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EDITORIAL COMMENT

The current classification of heart failure is obsolete

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A recent consensus document on the use of the left ventricular ejection fraction (LVEF) in the diagnosis and management of heart failure has suggested that, based on measurements of LVEF, patients may be classified into one of the following groups: HFrEF (heart failure with reduced LVEF ≤40%); HFmrEF (heart failure with mildly reduced LVEF 41%–49%); HFpEF (heart failure with preserved LVEF 50%–65%); HFsnEF (heart failure with supra-normal LVEF >65%) and, recognizing that LVEF often changes with treatment or disease progression, further classified as HFrecEF (heart failure with recovered LVEF); HFuncEF (heart failure with unchanged LVEF); and HFworEF (heart failure with worsening LVEF).[1]

These recommendations are designed to replace current heart failure guidelines that had only three categories: HFrEF, HFmrEF, and HFpEF.[2,3] Slicing LVEF into a complex, often arbitrary constellation of subgroups may not be in the best interests of science, medicine, doctors, or patients when the precision with which LVEF can be measured by echocardiography, the most widely used imaging method, is little more than 10%. The overlap amongst groups will be substantial. Indeed, a strong argument for the HFmrEF category is to allow clear separation of HFrEF from HFpEF by creating a zone of uncertainty where the clinician must exercise judgement in deciding the value of treatments indicated for HFrEF but not for HFpEF (e.g. beta-blockers).

A recent paper by Christersson *et al.*[4] illustrates some of the problems with the classification of heart failure using LVEF. They found that in 9716 new cases of heart failure with an available LVEF in Stockholm, Sweden, LVEF had a normal distribution rather than being neatly distributed according to the above LVEF thresholds. Moreover, the mean time spent before transition from HFmrEF to another LVEF category was, on average, <1 year, with <25% remaining in that category 1 year later. This follows on previous studies by Savarese *et al.*,[5] who found that 25% of those with HFrEF or HFmrEF appeared to improve by at least one category and that a third of those with HFmrEF or HFpEF appeared to deteriorate by at least one category in the following year. How much this reflects genuine change and how much reflects measurement error for patients already close to threshold values is unclear. These results are similar to those of Dunlay *et al.*,[6] who found that 39% of patients with HFpEF transitioned to HF with LV EF <50% during follow-up. Thus, for individual patients, LVEF values are often labile, passing through or oscillating amongst categories, either due to genuine changes in left ventricular function or to measurement error.

The concept of an LVEF trajectory is not new. As far back as 2007, a review suggested that the major difference between HFrEF and HFpEF (HFnEF at that time labelled as HFNEF -heart failure with a normal LV ejection fraction) was LV volume,[7] and that systolic and diastolic function were both impaired regardless of LVEF phenotype (*Table 1*). The review also suggested that 'LVEF was not a good measurement on which to base a classification that dichotomises patients with heart failure into two groups. Aetiology of cardiac dysfunction and the nature of remodelling (e.g. increased ventricular volumes or concentric hypertrophy) are clinically more useful approaches to classification'. Typical trajectories for the development of HFrEF following an acute myocardial infarction (MI), dilated cardiomyopathy, and for HFnEF due to hypertension, diabetes, and obesity are shown in *Figure 1*. In the same year (2007), De Keulenaer and Brutsaert[8] provided arguments against an LVEF-based bimodal view, suggesting that chronic heart failure is a single pathophysiology on a continuous spectrum. Ten years, later, in 2017, Konstam and Abboud[9] suggested that 'structural changes leading to increases or decreases in LVEDV will strongly influence the EF at a given level of contractility and stroke volume. EF change may not reflect contractility as much as it reflects ventricular remodelling'. Similar views were published in 2019 by Triposkiadis *et al.*[10]

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Conceptually, the trajectory of LVEF is heterogeneous, depending on the aetiology and severity of cardiac dysfunction, underlying disease progression, and the response to treatment.[4]

Table 1 Comparison of Heart failure with reduced LVEF with Heart failure with a normal LVEF

	HF with reduced LVEF	HF with normal LVEF
Gender	M > F	F > M
Age	50–60	60–80
Aetiology	Myocardial infarction Idiopathic DCM CKD	Hypertension, diabetes, AF, myocardial ischaemia, CKD
Clinical progress	Persistent HF	Often episodic HF due to onset of AF or other precipitating factors
Ventricular remodelling with increased LV volume	+++	0
LVH	+/–	+++
Dyssynchrony	common	Less common
Mitral inflow pattern	ARP or RFP	ARP
Peak mitral annular velocity GLS	Markedly reduced	Moderately reduced
LA pressure	Raised	Raised (especially on exercise)
LA volume	Increased	Increased

LVEF, LV ejection fraction; DCM, idiopathic dilated cardiomyopathy; AF, atrial fibrillation; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; ARP, abnormal relaxation pattern; RFP, restrictive filling pattern; GLS, global longitudinal strain (Modified from Sanderson[7]).

Despite this long concern about classification based on LVEF, guideline recommendations have not evolved substantially. This largely reflects the use of LVEF as an inclusion criterion for clinical trials showing the success or failure of treatments to improve outcomes. We now review the problems with using LVEF to classify patients, in particular for HFnEF, and we suggest a new simpler way of classifying HF patients based on cardiac volumes, both ventricular and atrial, and supplemented by biomarkers.

Basic principles of the left ventricular ejection fraction and misinterpretations

Left ventricular ejection fraction is LV stroke volume divided by LV end-diastolic volume (LVEDV). If stroke volume remains the same but the LVEDV increases, LVEF will be lower and, conversely, if the LVEDV becomes smaller due to concentric LV hypertrophy, the LVEF will be higher and may even become 'supra-normal'. For all LV phenotypes, until HF is severe, stroke volume will be fairly normal at rest; only during exercise does the failure of stroke volume to rise become apparent.[11] Thus, the measurement of LVEF is driven mainly by the LVEDV. Another aspect of LVEF is measurement accuracy.[10] Measuring one volume is moderately accurate. Measuring two volumes, subtracting them to derive stroke volume and then creating a ratio compounds errors in each measurement. Clinicians will usually make a visual estimate of LVEF but it is likely that what is being observed is an enlarged LV volume, which is then equated with a lower LVEF.

Heart failure with a normal/ preserved left ventricular ejection fraction

This was originally labelled as diastolic heart failure in guidelines until 2008, which at the time seemed reasonable, as it was assumed that a normal LVEF meant that the systolic function was normal and there was impaired diastolic relaxation or stiffness. However, in 2002, studies using Tissue Doppler imaging showed that long-axis systolic function, assessed by mitral annulus motion, was clearly abnormal in most

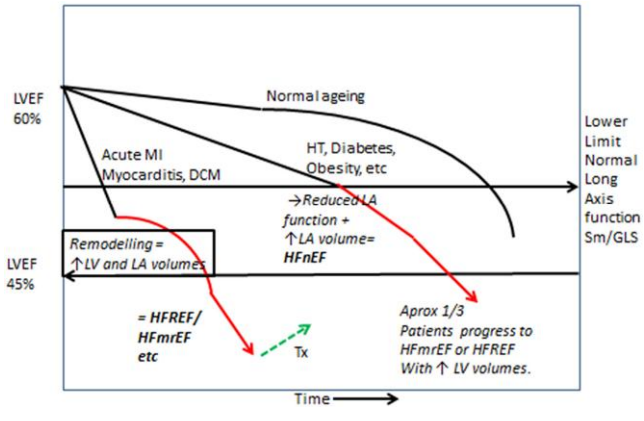

Figure 1 Heart failure phenotypes relate to the aetiology and the degree of remodelling of the left ventricle and left atrium. HFNEF, heart failure with normal ejection fraction; HFREF, heart failure with reduced ejection fraction; HFmREF, heart failure with mildly reduced ejection fraction; HT, hypertension; LA, left atrium; LV, left ventricle

A new classification of Heart Failure based on cardiac volumes

Is this heart failure?
[clinical suspicion may be aroused by symptoms and signs or by medical history (e.g. of myocardial infarction or long-standing hypertension or possible inherited cardiomyopathy)]
↓
BNP (and hsTroponin)
[note that symptoms and signs of congestion are not a pre-requisite for a diagnosis of heart failure]
↓
HF not excluded → Echocardiography
↓
Three groups for left sided disease (a similar algorithm can be used for right sided disease):

1. Enlarged LV & LA →
   - Loop Diuretics for congestion & GRMT for HFrEF & Treat Co-morbidity
2. Normal LV volume with enlarged LA →
   - Loop Diuretics for congestion & GRMT for HFnEF & Treat Co-morbidity.
3. Normal LV & LA volumes → Probably not heart failure
   - If in doubt, exercise to provoke symptoms and/or cardiac dysfunction
   - Consider other causes of symptoms such as obesity or respiratory disease.
   - Consider re-evaluation in 6-12 months

Note that cardiac dysfunction in the absence of evidence of congestion (enlarged atria & raised NT-proBNP) should not be termed 'heart failure'. NT-proBNP and atrial volume determine whether or not the patient has heart failure. LV volume and LVEF determine LV phenotype but are not required to make a diagnosis of heart failure. Other echocardiographic evidence of congestion may also be considered including IVC imaging, lung B-lines and ratio of jugular venous diameter during a Valsalva manoeuvre.

Further investigation (such as coronary angiography, investigations for amyloid, sarcoidosis and haemochromatosis) may be warranted to determine the underlying cause of heart failure if this will alter management, either a change in treatment or a change in advice about prognosis. Investigations done out of curiosity rather than because they will change management should generally be avoided. (the particular features of hypertrophic cardiomyopathy should be recognised).

A fourth uncommon form of HF is due to a high output. In this case LVEDV is large but LVESV is reduced or normal indicating increased contractility and increased stroke volume.

GRMT=guideline recommended therapy.

Figure 2 Simplified protocol for heart failure diagnosis and treatment based on left ventricular and left atrial volumes. GRMT, guideline recommended therapy

patients with 'diastolic' heart failure and the term HFnEF(heart failure with a normal LV ejection fraction) was created.[12,13] Later studies using strain techniques have confirmed these findings[11,14] and shown more complex abnormalities of LV systolic function in patients with HFnEF despite a normal LVEF.[11] Abnormalities at rest became more obvious on exercise, including a failure of stroke volume to increase and left atrial contractile function to improve.[11,15,16]

The term HFnEF was used in the 2007 European Society of Cardiology guidelines on heart failure.[17] However, the nomenclature was changed to 'heart failure with a *preserved* EF' based on the design of the compendium of CHARM trials that defined a reduced LVEF as ≤40% (i.e. HFrEF) and everything else as HFpEF.[18] However, the word 'Preserved' is inappropriate as LVEF is not preserved; quite the opposite as recent work has shown that it can change markedly in the same patient with HFpEF (preserved means 'maintaining something in its original or existing state'.)[19] However, the term HFpEF has persisted even in the latest consensus.[1] HFnEF is a more accurate description as there is general agreement that an LVEF of 55%–65% is in the

normal range, although some suggest it should be even more narrowly defined, because any deviation of LVEF from 60% to 65% is associated with a worse prognosis.[20] Over the last 20 years, there has been increasing realization that several conditions that are not primarily cardiac can produce this phenotype, including obesity and lung disease with an associated inflammatory state.[21] Systemic vascular stiffness (both arterial and venous) is also often increased, as is passive myocardial stiffness due to changes in the extracellular matrix and cardiomyocytes.[21] However, myocardial stiffness is usually measured at end-diastole, but it is the impairment of early diastolic filling that is important. It is not widely recognized that early diastolic filling is very dependent on the energy stored during the previous systole which drives the recoil and untwisting of the ventricle and creates ventricular suction (and causes the mitral valve ring to rise around the incoming blood from the left atrium [LA]).[11,22,23] Undoubtedly the decline of ventricular suction with age and disease has been overlooked in favour of the more easily measured 'stiffness' at end-diastole, forgetting that any chamber will be become 'stiff' if the pressure is high enough. Reduced early diastolic filling is compensated for by an increased atrial contribution (giving the commonly seen reduced mitral E and increased A waves—the abnormal relaxation pattern or ARP).

It is important to consider atrial volume and function both at rest and during exercise.[15,16] Patients become symptomatic when atrial systolic function fails to increase adequately to compensate for the loss of ventricular suction.[15] Increased LA size is a simple marker of both prolonged raised atrial pressure (and the possibility of incipient atrial failure) and therefore the basis for a diagnosis of heart failure in those with a normal LVEF.[24] Many patients with atrial fibrillation will have dilated atria but they also have raised plasma concentrations of natriuretic peptides and impaired exercise capacity suggesting that the diagnosis of heart failure has been missed, which accounts for why about twice as many patients with atrial fibrillation are prescribed loop diuretics than have a diagnostic record of heart failure.[25] Clearly, atrial fibrillation is also a key precipitant of clinically obvious heart failure. LA dilation indicates that the heart is failing regardless of whether the cause is myocardial or valve disease. However, the main difference between HFnEF and HFrEF is the size of the left ventricle (*Table 1*).

Heart failure with mildly reduced ejection fraction

Many early trials of heart failure required a low LVEF (≤40%; HFrEF) for inclusion, but many clinicians were uncomfortable with applying the term 'preserved' to an LVEF of 41%–49%. Indeed, investigator bias and measurement error meant that many patients with an LVEF of 41%–49% were included in trials that were supposed to be exclusively HFrEF. Recognizing that applying a single arbitrary threshold of 40% to a continuous range of LVEF, the term HFmrEF was coined to be applied to patients with an LVEF >40% but below the normal range (currently ≥50%).[1] Given the inaccuracy of measurement, placing a patient in a group with a 9% spread of LVEF (41%–49% inclusive) seems at best optimistic. Nonetheless, patients with HFmrEF share more features in common with HFrEF than with HFpEF, such as being somewhat more common in men, more often having a history of myocardial infarction and diabetes and, importantly, a greater LVEDV.[26] Furthermore, all of the main pharmacological treatments for HFrEF appear to work similarly well for HFmrEF, which is not the case for HFpEF, where the effects of these treatments are smaller, less certain, and may even be adverse (e.g. beta-blockers).[27]

Left ventricular remodelling with increasing left ventricular end-diastolic volume is the defining difference between the phenotypes of heart failure

After a myocardial infarction, complex changes in left ventricular function and volume occur (*Figure 1*), including recovery of stunned myocardium, an inflammatory reaction, neuro-hormonal activation, changes in the extracellular matrix and collagen, and fibrosis.[28] This leads to gradual enlargement of the LV. It is the presence and extent of ventricular dilation at end-diastole that is the distinguishing feature between the different LV phenotypes of heart failure, rather than LVEF and it is ventricular enlargement that is improved by many of the standard HF therapies used in HFrEF, either because they reduce congestion, or facilitate favourable remodelling or both. Therefore, the indications for these medications should be an enlarged LVEDV rather than a low LVEF. The normal range for LVEDV and other cardiac volumes is well established, but should be corrected for body size, which probably accounts for much of the difference between sexes.[29]

What is to be done?

The first question to answer is does the patient has the clinical syndrome of heart failure? Heart failure should be defined as cardiac dysfunction (based on imaging of ventricular and valve function) with congestion (based on natriuretic peptides, atrial size and function, and other extra-cardiac features of congestion).[30] Cardiac dysfunction, no matter how severe, that does not cause congestion (i.e. increased atrial pressure) is not heart failure. If cardiac function appears normal in the presence of distinctly abnormal blood biomarkers, this suggests that something has been missed, and further investigation should be considered. A useful pharmacological marker of congestion is treatment with loop diuretics. Many patients with a diagnostic label of HFpEF do not receive loop diuretics or have them withdrawn, and yet have no symptoms or signs of congestion and have a good prognosis. Many of these patients probably no longer have, or never had, heart failure.[31] Many patients are treated with loop diuretics but have not been investigated for or diagnosed with heart failure. These patients have a prognosis similar to patients with heart failure. Patients treated with loop diuretics should be investigated for heart failure unless there are good reasons not to do so (e.g. the patient is on a palliative care pathway).

Secondly, once a diagnosis of heart failure is made, the pathophysiology and aetiology should be assessed. The current classification based on LVEF and the terms HFpEF and HFmrEF should be re-considered. Left ventricular end-diastolic volume may be a better approach, classifying individuals into those with an enlarged, normal, or small LVEDV. Unfortunately, most HF trials did not report LVEDV at baseline or during follow-up, nor its ability to predict prognosis or therapeutic benefit (although this information must be available). However, a reduction in LVEDV is a key aspect of 'reverse remodelling'.[32,33] For instance, cardiac resynchronization therapy can cause a marked reduction in LVEDV, with 'super-responders' obtaining large clinical improvements.[30] Patients with an enlarged LVEDV should generally receive beta-blockers, angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNi), mineralcorticoid receptor antagonists (MRAs), sodium-glucose co-transporter 2 inhibitors (SGLT2) and, if congestion is symptomatic,

loop diuretics. Cardiac resynchronization therapy should be considered for those with a prolonged QRS duration and in sinus rhythm. Implantable cardioverter defibrillators should be considered if LVEDV remains grossly elevated despite guideline-recommended pharmacological therapy, provided symptoms and signs of congestion are adequately controlled. Those with a normal LVEDV and an enlarged LA should be given diuretics, MRAs, and SGLT2 inhibitors, but beta-blockers should be avoided. There is no evidence that patients with a normal LVEDV benefit from device therapy. Regardless of LVEDV, comorbidities, such as hypertension, iron deficiency anaemia, and atrial fibrillation, should be treated as appropriate.

This approach clarifies and simplifies the classification of heart failure and its management. Some treatments are best directed at congestion with little or no effect on cardiac function beyond reducing blood volume and atrial pressure, either by causing a diuresis or by reducing venous tone.[34] This therapeutic group includes diuretics, SGLT2i, and MRA. Although these agents might have ancillary actions, including potassium retention and anti-fibrotic actions for MRA[35] and anti-inflammatory and erythropoietic actions for SGLT2i,[36] these agents are effective primarily because they improve congestion regardless of LVEF. Relief of congestion might improve LV function slightly, but the effect is usually subtle and will disappear within days of stopping therapy unless underlying cardiac function has improved spontaneously or in response to disease-modifying therapies. A few patients with severe congestion might have a genuine congestive cardiomyopathy with gross tissue oedema, including the myocardium, accounting for the dramatic change in diuretic requirement sometimes observed after 'drying out' a severely congested patient. Other treatments are best directed at LV dilation and dysfunction, such as beta-blockers and cardiac resynchronization therapy. These interventions can have a profound effect on LVEDV and LV function. They will not work when LVEDV is normal, although beta-blockers may help with ventricular rate control regardless of LVEDV or LVEF. Beta-blockers do not improve congestion acutely and may make it worse. Some agents, such as digoxin, ACEi, and ARNi, probably improve both congestion and cardiac function and are most effective when both congestion and LV dilation exist (Figure 2).

It has taken a long time to get to this realization. This process has been summarized before 'All truth passes through three stages: First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident'.[37]

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Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data within this article is freely available.

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