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Heart failure with reduced, mildly reduced or preserved left ventricular ejection fraction: Has reasoning been lost?

Xanthopoulos A *et al*. HF with rEF, mrEF or pEF

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Abstract

The left ventricular ejection fraction (LVEF), defined as the left ventricular stroke volume divided by the end-diastolic volume, has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. HF has been classified into HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF using arbitrary, continuously changing LVEF cut offs. Further, a prerequisite for using this LVEF based terminology is knowledge of the LVEF normal range, which is lacking, and this may lead to erroneous conclusions in HF, especially at the higher end of the LVEF spectrum.

Key Words: Arbitrary; Cut off; Guidelines; Limitations; Normal left ventricular ejection fraction range; Phenotypic persistence

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Core Tip: The left ventricular ejection fraction (LVEF), has been consistently used for the diagnosis, classification, and management of heart failure (HF) over the last three decades. The LVEF based HF classification into HF with reduced LVEF, HF with midrange or mildly reduced LVEF, and HF with preserved LVEF has been based on arbitrary, ever changing LVEF cut offs. Further a prerequisite for using this terminology is knowledge of the LVEF normal range, which is lacking, and this may lead to erroneous conclusions, especially at the higher end of the LVEF spectrum.

TO THE EDITOR

The left ventricular (LV) ejection fraction (LVEF), defined as the LV stroke volume divided by the LV end-diastolic volume, is the only biomarker that has been systematically used for the diagnosis, classification, and management of heart failure (HF) over the last three decades[1]. Accordingly, HF has been classified into HF with reduced LVEF (HFrEF), HF with midrange or mildly reduced LVEF (HFmrEF), and HF with preserved LVEF (HFpEF) using various, continuously changing LVEF cut offs. Further, a mandatory prerequisite for the use of this LVEF based terminology is the definition of the normal LVEF range which is lacking. In this perspective we discuss the limitations related to the current LVEF based classification of HF and provide examples of erroneous conclusions that can be drawn, especially in HF patients at the higher end of the HF spectrum.

The LVEF based classification of HF was initially applied a few decades ago in the clinical trials of neurohormonal inhibitors in which LVEF cut offs of < 35% or 40% were chosen arbitrarily to define patients with HF perceived to be at greatest risk (HFrEF). Several years later, clinical trials with similar agents and end points were conducted in patients with HF with LVEF of ≥ 40% to 50% (HFpEF), but they were considered unsuccessful for diverse reasons[2,3]. Recently, another HF phenotype (HFmrEF) was added on the basis of under-representation of patients with HF with an LVEF of 40% to 50% in clinical trials. The LVEF cut offs used for HF classification have varied continuously in the guidelines issued by the scientific societies (Figure 1)[4]. The 2013 American College of Cardiology Foundation/American Heart Association guidelines defined HFrEF by a LVEF ≤ 40%, borderline HFpEF by a LVEF 41%-49% and HFpEF by a LVEF ≥ 50%[5]. In contrast, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines defined HFrEF and HFpEF by a LVEF < 50% and ≥ 50% respectively and did not recognize borderline HFpEF or HFmrEF as a distinct entity[6]. Further, in the recent Universal Definition and Classification of Heart Failure[7] which was adopted by the European Society of Cardiology[8], HF classification includes HFrEF with an LVEF of ≤ 40%, HFmrEF with

an LVEF of 41%-49%, and HFpEF with a LVEF of ≥ 50%. A little bit later, another classification of HF was proposed, which defines HFrEF by a LVEF < 40%, HFmrEF by 40% ≤ LVEF < normal, and HF with normal ejection fraction by a LVEF of ≥ 55% in men and ≥ 60% in women [9]. Reduced, mildly reduced, preserved or normal LVEF. However, which is the normal LVEF range? According to the 2015 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging the normal reference range for the LVEF is 52%-72% for males and 54%-74% for females[10]. The latest guidelines from the British Society of Echocardiography define as normal (preserved) a LVEF ≥ 55%[11]. However, several recent studies raise serious concerns regarding the normal LVEF range as proposed by the echocardiographic societies. Wehner *et al*[12], investigated the relationship between LVEF and survival by linking physician-reported LVEF on 403977 echocardiograms obtained from 203135 patients to all-cause mortality in United States and validated their findings in a dataset including 45531 echocardiograms and 35976 patients from New Zealand. During follow-up unadjusted hazard ratios for mortality showed a U-shaped relationship for LVEF with a nadir of risk at an LVEF of 60%-65% in both datasets and the results were similar after adjustments for conditions associated with an elevated LVEF, including mitral regurgitation, increased wall thickness, and anemia and when restricted to patients reported to have HF at the time of the echocardiogram (Figure 2). Slightly different but towards the same direction were the findings of another study including approximately 500000 participants, which reported that in both women and men, mortality was lowest at a LVEF level of 65.0%–69.9%[13]. However, in the same study sex dependent differences in the relationship between LVEF and mortality were observed. In women an increased risk for cardiovascular-related mortality persisted to a LVEF level of 60.0%–64.9%, whereas in men the equivalent LVEF level was lower (55.0%–59.9%) (Figure 3)[13]. Sex related differences were also reported in 4632 patients from the coronary computed tomography angiography evaluation for clinical outcomes: An international multicenter registry in whom LVEF was measured by cardiac computed tomography and participants were categorized according to LVEF (low <

55%, normal 55%–65%, and high > 65%)[14]. After 6 years of follow-up, no difference in mortality was observed in patients with high LVEF in the overall cohort. However, when data were stratified by sex, women with high LVEF died more often from any cause as compared to women with normal LVEF, while an opposite trend was observed in men [14]. Thus, the LVEF based terminology for HF classification is challenged based on recent evidence.

It is, therefore, not surprising that the LVEF based classification might lead to erroneous conclusions when interpreting the results of the various studies enrolling HF patients at the upper end of LVEF spectrum (Table 1). A typical example is the recently published Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-preserved trial), which reported a benefit with Empagliflozin (compared with placebo) in HFpEF defined by a LVEF > 40%[15,16] which is different from the 50% cut off recommended in the Universal Definition and Classification of Heart Failure[7]. It is noteworthy that in the EMPEROR-preserved trial ≈ 90% of the patients suffered from hypertension, ≈ 49% from diabetes, and ≈ 51% from atrial fibrillation. In contrast, in the study of Lupon *et al*[17], which was used as evidence supporting phenotypic persistence in HFpEF[18], a LVEF cut off of 50% was used and the patient characteristics were entirely different from those in the EMPEROR-preserved trial with approximately 12% of the participants suffering from hypertrophic cardiomyopathy and 36% from valvular heart disease. Thus, when interpreting these two HFpEF studies it would be challenging to extrapolate the findings of the one to the other. Therefore, no firm conclusions can be drawn regarding the effectiveness of empagliflozin or phenotypic persistence in HFpEF.

LVEF based classification of HF phenotypes has served as well over all of these years. However, HF is such a complex syndrome that no single marker can be used to classify those patients. Accumulating data from recent studies show that markers of contractility such as the longitudinal strain[19] and cardiac power[20] outperform the LVEF. The incorporation of artificial intelligence in diagnostic modalities, outcome-predictions, and management of HF (individualized precision medicine) constitutes a

major development in the field of cardiovascular medicine. In this regard, developing and validating universally accepted scoring systems based on AI would be a fruitful area of research. The LVEF has been considered the Holy Grail for HF classification treatment guidance for years. The time to be ejected has come unless one wants to justify those claiming that most published research findings are false[21].

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