Viewpoint

Rethinking the Definition of Heart Failure Based on Ejection Fraction: Reflections with Impact on Therapy

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The universal definition of heart failure (HF) has been in a state of constant change in the last decades. It is necessary for the definition to be simple, comprehensible, and easily applied in clinically, as well as capable of differentiating patients' stages and severity, allowing stratification of levels of care, especially regarding candidates for specific therapies.

In relation to ejection fraction (EF), which is the subject of our reflection, the most recent document proposed the following subdivisions according to left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF), EF ≤ 40%; HF with midrange ejection fraction (HFmrEF), EF 41% to 49%; HF with preserved ejection fraction (HFpEF), EF ≥ 50%; and HF with improved EF (HFiEF), HF with EF ≤ 40% that has increased by at least 10 points, with the second measurement reaching > 40%.[1]

Let's discuss a few problems regarding EF. To put it simply, LVEF reflects the percentage of blood ejected by the left ventricle in relation to the amount of blood present in this cavity. Let's consider a few aspects. First, we will discuss contractile reserve (CR), which reflects the difference between resting contractility and contractility under stress, whether induced by exercise (stress test) or pharmacologically induced (for example, dobutamine).[2] How many of us use stress echocardiography (echo) to calculate CR, that is, left ventricular performance under stress? In short, we know nothing about CR, and we are satisfied with the information about resting EF. Second, let's analyze ventricular dimensions versus the concept of function. In Figure 1, we have 4 examples with different left ventricular dimensions, which nonetheless generate the same systolic volume (SV). A smaller left ventricle (for example, aortic stenosis or hypertrophic cardiomyopathy), under stress, will attempt to increase the SV in a hyperdynamic manner. At the other end of the spectrum, we have a large, hypodynamic left ventricle, which adapts to stress conditions through cavity dilation. Notice that SV is the same with different EF values. What do they have in common? The inability to generate greater SV under stress conditions.[3] EF is not telling us much.

Third, let's talk about Simpson's method, which has been recommended for calculating EF. We used the apical, 4- and 2-chamber (Ap4c and Ap2c) views of the left ventricle, assuming various geometric shapes to calculate ventricular volumes and EF. What do we omit to calculate using this strategy? In addition to these formulas working in symmetrically contracting ventricles, the use of these two sections does not include the inferolateral wall of the left ventricle, studied in the apical longitudinal section (also called the tricameral section). In other words, to encompass the left ventricle as a whole, we need the three-dimensional method (3D echo).[4] How many of us receive EF calculated by 3D in our reports? What is the availability of 3D echo in clinical practice? How many studies of HF with ischemic etiology have been presented over the years, considering only the traditional Simpson method? And how many of these had left ventricular lateral wall infarction? Figure 2 exemplifies these problems.

Finally, let's remember that changes in left ventricular preload and afterload influence the calculation of EF.[5] The presence of mitral regurgitation is very common in the clinical setting of HF. What is the "ideal" EF in the presence of severe mitral regurgitation (Figure 3)?

In spite of all these limitations, EF estimated by echo remains the method of choice. This tool is practical, easily applicable, and widely disseminated in the literature. Resonance plays an important role in cases with technical difficulties to echo and/or in doubtful cases, but there are important limitations to using it on a large scale.[6]

Also, what is the reason for subdividing according to EF, in particular the concept of mid-range (HFmrEF)? Let's analyze the definitions of HF from the past five decades:[7-11]

- 1980 – 1990: Inability to pump the blood necessary for metabolic demands or only pumping the blood at the expense of increased left ventricular filling pressures, basically a hemodynamic classification.
- 1991 – 2000: We practically considered only the HFrEF model (the dysfunction that we had in mind was basically systolic).
- 2001 – 2010: The concept of HFpEF is developed. Even with preserved systolic function, HF is diagnosed in the presence of signs and symptoms, structural changes (left atrial dilatation, left ventricular hypertrophy), and elevated natriuretic peptides.
- 2011 – 2020: In this decade, large studies on HFrEF were based on EF < 40%, even though the guidelines'

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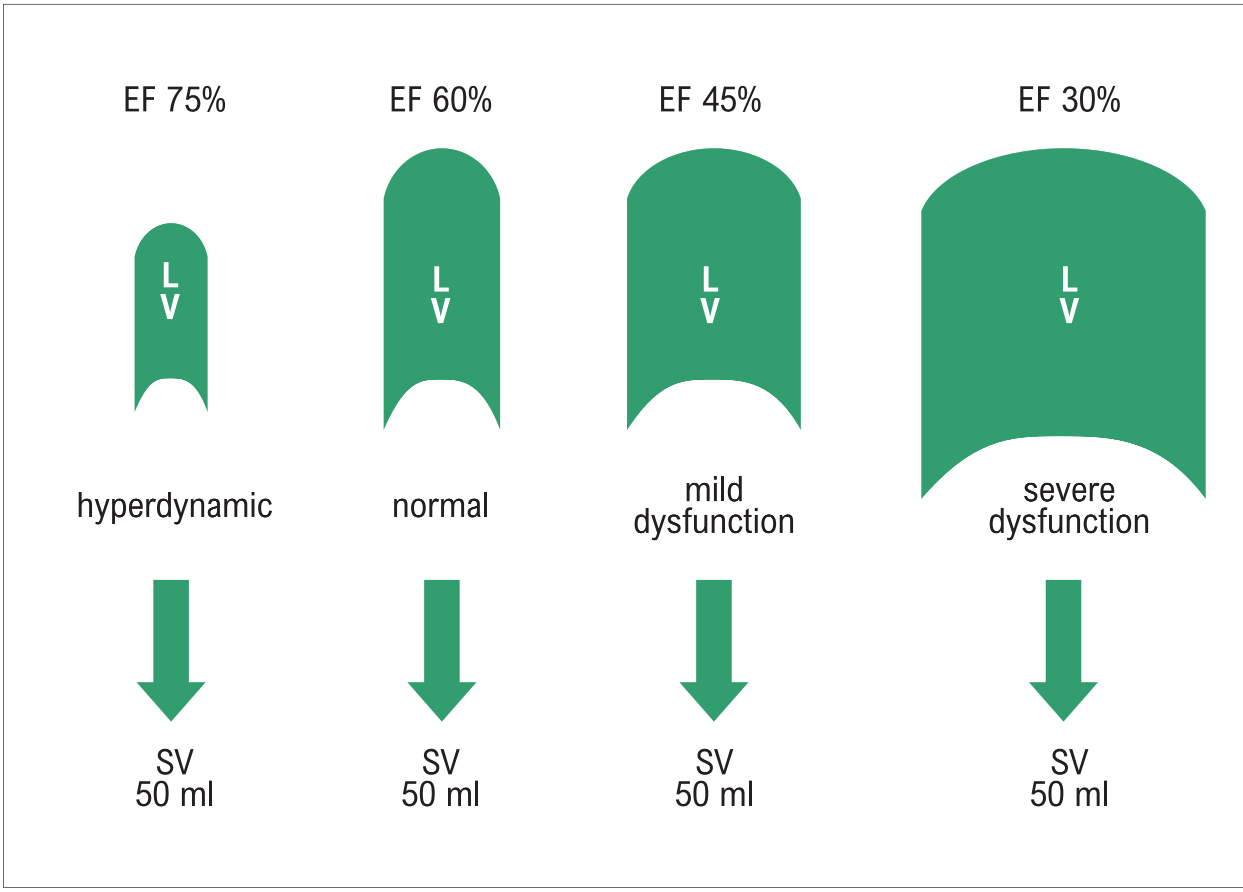
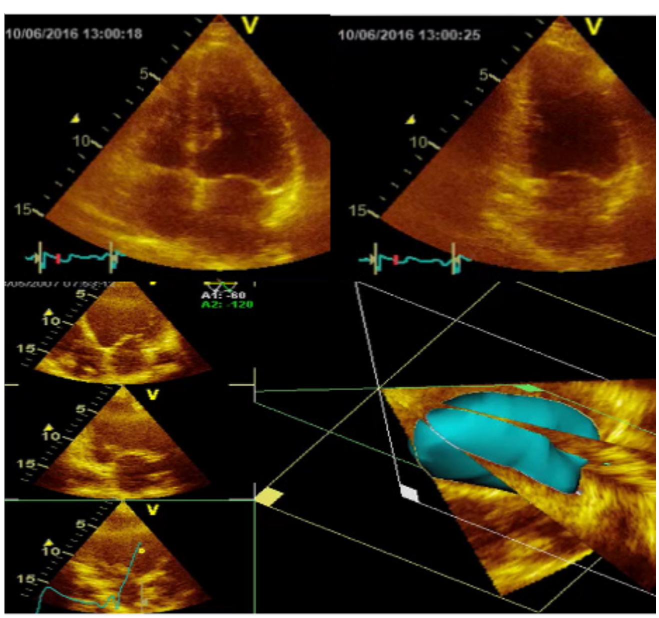


Figure 1 – *Schematic representation of different left ventricle (LV) sizes, with different ejection fraction (EF), which nonetheless generate the same systolic volume (SV)*



A – LVEF calculated by Simpson's method, using only Ap4c and Ap2c views.

B. LVEF calculated by the three-dimensional method, where cavity volumes are calculated in a global manner.

Figure 2 – *In image A, an example of calculation of left ventricular ejection fraction (LVEF) by Simpson's method. In image B, LVEF using the three-dimensional method.*

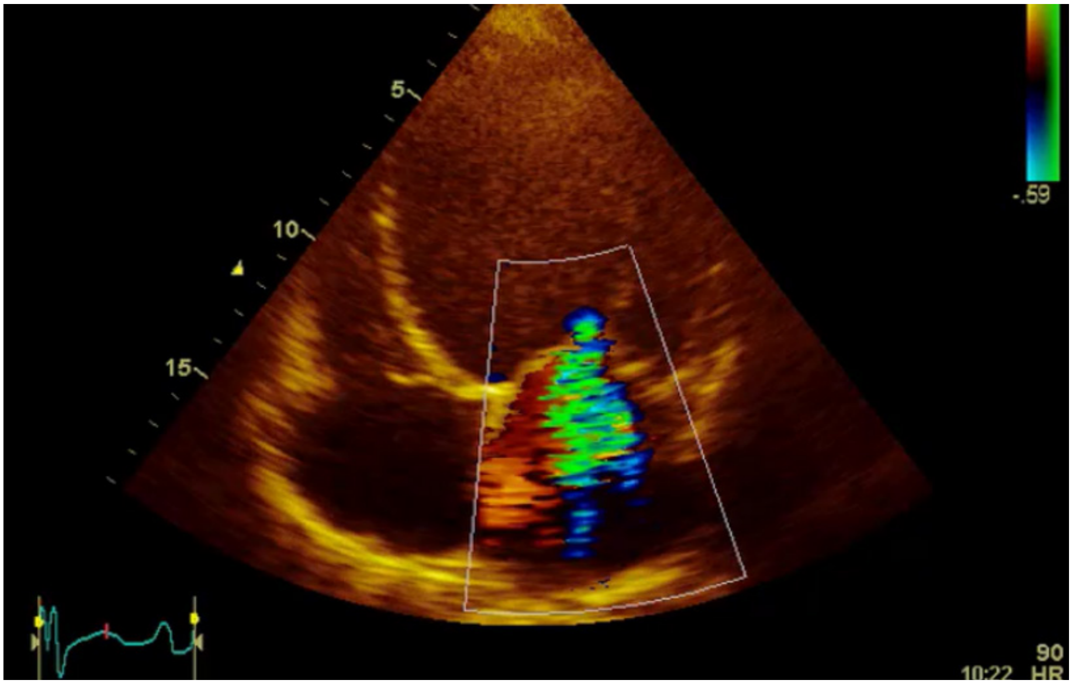


Figure 3 – *Mitral insufficiency secondary to valve ring dilation (tethering).*

definition had established EF < 50%. If we analyze the echo guidelines, the cutoff point is EF < 55%.

• 2021 – 2030: How will the next decade be? We have the following gap to study:

"Large studies of EF < 40% (HFrEF) versus EF > 50% to 55% (HFpEF)"

What happens in patients with intermediate ejection fraction? (EF 40% to 49%). The interest in this group, called HFmrEF, has gained strength, mainly after the results of the PARADIGM[12] study and, more recently, the PARAGON[13] study, both of which used sacubitril/valsartan instead of enalapril. Even in patients whose EF is still preserved, the closer to the lower limit of normality, the greater the benefits of the drug, especially in some specific scenarios, as demonstrated in women. Despite the favorable result in analysis of subgroups, in a syndrome as heterogeneous as HFpEF, when we are actually dealing with different diseases and different phenotypes, the strategy of studying intervention measures that can attenuate the evolution is always a challenge. If we cite only recent studies on HFrEF and HFpEF, we will see that the cut-off points in EF are quite heterogeneous, which makes it difficult to apply them in clinical practice.

The tool of EF will continue to be our main parameter; therefore, we must keep the following in mind: 1) EF is not a static parameter; it changes over time and with the evolution of the disease. 2) We need to consider other variables provided by echo, especially volume measurement. Hypervolemia is the main cause of decompensation in our patients. 3) How accurate is the method in differentiating EF 39% from EF 41%? This would place the patient in different categories, and the treatment decision will always be a clinical one. 4) How many of us actually receive estimated EF by Simpson's method (Figure 4)?

The evolution of imaging methods will certainly help us to standardize this important tool. Incorporating evaluation of left ventricular myocardial strain study in a friendlier manner and implementing predetermined machine learning algorithms[14] will play fundamental roles in the accurate determination and automated estimation of LVEF.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

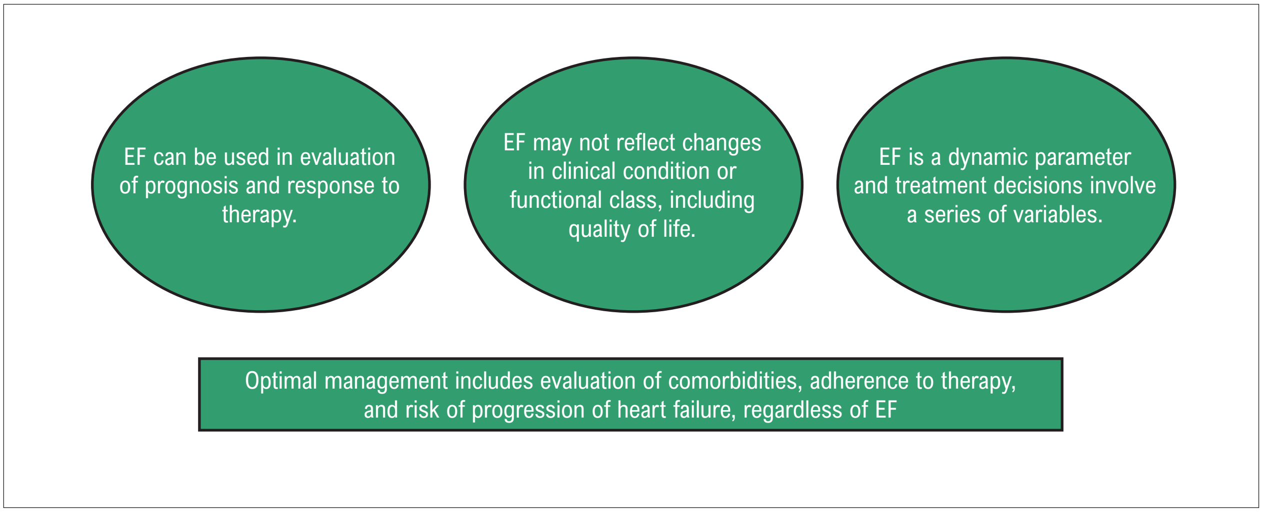

Figure 4 – *Ejection fraction (EF) in the context of heart failure.*

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