EDITORIAL COMMENT

LV Strain Superiority Over LVEF in HFmrEF

Is the Job Done After David's Victory Over Goliath?*

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Heart failure (HF) affects 64 million people worldwide and represents the first cardiovascular (CV) cause of hospitalization and one of the most common causes of death carrying a prognosis worse than many cancers. Since 1991, when the SOLVD trial was published, a threshold of left ventricular ejection fraction (LVEF) ≤35% has been used to define HF with reduced ejection fraction (HFrEF). Therefore, from that time, LVEF has been used as a referral point for characterizing HF, and based on this parameter, many classifications of HF have succeeded over the decades. In 2016, the Heart Failure Association of the European Society of Cardiology introduced the new entity of HF with a "mid-range" ejection fraction (LVEF 41%-49%) having as a major aim a better understanding and characterization of this HF population. This novelty had the major merit of stimulating research in the field, so that in the universal definition of HF, the HFmrEF group has been renamed as "mildly reduced ejection fraction" underlining the concept that this population was slightly more similar to HFrEF than to the Heart failure with preserved ejection fraction (HFpEF) population. Furthermore, in the universal definition has been created a new group HF with improved ejection fraction (HFimpEF) for describing one of the trajectories of the HFmrEF population, that is, that with HFrEF that improves and ameliorates after the start of drugs and devices recommended from HF guidelines.
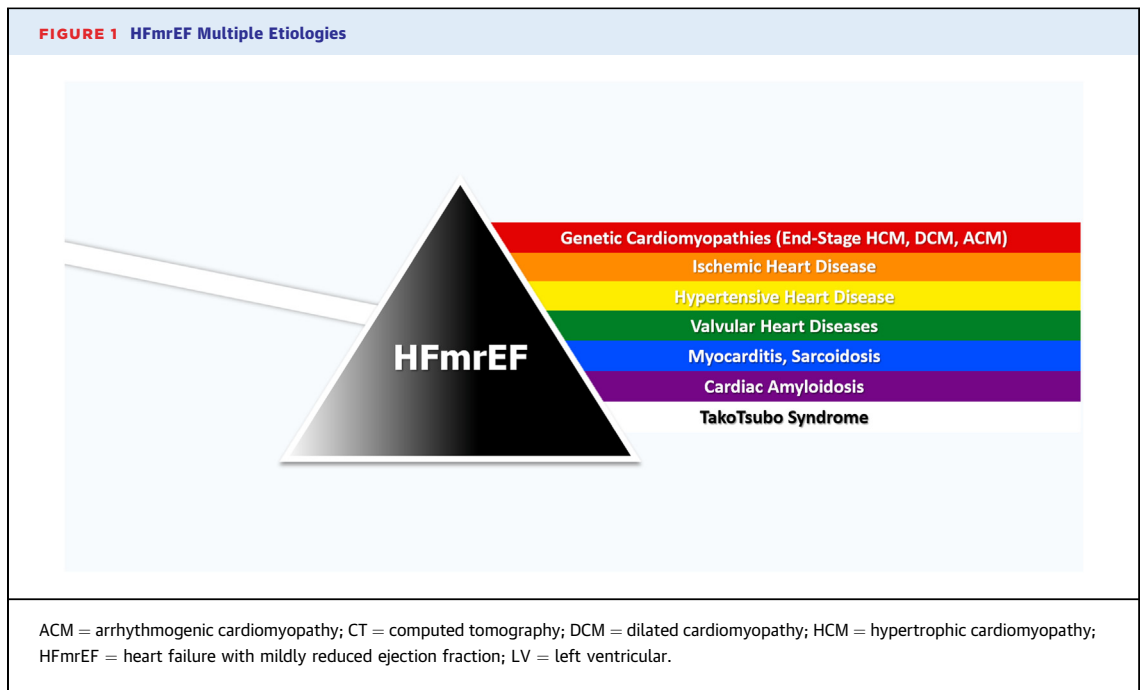
After 7 years of research, 2 main principles about HFmrEF have been identified, the first is that HFmrEF is a transition phenotype, indeed the majority of new-onset HF start as HFrEF and HFpEF and after they fall in the HFmrEF label accordingly to an improvement or to a deterioration of the LVEF, the second is that mortality after HF onset is very similar among the 3 groups and independent of LVEF.[1,2] Indeed, the HF population carries a very high risk of mortality that is related to the fact of having or not having HF across the full spectrum of LVEF. Therefore, the "time-honored" parameter, that is, LVEF, in HF showed to be a poor predictor of mortality. Despite this fact, the debate on new classifications of HF is still ongoing and every year we have a new proposal for reclassification.[3]

In this issue of *JACC: Advances*, Chung et al[4] presented their retrospective study where it has been compared the discriminative role of LV strain vs LVEF in 1,075 HFmrEF patients hospitalized for the first time in 2 centers in Asia. The authors demonstrated that a compromised LV strain was significantly associated with a higher risk of all-cause death, CV death, and hospitalization for HF (HHF), whereas LVEF failed in predicting this risk over a mean 1.8-year follow-up. Furthermore, the authors stratified LV strain (≥12.4% vs <12.4%) combined with the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) category and they found incremental prognostic values when compared to MAGGIC-LVEF strata. This study also showed some clinical features and comorbidities more frequent in the group with

FIGURE 1 HFmrEF Multiple Etiologies

ACM = arrhythmogenic cardiomyopathy; CT = computed tomography; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HFmrEF = heart failure with mildly reduced ejection fraction; LV = left ventricular.

compromised LV strain and that the HFimpEF group presents lower LV strain vs HFmrEF (non-HFimpEF) that comes from HFpEF deterioration or directly starts with a mildly reduced LVEF. Finally, the authors tried to use left ventricular strain as a tool to identify the HF patients who likely receive the most benefit from ARNI vs angiotensin converting enzyme inhibitor/ARB, and they speculated that the more compromised the left ventricular strain, the higher the benefit under ARNI.

Despite the manuscript having several limits—the major is the retrospective design that makes all the results about hard outcomes merely hypothesis generators—it confirms previous studies that demonstrated the superiority of LV strain across the full spectrum of HF phenotypes beyond the LVEF.[5] This finding has also previously been demonstrated in acute HF across the full spectrum of LVEF where global longitudinal strain showed to have greater prognostic value than LVEF.[6]

Therefore, when David defeats Goliath or in other words, when the LV strain proves its superiority over LVEF, will the job be done?

In reality, all these findings should be put in the correct perspective otherwise the unperceived risk is to substitute an older less performative parameter with a more recent one created by a new technology. Therefore, the risk is to repeat the mistake made with the LVEF in the science's attempt to follow technology when it should be the opposite.

Indeed, HF is just a diagnostic label for a very complex syndrome which is the final result of hundreds of diseases. Current phenotyping of HF should be multiparametric including advanced imaging such as cardiac magnetic resonance, cardiac CT, scintigraphy, and positron emission tomography, biomarkers, and new technologies for assessing and identifying subclinical congestion.

In the current scenario, there is a strong need for etiological phenotyping and characterization going beyond the superficial etiquette of HFrEF, HFmrEF, and HFpEF. The classification of HF based on LVEF is just a very initial starting point of a longer diagnostic work-up that lets physicians achieve that final specific diagnosis.[7]

Focusing only on HFmrEF, inside this diagnostic box there are several diseases, encompassing ischemic heart diseases, hypertensive heart disease, familiar/genetic dilated (or mildly dilated) cardiomyopathy, end-stage hypertrophic cardiomyopathy, valvular heart diseases, myocarditis, sarcoidosis, amyloidosis, Takotsubo syndrome, and many other etiologies (**Figure 1**).

Each etiology portrays different outcomes and different risks of death. For example, within HFmrEF with hypertrophic phenotype, cardiac amyloidosis portrays a higher mortality when compared to Anderson-Fabry disease or sarcomeric hypertrophic cardiomyopathy.[8] Dilated cardiomyopathy due to laminopathies carries a high risk of sudden cardiac

death even when LVEF is only mildly reduced.[7] Specific patterns of late gadolinium enhancement in myocarditis correlate with major cardiac events, as well sarcoidosis even in HFmrEF can have a high risk of malignant arrhythmias.[9] HFmrEF caused by an end-stage HCM portrays an 11.1% per year risk of death that is significantly higher when compared to HFmrEF caused by hypertensive heart disease and that underlies a significant amount and extent of myocardial fibrosis.[10]

This concept is important for developing specific therapies for specific etiologies beyond the 4 pillars (angiotensin receptor neprilysin inhibitor, sodium-glucose co-transporter type 2 inhibitor, beta-blocker, mineralocorticoid receptor antagonist) that demonstrated to reduce morbidity and mortality in HF. For example, making a diagnosis of cardiac transthyretin-related amyloidosis will prioritize the start of tafamidis. Moreover, the phenotyping should include also the vessels' function, and in particular that of arteries that currently are considered as mere bystanders (or "passive tubes"), whereas they cover an important and poorly studied role.[11]

A substudy of PARAGON-HF dedicated to LV strain showed that global longitudinal strain predicted CV death and HHF irrespective of LVEF but not independently from NT-proBNP, underlying the need for a multiparametric approach.[12]

Finally, sex differences are of paramount importance in the characterization and management of HF. This has been demonstrated by the PARAGON-HF trial, in which prespecified analyses showed a significant benefit of ARNI over ARB in HF patients with LVEF <57% and in women.[13] These results can be explained by the activation of different pathways in women such as the decrease of estrogen-dependent stimulation of natriuretic peptides after menopause

that cause a further reduction of the NO/cGMP pathway. ARNI demonstrated to activate this pathway that can be more beneficial in women than in men. A pooled analysis of PARADIGM-HF and PARAGON-HF confirmed this finding, and considering this, the FDA on February 2021 approved the indication of sacubitril/valsartan also for HFmrEF, while the response of EMA is still lacking. Beyond all these considerations, ARNI would have been already approved as a Class I indication both in HFmrEF and in HFpEF if PARAGON-HF[14] had used the same endpoint of DAPA-HF, that is, CV death/HHF and an urgent visit for HF.

In conclusion, using a single parameter to classify HF and select treatments for specific HF populations is an oversimplification already done with LVEF that in the long run showed all its many limits. Using new tools separately for repeating this mistake is not the way, while integrating them in a multiparametric approach to identify specific phenotypes is the key to developing new dedicated and patient-tailored therapies. Only SGLT2i represented the exception in HFmrEF and HFpEF achieving a Class I indication, likely for their multiple mechanisms of benefits.

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REFERENCES

1. Bayés-Genís A, Núñez J, Lupón J. Heart failure with mid-range ejection fraction: a transition phenotype? *Eur J Heart Fail*. 2017;19: 1635–1637.

2. Bhambhani V, Kizer JR, Lima JAC, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2018;20: 651–659.

3. Packer M. A reclassification of heart failure based on recognition of heart failure with normal to supernormal ejection fraction, a clinically common form of cardiac contracture, with distinctive pathophysiological and

therapeutic features. *Eur J Heart Fail*. 2023;25: 669–672.

4. Chung F-P, Chao T-F, Lee A-S, et al. Discriminative ability of left ventricular strain in mildly reduced ejection fraction heart failure. *JACC: Adv*. 2023;2:100654.

5. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *J Am Coll Cardiol Img*. 2018;11(2 Pt 1):260–274.

6. Park JJ, Park JB, Park JH, et al. Global longitudinal strain to predict mortality in patients with

acute heart failure. *J Am Coll Cardiol*. 2018;71: 1947–1957.

7. Seferović PM, Polovina M, Bauersachs J, et al. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21: 553–576.

8. Rosmini S, Biagini E, O'Mahony C, et al. Relationship between aetiology and left ventricular systolic dysfunction in hypertrophic cardiomyopathy. *Heart*. 2017;103:300–306.

9. Galati G, Leone O, Rapezzi C. The difficult diagnosis of isolated cardiac sarcoidosis:

usefulness of an integrated MRI and PET approach. *Heart*. 2014;100:89–90.

10. Galati G, Leone O, Pasquale F, et al. Histological and histometric characterization of myocardial fibrosis in end-stage hypertrophic cardiomyopathy: a clinical-pathological study of 30 explanted hearts. *Circ Heart Fail*. 2016;9:e003090.

11. Galati G, Germanova O, Iozzo RV, et al. Hemodynamic arterial changes in heart failure: a proposed new paradigm of "Heart and Vessels Failure (HVF)". *Minerva Cardiol Angiol*. 2022;70: 310–320.

12. Shah AA, Cikes M, Liu L, et al. Prognostic relevance of left ventricular longitudinal strain in HFpEF: insights from the PARAGON-HF Echocardiographic Sub-Study. *Eur J Heart Fail*. 2020;22(Suppl. S1):2–415.

13. Galati G, Sabouret P, Germanova O, et al. Women and diabetes: preventing heart disease in a new era of therapies. *Eur Cardiol*. 2021;16:e40.

14. Vaduganathan M, Cunningham JW, Claggett BL, et al. Worsening heart failure episodes outside a hospital setting in heart failure with preserved ejection fraction: the PARAGON-HF trial. *J Am Coll Cardiol HF*. 2022;9:374–382.