Left ventricular ejection fraction as the primary heart failure phenotyping parameter

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Heart failure (HF) is the most common cause of hospitalization and among the most common causes of death (1). Left ventricular ejection fraction (LVEF) measured by echocardiography has for decades been and remains the standard parameter for diagnosing and categorizing HF. Classification and treatment of patients remains based on the ejection fraction (2, 3). *Every time we encounter a patient with suspected or manifest heart failure, the first thing we ask is "what is the ejection fraction?"*

So it is surprising the extent to which LVEF and HF categorization based on LVEF has come under criticism in recent years (4-6). LVEF has limitations (4). With improved understanding of the complexity of the HF syndrome, and with improved clinical, biomarker, imaging, invasive hemodynamic, and composite score and big-data analytical tools to characterize HF, the LVEF has been increasingly viewed as too primitive. But in no instance have critics of the LVEF provided a validated alternative to LVEF. Decades of progress in HF treatment remain based on studies where reduced LVEF was the main inclusion criterion. In this viewpoint therefore, as has also recently been done by others (7), we provide a pragmatic rationale for why echocardiography with measurement of LVEF and categorization of HF into HF with reduced EF (HFrEF, LVEF≤40%); HF with mildly reduced EF (HFmrEF, LVEF 41-49%), and HF with preserved EF (HFpEF, LVEF≥50%) (2)remains the primary clinical tool in assessment of patients with suspected or manifest HF, until better and actionable alternatives emerge (**Figure**).

Is Echocardiography Useful?

Echocardiography is easy to perform, inexpensive, safe and can be performed without discomfort for the patient. Echocardiography provides an extensive array of structural and functional measurements. Parameters such as LV mass and left atrial size, myocardial strain and measures of LV diastolic function, right ventricular function and valvular heart disease are useful in characterizing patients with HF and potentially as adjunct eligibility criteria and surrogate endpoints in clinical trials. However, they are complementary to and do not substitute for LVEF (2).

Technological advancements are providing alternatives to echocardiography. However, echocardiography has also evolved, and is now widely available with small, portable and inexpensive devices for point-of-care ultrasonography (POCUS) (8). These are proving useful for reproducible point-of-care assessment of cardiac structure and function, but also of other parameters relevant in HF, such as lung ultrasound for interstitial fluid (B-lines) or pleural effusion (9). Interpretation of echocardiography has also evolved, with machine learning and artificial intelligence able to provide accurate automated LVEF measurements (10). Echocardiography is nearly universally available at least in high and medium income countries (11). Costs of standard transthoracic echocardiography (TTE) are highly variable but generally much lower in comparison to most medical diagnostics or therapeutics. Thus echocardiography remains a firmly established diagnostic technology in HF and cardiovascular medicine.

Is Left Ventricular Ejection Fraction Useful ?

The LVEF parameter is familiar to all clinicians regardless of training and specialty. Together with other structural and functional parameters from the echocardiogram (but even to some extent alone), it provides not definitive answers but important clues as to the etiology of, severity of, prognosis of, and therapeutic possibilities in HF. A common criticism is that LVEF is variable and the implication is that it is therefore unreliable. LVEF varies according to imaging technology and measurement methods. LVEF has inter- and intra-observer variability. When healthy volunteers had separate-day measurements the coefficient of variation was 11%, compared to 7% for cardiac magnetic resonance imaging (CMR). Interestingly, in this study the reproducibility of global longitudinal and circumferential strain was more reproducible with echocardiography than with CMR (12). In addition, measurements were on separate days. A well-established parameter of HF severity, such as NT-proBNP, has low variability when repeated on the same sample, but is very variable over even short periods of time in the same patient, and low values may be difficult to interpret in patients with HFpEF or obesity. A prospective study aimed at the use of changes in NT-

proBNP levels to predict and prevent acute HF events was stopped prematurely for slow enrolment and the belief that an algorithm for assessing natriuretic peptide trends was needed. BNP values were highly variable within a patient with dispersion between serial BNPs values of 39.3%, 57.7%, and 73.6% for 1, 60, and 120 days between measures, respectively (13). In another study, the intraindividual coefficient of variation of NT-proBNP levels measured at a 6 weeks interval was of 21.8% with a reference change value that may indicate a relevant change of 61.7% (14). LVEF for clinical trial entry has been reported to differ and often be higher when adjudicated as compared to reported by investigators (15), but some authors have argued that local interpretation in clinical trials is a strength since it reflects routine care and improves generalizability (7). Finally,

Is categorization of patients with HF according to LVEF useful ?

The definition of the HF syndrome does not require any specific cut-off for (or even knowledge of) LVEF. Categorization based on LVEF was dictated since the 1980's by clinical trial design requiring an LVEF generally below 30-40% (2). In patients with HF but a normal LVEF, diagnosis of HF was unreliable (and sometimes remains so). It was understood that patients with lower LVEF had greater HF severity and greater risk of cardiovascular and HF events, and thus enriching trials by setting cut-offs at LVEF 30-40% would ensure the presence of HF and reduce sample size and increase trial feasibility. In addition, it was believed that maladaptive neurohormonal activation was relevant predominantly in patients with lower LVEF. These considerations certainly proved prescient. They set the stage for an era of fantastically successful clinical trials in HFrEF, delivering immensely effective therapy for a common and severe syndrome and helping countless patients to better and longer lives.

Are the HFrEF (≤40%), HFmrEF (41-49%) and HFpEF (≥50%) categories useful?

Categorization of LVEF has been criticized because it is a continuous parameter that reflects a spectrum of HF characteristics and severity and therefore cut-offs are by necessity arbitrary.

However, the relation between LVEF and outcomes, namely mortality, is not linear but rather U-shaped, with higher mortality with lower EF, lower mortality with normal LVEF, and again higher mortality with with supranormal values (HFsnEF), above 70% (16). Even though it may have been necessary for enrichment, by excluding patients with HFmrEF from the landmark HFrEF trials, an opportunity was perhaps missed to provide effective therapy also for this group. Categorization of HF into HFrEF, HFmrEF and HFpEF (and more recently also into HF with improved EF, HFimpEF, and HF with supra-normal EF, HFsnEF) is a relatively recent development. The 2012 ESC HF guidelines defined LVEF in the range of 35-50% as a "grey area". Subsequent commentary largely considered this range as "the middle child" intermediate between HFrEF and HFpEF (17), and the 2016 ESC HF Guidelines coined a new term, HF with mid-range EF (HFmrEF). As intended, this new category prompted extensive clinical research and renewed interest in previously conducted and overall neutral randomized trials in HFpEF (≥40%, which included HFmrEF) (18). This research proved this classification to be prescient but that HFmrEF was "intermediate" in some but not in many other important respects, and led the 2021 ESC HF Guidelines to conclude that "patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF" (2).(18)

Finally and of great relevance for clinical care and clinical trials design, patients with HFmrEF appear to respond similarly to patients with HFrEF to neurohormonal antagonists (ACE-inhibitors and angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists [MRAs]); and neurohormonal modulators (the angiotensin-neprilysin inhibitor sacubitril-valsartan) (18). In post-hoc and sub-group analyses of HFpEF trials (which included patients with LVEF down to 40-45%), patients in the HFmrEF range had similar relative risk reduction (and because HFmrEF is milder, lower absolute risk reduction), generally on the order of 20% lower risk of the primary trial endpoint, as did patients with HFrEF in the analogous HFrEF trials. In contrast, patients with HFpEF derived no benefit at all. This was especially distinct in the CHARM programme (19), the beta-blocker meta-analysis consortium (20), and in PARAGON-HF (21). For MRAs, the TOPCAT trial hinted at a potential benefit among patients in the lower range of HFmrEF/HFpEF, but there are ongoing

trials with generic and proprietary MRAs that should determine whether MRAs are effective in HFmrEF, and potentially in HFpEF, with greater certainty.

For catheter-based, device, and surgical interventions in HF, the LVEF is an important component in the comprehensive assessment of potential indications. Decisions for advanced HF interventions are based on sophisticated multifactorial considerations beyond LVEF (22), but referral to advanced HF centers are very much determined by LVEF (23). Thus, not only has EF categorization proven useful, but the cut-offs for HFrEF, HFmrEF and HFpEF do also appear to be appropriate. The normal and lower limit of normal LVEF is around 62% and 52% in men and 64% and 54% in women, respectively (24). Drugs that appear effective in HFmrEF may possibly be effective also into the low 50% range, or even higher in women. There have been calls to return to using the term HF with normal EF (HFnEF) instead of HFpEF (25), but whether this should be 50% for reasons of consistency and practicality, or whether it should be higher and/or different in men and women remains a matter of debate.

One reason often suggested for why HFpEF trials failed has been that HFpEF is "heterogeneous". Indeed, the range of and confounding by comorbidities, age and frailty has confounded clinical trial design. For example, recently it has become clear that many patients with HFpEF have aTTR amyloidosis. These patients may benefit from specific therapy (2) and it has been assumed that they do not benefit from standard HF drugs, although recent exploratory data suggest that in fact they may (26). An alternative view may be that this perceived heterogeneity reflects inclusion of both HFmrEF and HFpEF, where HFmrEF resembles HFrEF, and HFpEF is different from but no more heterogeneous than any other category. According to this theory, HFrEF and HFmrEF are results of some initial myocardial injury, followed by maladaptive neurohormonal activation and secondary remodeling, whereas HFpEF is a consequence of long-standing comorbidity-driven systemic inflammation, leading to progressive changes in the heart as well as in other organs (27).

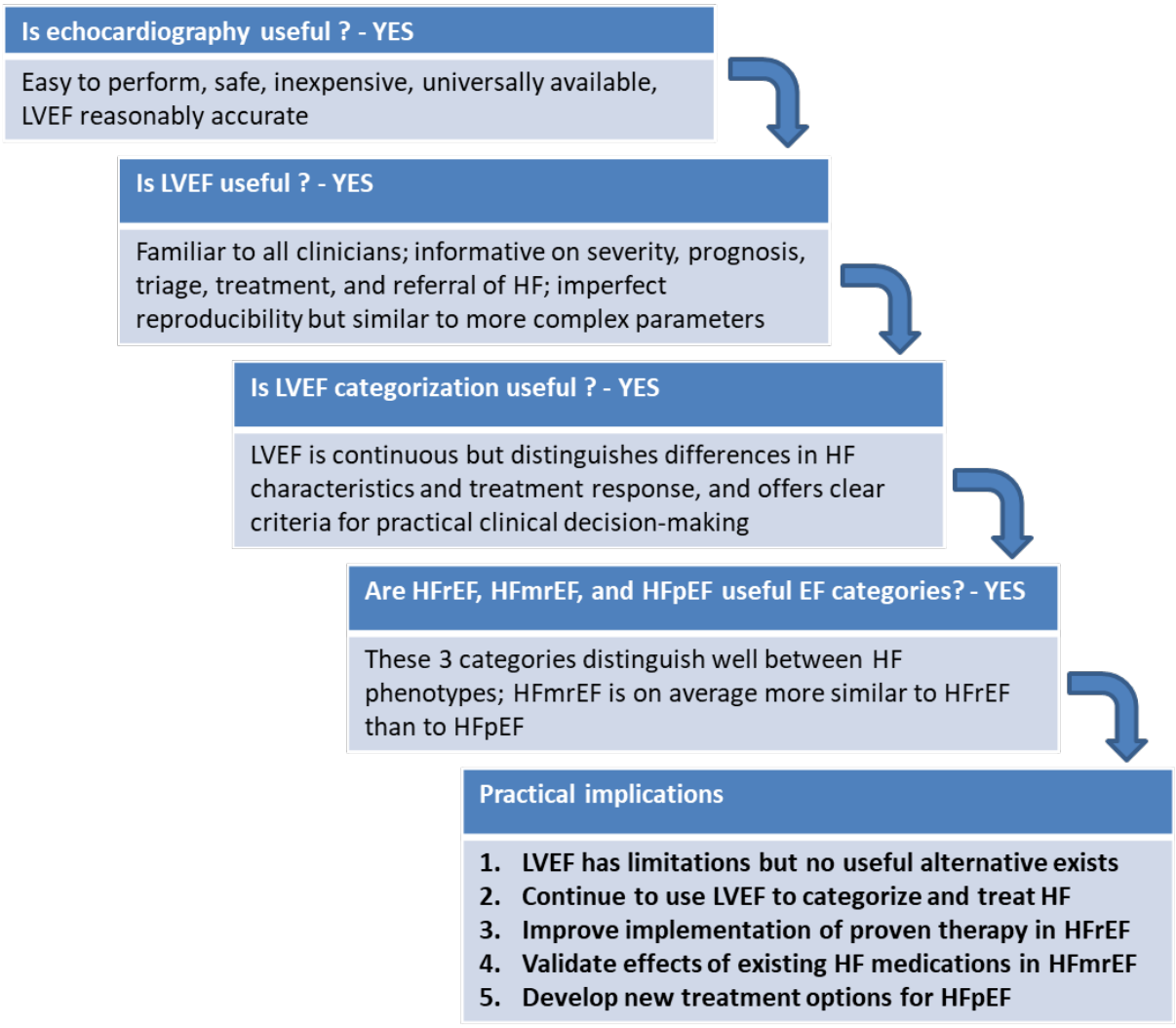
Recently, the SOLOIST trial demonstrated efficacy with the SGLT2/1-inhibitor sotagliflozin in patients with type 2 diabetes mellitus across the LVEF spectrum (28), and EMPEROR-Preserved

demonstrated efficacy of the SGLT2-inhibitor empagliflozin in HFmrEF and HFpEF (29). Thus SGLT2/1-inhibitors appear to be the first class of drugs effective in HF regardless of LVEF, which is consistent with the many putative mechanisms of action that extend well beyond neurohormonal antagonism and modulation, and targets the cardiac, kidney and vascular remodeling that occurs in HF generally, whether it is secondary to an initial myocardial injury as in HFrEF and HFmrEF, or part of the primary disease process in as in HFpEF.

Conclusions

LVEF is the most commonly used and comprehensive parameter for HF diagnosis, characterization, prognosis, monitoring, therapeutic decision making, and eligibility for HF clinical trials (**Figure**). LVEF categorization into HFrEF, HFmrEF and HFpEF has been criticized as arbitrary but has proven remarkably prescient, properly characterizing patients with HF into different etiologies, characteristics, risk of different cause-specific outcomes, and response to therapy. It is hard to imagine what more one could ask of a simple, inexpensive, safe and widely available clinical tool. Critics of the LVEF parameter have proposed many but not demonstrated utility of any alternative parameters to manage patients with HF. There are indeed many unmet needs in HF: wider implementation of proven HFrEF therapy, verification of potential effects of standard HF drugs in HFmrEF, and development of novel treatments in HFpEF; but a replacement for LVEF is not one of them. However, we still encourage the search and validation of new biomarkers that will add insight and predictive ability to subsets within the LVEF categories, HFrEF, HFmrEF and HFpEF.

FIGURE. Rationale for Continued Use of Left Ventricular Ejection Fraction in Heart Failure



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