratio

[HR], 0.76 [95% CI, 0.61-0.96]), but not in 1953 patients with LVEF of 50% or higher (HR, 0.95 [95% CI, 0.79-1.14]).

Similarly, the TOPCAT trial[7] evaluated the effects of the mineralocorticoid receptor antagonist spironolactone in 3445 patients with LVEF of 45% or higher. The drug reduced the risk of cardiovascular death and hospitalization for heart failure in geographical regions where patients had heart failure and received the study medications, but this apparent benefit was confined to patients with LVEF lower than 50%. The HR for spironolactone was 0.55 (95% CI, 0.33-0.91) in the 197 patients with LVEF lower than 50%; 0.83 (95% CI, 0.56-1.25) in the 289 patients with LVEF of 50% to 55%; and 0.89 (95% CI, 0.69-1.15) in 858 patients with LVEF of 60% or higher.

Most recently, the PARAGON-HF trial[8] evaluated the effects of sacubitril-valsartan (vs valsartan alone) in 4822 patients with heart failure and LVEF of 45% or higher. The rate ratio for the effect of neprilysin inhibition on cardiovascular death and total hospitalizations for heart failure was 0.87 (95% CI, 0.75-1.01; $P = .059$). However, among 12 prespecified subgroup analyses, the HR for the effect of sacubitril-valsartan on the primary end point in 2495 patients with LVEF of 57% or lower was 0.78 (95% CI, 0.64-0.95) vs 1.00 (95% CI, 0.81-1.23) in 2301 patients with an LVEF higher than 57%.

In a patient-level meta-analysis of the results of 11 randomized, double-blind, placebo-controlled trials of β-blockers,[9] the HR for the association between β-blocker treatment and cardiovascular mortality was 0.48 (95% CI, 0.24-0.97) in the 570 patients with an LVEF of 40% through 49% in sinus rhythm vs 1.77 (95% CI, 0.61-5.14) in the 241 corresponding patients with an LVEF of 50% or higher. The association among patients with an LVEF of 40% through 49% was comparable to that seen in patients with an LVEF lower than 40%.

Conclusions

The current approach to classifying patients with heart failure based on the measurement of LVEF lacks a strong clinical, pathophysiological, or evidentiary basis. In particular, the concept that there exists a unique group of patients with an LVEF of 40% to 50% that differs from those with an LVEF lower than 40% is based on an arbitrary historical distinction. Patients who have "heart failure with a mid-range ejection fraction" do not have a unique pattern of symptoms or pathophysiology; the range of values for those with a mid-range LVEF is so narrow that delineation of the subgroup is inconsistent with the accuracy and reproducibility of the methods routinely used to assess systolic function in clinical practice. Furthermore, consistent evidence across several classes of drugs now indicates that treatments that are effective in reducing the risk of major adverse clinical outcomes in patients with an LVEF of 40% or lower are also beneficial in those with an LVEF of 41% to 50%.

The precise number of patients with heart failure and LVEF of 41% to 50% is not known. Yet it is important to emphasize that this proposal applies only to patients with LVEF of 41% to 50% who have established symptoms of chronic heart failure. Any role of neurohormonal antagonists in asymptomatic patients with such mild impairment of systolic function has not been evaluated or established.

The current approach of distinguishing patients with HFrEF from those with HFpEF based on a threshold of 40% reflects the consequences of a nonphysiological distinction made by clinical trialists 30 years ago. Reliance on such a threshold may deprive patients who truly have impaired systolic function and a subnormal LVEF from treatments that are likely to reduce morbidity and mortality. It appears reasonable for physicians to consider patients with an abnormally low LVEF and established symptoms of heart failure to belong to the same group, ie, heart failure with a reduced LVEF, and to provide such patients the benefits of treatment known to be effective in HFrEF. Based on the findings of clinical trials and the need to reduce the adverse consequences of heart failure on public health, serious consideration should be given to increasing the LVEF threshold for the use of evidence-based treatments from its current value of 40% to a value of 50%.

ARTICLE INFORMATION

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