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The continuous heart failure spectrum: moving beyond an ejection fraction classification

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Randomized clinical trials initially used heart failure (HF) patients with low left ventricular ejection fraction (LVEF) to select study populations with high risk to enhance statistical power. However, this use of LVEF in clinical trials has led to oversimplification of the scientific view of a complex syndrome. Descriptive terms such as 'HFrEF' (HF with reduced LVEF), 'HFpEF' (HF with preserved LVEF), and more recently 'HFmrEF' (HF with mid-range LVEF), assigned on arbitrary LVEF cut-off points, have gradually arisen as separate diseases, implying distinct pathophysiologies. In this article, based on pathophysiological reasoning, we challenge the paradigm of classifying HF according to LVEF. Instead, we propose that HF is a heterogeneous syndrome in which disease progression is associated with a dynamic evolution of functional and structural changes leading to unique disease trajectories creating a spectrum of phenotypes with overlapping and distinct characteristics. Moreover, we argue that by recognizing the spectral nature of the disease a novel stratification will arise from new technologies and scientific insights that will shape the design of future trials based on deeper understanding beyond the LVEF construct alone.

Keywords

Heart failure • Ejection fraction • Pathophysiology • Endothelium

Introduction

Heart failure (HF) is a progressive, multi-factorial, and heterogeneous syndrome, in which important therapeutic progress has been made based on clinical trials.¹ These trials were initially designed predominantly on logistics more than on pathophysiological considerations, aiming to increase the statistical power and to limit trial costs, by enrolling patients with poor prognosis based on low left ventricular (LV) ejection fraction (LVEF).² These practical enrolment criteria, however, had a profound impact on how we perceive the complex syndrome of HF. Clinical diagnosis, management and even basic physiological research has been inseparably linked to LVEF, which has become the foundational biomarker to classify HF. Connotations like 'HFrEF' (HF with reduced LVEF), 'HFpEF' (HF with preserved LVEF), and more recently even 'HFmrEF' (HF with mid-range LVEF), have now emerged as distinct 'disease' entities, and have been studied as if unrelated syndromes, separated by arbitrary LVEF cut-offs.³

In this article, we challenge the epidemiological, clinical, mechanistic, pathophysiological, and therapeutic basis for classifying HF solely according to LVEF. Left ventricular ejection fraction-based taxonomy of HF and its implications have been criticized.^{4–6} Here, we advocate the consideration of HF as a syndrome across a spectrum of phenotypes, in which each patient follows a unique trajectory based on the initial trigger(s), the genetic, clinical, and sociodemographic background, and available treatment. As HF progresses, the heart remodels causing functional and structural 'biomarkers' to evolve in unique patterns with levels differing among patients without specifying HF subpopulations. This creates a spectrum of overlapping HF phenotypes necessitating the design of clinical studies based on deeper pathophysiological reasoning.

In this manuscript, we present a consensus opinion authored by 42 scientists studying HF in diverse ways, both clinically and fundamentally. These scientists interacted with each other on several occasions and shared concerns about current HF taxonomy. A few authors took the initiative to summarize arguments, which resulted in a consensus document after several months of intense interactions and input by all authors.

Left ventricular ejection fraction-based taxonomy of HF is imprecise and incomplete

Left ventricular ejection fraction has imprecise physiological implications

Left ventricular ejection fraction is the stroke volume (SV) expressed as a fraction of the LV end-diastolic volume (LVEDV). A normal LVEF simply indicates that the SV is appropriate for the LVEDV and vice versa.⁷ In acute myocardial infarction, the reduction in contractility results in a decreased SV in the presence of relatively normal LVEDV, resulting in reduced LVEF. However, LVEF is also dependent on loading conditions which becomes especially important in conditions such as mitral regurgitation, aortic stenosis, etc., that alter ventricular preload or afterload.^{5,8} Furthermore, LVEF may be preserved or even augmented in patients with LV hypertrophy even in the presence of myocardial systolic dysfunction. Although circumferential strain is not always reduced in patients with HFpEF compared with age-matched controls, global longitudinal strain is often reduced.⁹ As a result, myocardial strain has been increasingly advocated as a complementary metric to LVEF.⁶

Substantial variability between LVEF measurements modalities

There is substantial variability between imaging modalities for LVEF measurement. In a study including 2032 patients with LVEF \leq 35%, the correlation between modalities was modest.¹⁰ Bland-Altman plots showed moderate agreement in LVEF measurements with no consistent overestimation or underestimation by any modality (Figure 1). One might argue that this weakness can be overcome by establishing one imaging modality for the measurement of LVEF in HF patients. For echocardiography, however, which is the most common imaging modality, intra-observer and inter-observer reliability of LVEF assessment is only reasonable among highly experienced echocardiographers with an intra-class correlation coefficient of only 0.78.¹¹ In addition, as mentioned by Pelikka *et al.*, even the clinically most accessible method to quantify LVEF in daily practice (biplane Simpson method by echocardiography) is feasible in only 46%.¹⁰

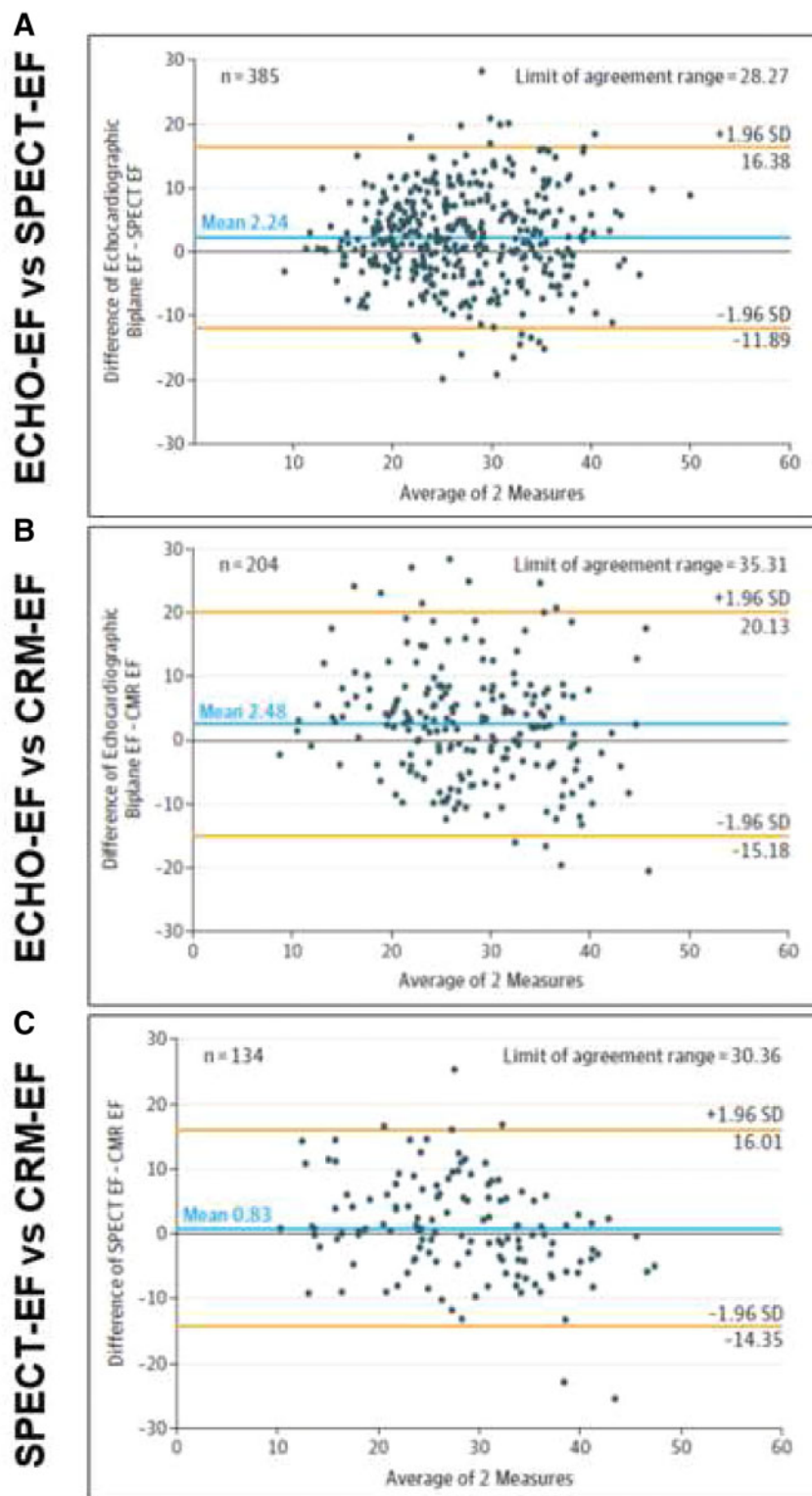


Figure 1 Variability in left ventricular ejection fraction (EF) measurements. Bland-Altman plots for EF compared for biplane Simpson method by echocardiography and gated single-photon emission computed tomography (SPECT) (A), biplane Simpson method by echocardiography and cardiovascular magnetic resonance (CRM) (B), and SPECT and CRM (C). Modified from Ref.¹⁰

Left ventricular ejection fraction cut-offs are arbitrary

International HF guidelines use varying cut-offs and LVEF-based taxonomy, illustrating the disadvantage of using a continuous variable of vague pathophysiological significance to an ordinal variable in order to describe different HF phenotypes. The American College of Cardiology Foundation/American Heart Association guidelines categorize patients as HFpEF ($\geq 50\%$) and HFrEF ($\leq 40\%$). Left ventricular ejection fraction 41–49% is defined as borderline HFpEF, whereas LVEF $>40\%$ in patients with previous HFrEF is defined as HFpEF-improved.¹² The European Society of Cardiology guidelines classify patients as HFrEF ($<40\%$), HFmrEF (40–49%), and HFpEF (LVEF $\geq 50\%$).³ Finally, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines classify HFrEF as $<50\%$ and HFpEF as $\geq 50\%$ and do not recognize HFmrEF as a distinct entity.¹³ Interestingly, none of these guidelines classify acute HF based on LVEF.³ A plausible explanation is that outcomes following hospitalization for acute HF are poorly related to LVEF.¹⁴

Left ventricular ejection fraction transitions

Several studies indicate that during the HF disease journey, bidirectional LVEF transitions occur, which may lead to patient misclassification and failure to implement the appropriate treatment.⁶ In one community, cohort of incident HF patients LVEFs were assessed by echocardiography from initial HF diagnosis until death or last follow-up.¹⁵ In those with HFpEF, LVEF decreased by 5.8% over 5 years with greater declines in older individuals and those with coronary disease. Conversely, LVEF increased in HFrEF on average by 6.9% over 5 years. Overall, 39% of HFpEF patients had a LVEF $<50\%$ and 39% of HFrEF patients had a LVEF $\geq 50\%$ at some point after diagnosis. Decreases in LVEF were associated with reduced and increases with improved survival.¹⁵ Up to 25% of treated HFrEF patients show LVEF recovery.¹⁶

In another study, 2413 HF patients had ≥ 2 LVEF measurements after discharge separated by ≥ 30 days.¹⁷ In total, 8183 LVEF transitions were observed. Women and patients adherent to β -blockers were more likely to transition from low to normal LVEF. Patients with previous myocardial infarction were more likely to transition from HFpEF to HFrEF.¹⁷ Clinically relevant LVEF transitions were also observed in the Swedish Heart Failure Registry.¹⁸ Finally, in a prospective registry of HF outpatients¹⁹ long-term LVEF trajectories showed a marked rise during the first year, maintained up to a decade, and a slow decline thereafter.

Right ventricular dysfunction/failure

The right ventricle (RV) and LV share common characteristics when they adapt to adverse loading or when they fail. Moreover, through shared myocardial fibres, the interventricular septum and the common pericardium, LV contraction contributes to RV pressure development, and RV loading affects LV function.²⁰ Thus LVEF may be affected by RV dysfunction.

In conclusion, the above data support the view that classification of HF patients based on LVEF has serious limitations.⁴

Epidemiological, clinical, pathophysiological, and therapeutic features are common across the HF spectrum

In this section, we will outline that despite the differences between HF patients over the LVEF spectrum, patients with HF also share many epidemiological, clinical, and pathophysiological characteristics regardless of LVEF. A disadvantage of LVEF-based HF classification is that it separates overlapping groups of patients as if they would be unrelated.

Left ventricular systolic and diastolic dysfunction and left atrial dysfunction

Both diastolic and systolic dysfunctions are found in HF independent of LVEF. Brucks et al.²¹ studied 206 patients with HF and 72 age-matched controls. Diastolic dysfunction was present in $>90\%$ of patients independent of LVEF. Increased passive stiffness of cardiomyocytes related to hypophosphorylation of the protein titin²² occurs both in HFpEF and HFrEF.^{23,24}

Systolic function may be impaired in patients with LVEF $\leq 40\%$ and those with $\geq 50\%$. Tan et al.²⁵ reported reduced ventricular systolic strain, reduced systolic and diastolic longitudinal functional reserve, reduced ventricular systolic twist and delayed ventricular untwisting, and reduced rise in SV on exercise in HFpEF. Kraigher-Krainer et al.²⁶ demonstrated that HFpEF patients had lower longitudinal and circumferential strain compared with normal controls and hypertensive patients. In another HFpEF trial population, LV global longitudinal strain was abnormal in 65% of patients.²⁷

Left ventricular dysfunction is associated with left atrial (LA) dilation and mechanical failure, frequently resulting in atrial fibrillation. Left atrial mechanical failure is accompanied by LA endocrine failure, contributing to volume overload.²⁸ Left atrial mechanical dysfunction is present both in HFpEF and HFrEF and associated with pulmonary hypertension and right-sided HF. Left atrial volume and function predict HF outcomes regardless of LVEF.²⁸ Increased LA size and dysfunction are associated with impaired exercise capacity both in HFpEF and HFrEF.^{29,30}

Thus, systolic and diastolic myocardial dysfunctions frequently co-exist in HF regardless of the LVEF and result in atrial dysfunction, present across the HF spectrum. Myocardial strain measurements have endorsed this concept.

Comorbidities

It has been argued that a LVEF-based classification of HF is tracked by the distribution of comorbidities that are directly linked to a pathophysiological framework for HFpEF.²² The term *comorbidity* is often interchangeably used with the terms *risk factor* and *disease modifier*, and this creates significant misinterpretations.³¹ Differences are known regarding the prevalence of risk factors for HFpEF and HFrEF (e.g. hypertension, obesity, and coronary artery disease) and disease modifiers (e.g. sex and age). However, these differences are quantitative and as such there is clearly no risk factor or disease modifier unique for HFpEF or HFrEF.³² Results of the studies assessing the prevalence of comorbidities (e.g. anaemia, chronic kidney disease,

ENDOTHELIAL ACTIVATION and DYSFUNCTION IN HEART FAILURE

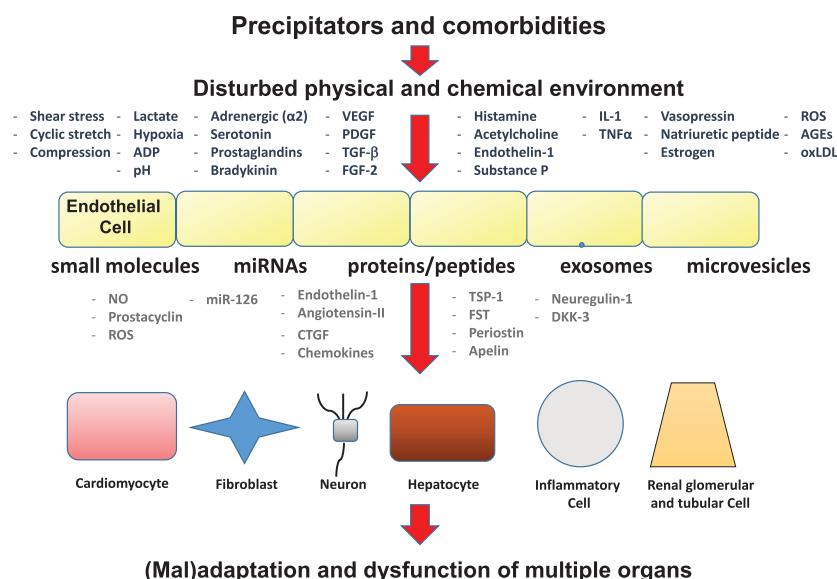


Figure 2 Endothelial physiology: more to say than just NO. Schematic figure illustrating the putative role of endothelial cell activation and dysfunction in heart failure. Albeit too often restricted to an interaction between endothelial cells and adjacent cells through nitric oxide (NO), the physiology of the endothelium and its role in the pathophysiology of heart failure very complex. Endothelial cells have a sensing function to detect changes in the mechanical (shear stress, cyclic stretch, and compression), chemical (lactate, hypoxia, ...) and neurohormonal (endothelin-1, acetylcholine, ...) environment, and an effector function by the release of many bioactive factors (prostacyclin, endothelin, neuregulin, ...) influencing targets cells in many different organs. When endothelial cells become dysfunctional, such as in heart failure, homeostatic balances in virtually each organ system will be affected in a pleiotropic fashion. For more detailed information, we refer the reader to Ref.⁴⁰ ADP, adenosine diphosphate; AGE, advanced glycation end products; CTGF, connective tissue growth factor; DKK-3, Dickkopf-related protein 3; FGF, fibroblast growth factor; FST, follistatin; IL-1, interleukin-1; miR, microRNA; NO, nitric oxide; oxLDL; oxidized low density lipoproteins; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TGF, tissue growth factor; TNF, tumour necrosis factor; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor.

chronic obstructive pulmonary disease, etc.) in HF subtypes were inconsistent.^{32–34} Comorbidities were highly prevalent both in HFpEF and HFrEF and similarly correlated with symptoms and outcomes.³⁵ Treating comorbidities may prove beneficial across the LVEF spectrum.

Regarding risk factors there is substantial overlap between incident HFpEF and HFrEF.³⁶ An example depicting this complexity is visceral adiposity, which is related to three HF phenotypes (HFpEF, HFrEF, and high-output HF), related to activation of the leptin-aldosterone-neprilysin axis.³⁷

Endothelial dysfunction and cardiomyocyte injury

HFpEF is proposed to be driven by coronary microvascular endothelial inflammation and oxidative stress, induced by comorbidities, whereas HFrEF by cardiomyocyte loss.²² Although this may be true at the extremes of the LVEF spectrum, endothelial dysfunction is not a specific pathophysiological characteristic of HFpEF and cardiomyocyte death is not a specific phenomenon for HFrEF. Endothelial dysfunction is common in HF regardless of LVEF,^{38,39} and seen in all circulatory beds, involving microvasculature, large conduit, and small resistance vessels.^{38,40} This widely

proposed HFpEF paradigm couples endothelial dysfunction with diastolic dysfunction related to the disturbed nitric oxide (NO)-cGMP-protein kinase G pathway. Endothelial cells, however, secrete numerous cardio-active proteins besides NO (Figure 2) and some of these contribute to LV remodelling over the whole LVEF spectrum. Thus, the role of endothelial dysfunction in HF extends beyond NO.^{41,42} It is noteworthy that recent HFpEF trials aiming at improving symptoms targeting the NO/cGMP pathway were negative, suggesting that endothelial dysfunction in HF is more complicated than originally anticipated and to date remains an attractive but still unproven therapeutic target.^{43–45}

Similarly, although not all HF patients suffer from cardiomyocyte injury, signs of cardiomyocyte injury can be found in patients with HF throughout the HF spectrum, independent of LVEF. Levels of cardiac troponin (cTn) T may be elevated in both HFrEF and HFpEF.⁴⁶ High sensitivity (hs)-cTnI and hs-cTnT⁴⁷ are associated with all-cause mortality or HF hospitalization in HFpEF and HFrEF.⁴⁸ In a recent study of HFpEF patients,⁴⁹ cTn was greater than two-fold higher compared with controls in subjects with HFpEF at rest and during exercise and correlated with LV filling pressures. Finally, hs-cTn levels predicted both incident HFrEF and HFpEF in a pooled analysis of 22 756 subjects at risk for developing HF.⁵⁰

The Heart Failure Spectrum

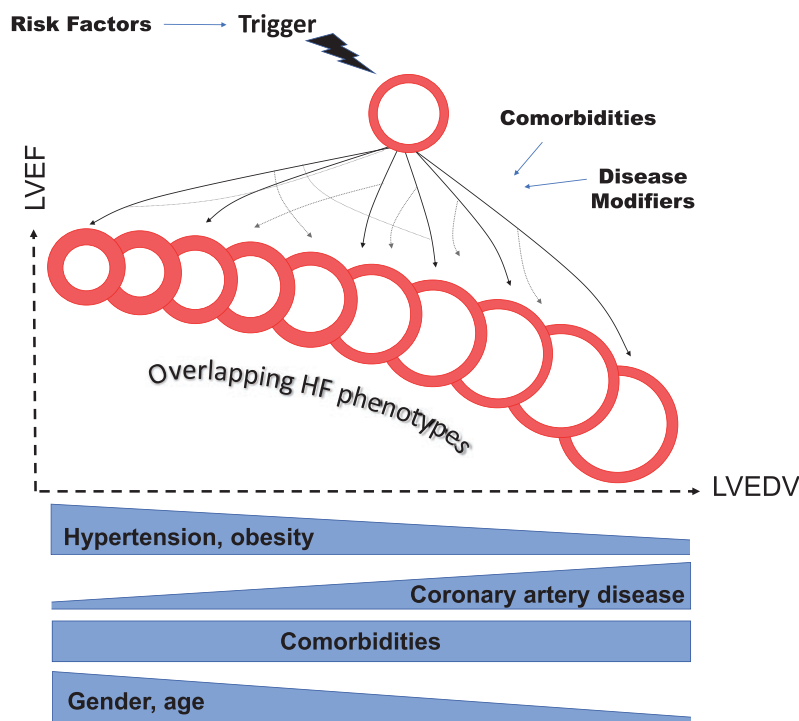


Figure 3 Heart failure a spectrum across phenotypes. Each heart failure phenotype is the result of a patient-specific trajectory wherein the heart remodels towards concentric hypertrophy, eccentric hypertrophy, or a combination of both. The way of entry and the subsequent path of the trajectory depend on the patient's risk factor(s), comorbidity(ies), and disease modifiers. Risk factors are disease entities that always precede the development of heart failure and are associated with an increased heart failure incidence. Comorbidities may precede or develop after heart failure and usually coexist with heart failure in groups of two or more (multi-morbidity). Modifiers are specific patient characteristics that contribute to the development of the entry phenotype and heart failure progression. Across the heart failure spectrum left ventricular ejection fraction variability relates with left ventricular end-diastolic volume in a non-linear relationship. Despite quantitative differences between the extreme left and right sides of the spectrum, there is important overlap between the phenotypes along the entire spectrum. Any subdivision of the spectrum by a single biomarker is artificial. Afib, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM-II, type II diabetes mellitus; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnoea syndromes.

Neurohumoral axis activation

Arterial underfilling triggers neurohumoral overactivity in HF. In the Studies of Left Ventricular Dysfunction (SOLVD), baseline plasma norepinephrine (PNE), plasma renin activity (PRA), plasma atrial natriuretic factor (ANF), and plasma arginine vasopressin (AVP) were increased in HFrEF ($\leq 45\%$), whereas only PRA and AVP were increased in HFpEF (LVEF $> 45\%$).⁵¹ However, PNE values did not differ between HFrEF and HFpEF in another study.⁵² Finally, it was recently demonstrated that muscle sympathetic nerve traffic is increased in HFpEF, HFmREF, and HFpEF.⁵³ Thus, neurohumoral overactivity is present in all HF phenotypes, being highest on the low LVEF side and lowest on the high LVEF side of spectrum.

Myocardial fibrosis

Myocardial fibrosis (MF) plays a major role in LV remodelling independent of LVEF. Accordingly, although the degree of MF varies among HF patients, MF may be present throughout the HF spectrum.

The collagen volume fraction in endomyocardial biopsies was similar in HFpEF and HFrEF.⁵⁴ Moreover, in both HFrEF and HFpEF, MF estimated on CMR was independently associated with a higher risk of all-cause death and HF hospitalization.⁵⁵

Skeletal myopathy

Skeletal myopathy contributes to the impaired exercise capacity in HF.⁵⁶ Both HFpEF and HFrEF patients with exercise intolerance manifest early exercise-induced declines in skeletal muscle high-energy phosphates and reduced oxidative capacity compared with healthier and low-fatigability HF patients.^{57,58}

Benefit with neurohumoral inhibition

The success of treatment with neurohumoral inhibitors in HFrEF is not fully reproduced in HFpEF. However, there are undeniable signals for a benefit in HFpEF as well as explained in the following paragraphs and references.

Table 1 Features of heart failure found throughout the full heart failure spectrum

Risk factors, comorbidities, and disease modifiers (quantitative differences depending on LVEF)
Bidirectional transitions of LVEF due to disease treatment and progression
Endothelial dysfunction, cardiomyocyte dysfunction, and cardiomyocyte injury
Systolic and diastolic left ventricular dysfunction
Left atrial dysfunction
Myocardial fibrosis
Skeletal myopathy
Heart failure serum markers (quantitative differences depending on LVEF)
Neurohumoral activation (quantitative differences depending on LVEF)
Effectiveness of neurohumoral inhibitors (quantitative differences depending on LVEF)

LVEF, left ventricular ejection fraction.

Table 2 Possible directions to create a new stratification of heart failure

Hypothesis-driven approach

Stratification based on disease aetiology/mechanism

Ischaemic cardiomyopathy, non-ischaemic dilated cardiomyopathy, light chain amyloid cardiomyopathy, transthyretin amyloid cardiomyopathy, hypertrophic cardiomyopathy, hypertensive cardiomyopathy, diabetic cardiomyopathy, tachy-cardiomyopathy, post-partum cardiomyopathy, doxorubicin- or alcohol-induced cardiomyopathy, myocarditis-induced cardiomyopathy, lamin A/C cardiomyopathy, etc.

Stratification based on activity of pharmaceutical pathway

Endothelin serum levels, cytokine serum levels, vasopressin serum levels + serum sodium levels, endothelial dysfunction + low tissue cGMP, etc.

Data-driven, hypothesis-free approach

Phenotypic characterization based on outcome analysis and stratification by large series of dense phenotypic data.

Identification of signatures to distinguish between groups with different outcomes

cGMP, cyclic guanosine monophosphate.

Perindopril in HF patients with LVEF $\geq 45\%$ improved symptoms and exercise capacity, and lowered hospitalizations.⁵⁹ In a recent analysis of the CHARM trial with LVEF as a continuous spline variable, candesartan reduced the primary outcome (cardiovascular death or HF hospitalization) until LVEF well over 50% and recurrent HF hospitalizations until LVEF well over 60%.⁶⁰ A meta-analysis of 13 studies concluded that renin-angiotensin system inhibitors may have a role in improving outcomes in HFpEF.⁶¹

Too few patients have been studied in trials of beta-blockers in HFpEF. However, in a pre-specified sub-analysis of the Study of

the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with HF (SENIORS), the benefit with nebivolol in elderly patients with HF was unrelated to LVEF.⁶² A meta-analysis involving 21 06 HFpEF patients demonstrated that β -blocker exposure was associated with a 9% reduction in relative risk for all-cause mortality.⁶³

Aldosterone receptor blockade is associated with reductions in risk for HF hospitalization in patients with HFpEF and while there was regional heterogeneity, the primary outcome including cardiovascular mortality was reduced by spironolactone in the Americas.⁶⁴

Thus, effectiveness of treatment with neurohumoral inhibitors is highest in the low LVEF side and lowest in the high LVEF side of spectrum, consistent with the degree of neurohumoral overactivity.

QRS duration/ventricular dyssynchrony

Ventricular dyssynchrony based on QRS duration is independent of LVEF. In the Swedish Heart Failure Registry 31% of 25 171 patients had a QRS duration ≥ 120 ms, with a significant impact on the adjusted risk for all-cause mortality. There was no interaction between QRS width and LVEF.⁶⁵ In the TOPCAT study, a QRS duration of ≥ 120 ms was independently associated with an increased risk of the primary outcome,⁶⁶ and this risk was independent of the type of conduction abnormality underlying the prolonged QRS.⁶⁶ In the Predictors of Response to CRT (PROSPECT) trial, adjudicated LVEF above the entry criterion of 35%, responded similarly to CRT as those with lower LVEF.⁶⁷

Sudden cardiac death

Therapy with an implantable cardioverter defibrillator (ICD) for the primary prevention of sudden cardiac death (SCD) is recognized when LVEF $\leq 35\%$.³ However, data from two large community-based studies suggest that about two-thirds of SCD cases would not be eligible for an ICD before the cardiac arrest based on having an LVEF $> 35\%$.⁶⁸ In 1767 HFpEF patients enrolled in the Americas in TOPCAT, SCD accounted for $\approx 20\%$ of deaths.⁶⁹ In a systematic review of 8 randomized trials and 24 epidemiological studies in HFpEF, SCD accounted for 25–30% of deaths.⁷⁰ Obviously, it remains to be proven whether SCD can be prevented with ICD therapy in HFpEF.

Future direction

HF is a heterogeneous syndrome in which functional and structural biomarkers change dynamically during disease progression in a patient-specific fashion. This creates a spectrum across overlapping phenotypes (Figure 3). The spectrum view challenges a categorical HF classification based solely on LVEF. Epidemiological, clinical, mechanistic, pathophysiological, and therapeutic data reviewed in this article show that LVEF-based HF subgroups are more overlapping than previously appreciated (Table 1).

A spectrum view does not imply that all LVEF-based HF phenotypes are totally alike. The extremes of a spectrum exhibit per definition significant differences, for example, a patient with concentric LV hypertrophy and hypertensive HF differs from a HF patient with eccentric hypertrophy awaiting transplant (Figure 3). The middle area of a spectrum consists of related and overlapping phenotypes. Any LVEF-based subdivision is artificial. Accepting the extremes as

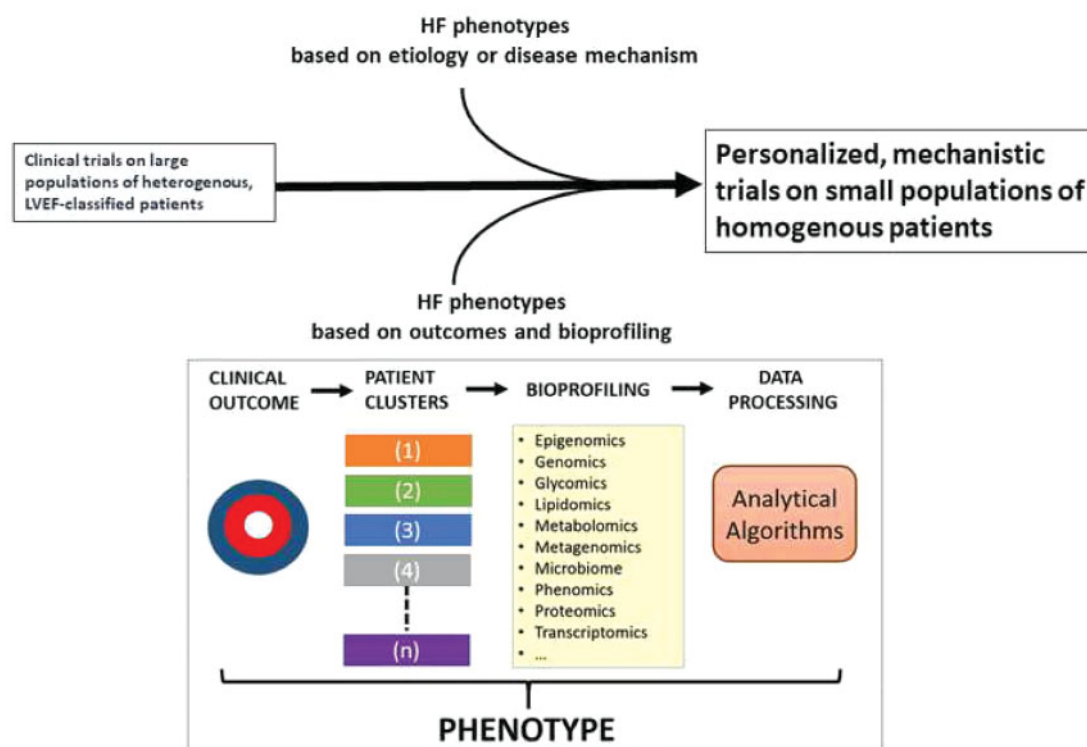


Figure 4 Evolution of heart failure research. Phenotype-oriented research in heart failure will emerge from an updated heart failure classification recognizing phenotypes across the left ventricular ejection fraction spectrum. These may either be based on mechanisms or aetiology of disease, or from unbiased data-driven approaches (see inset). Advances in both technology and computing now provides unprecedented opportunity to understand biologic subgroups of patients to target personalized therapy that maximizes chances of benefit and minimizes chances of risks. One such scheme could be to stratify patients across the risk spectrum and study their biologic, sociologic, demographic, and other determinants in detail to describe not only prediction more accurately (to guide use of existing therapy) but also the relevant biologic pathways involved (to guide development of new therapies).

'prototypes' creates the misleading perception of a categorical nature of HF.

The logic for a more precise characterization of HF phenotypes is supported by the advances in oncology.⁷¹ Introduction of innovative technologies such as next generation sequencing has personalized cancer treatment.

How should we then approach the heterogeneity of HF? One may envision two major directions for progress. The first would be hypothesis-driven, the other data-driven (Table 2).

In the hypothesis-driven approach, patients are stratified by a combination of features that are thought to be mechanistically important (e.g. cardiac resynchronization therapy for wide QRS duration or implantable cardioverter defibrillator for ventricular tachycardia/fibrillation). In fact, this approach, which is aetiological and more clinically significant than the current, oversimplified LVEF-based classification, should be incorporated in the current everyday practice, provided that the underlying aetiology is known. When it is not, the disease should be included in a category (e.g. idiopathic dilated cardiomyopathy), a practice that will inevitably shrink in parallel with the increase in knowledge regarding HF. It is reassuring to note that this strategy has already provided some successes with the identification of aetiology-specific therapies, such as transthyretin stabilization

with tafamidis for transthyretin amyloid cardiomyopathy.⁷² A prerequisite for this approach is better characterization of less established phenotypes (e.g. obesity, uraemic cardiomyopathy, metabolic cardiomyopathy, etc.). Given the spectacular evolution in many fields of medicine, including imaging modalities, machine learning, biomarkers, genotyping, etc., one might expect rapid progress during the characterization of such phenotypes.

A variant of the hypothesis-driven approach is the stratification based on the activity of a drug pathway over the spectrum, for example, studying a vasopressin antagonist in patients with high co-peptin levels or low serum sodium or etanercept in patients with high levels of tumour necrosis factor alpha, etc. This approach would likely result in study populations with a wide range of LVEF, and perhaps lead to better clinical outcomes compared with previous trials on these pathways in patients selected by LVEF.

The data-driven approach is hypothesis free. Patient clusters are generated defined by clinical outcomes. Each patient cluster is identified based on similarities or differences in measured characteristics, with strong associations among members of the same cluster and weak associations among members of other clusters. After this process, data are analysed to identify which variables distinguish clusters with different outcomes ('signatures'). Pairing phenotypes identified

with cluster analyses with an 'omics' approach (genomics, metabolomics, proteomics, etc.) may allow for a more advanced classification scheme founded on the underlying biology. Moreover, artificial intelligence will enable computers to find hidden insights without being explicitly programmed where to look and integrate and interpret complex data in scenarios where traditional statistical methods may not be able to perform.⁷³ This could set the stage for a more rational clinical trial design for HF, which is likely necessary.

Estimation of LVEF will likely remain temporarily part of the assessment of HF, as a prognosticator, as a rough measure of a patient's sensitivity to neurohormonal inhibitors, and during a transition phase to incorporate current evidence-based medicine into a more personalized evidence-based HF management scheme. For example, when testing a drug in an appropriate HF phenotype (defined without limitations of LVEF), patients will be randomized to receive the active drug or placebo on top of standard therapy, the latter which will require some measure of individual patient's LVEF. However, HF care will be accompanied by a greater awareness of the inaccuracies of LVEF measurement and of its vague pathophysiological significance. By accepting the limitations of LVEF and embracing the spectral nature of HF, the HF field will move from an originally unspecified approach based on statistical analyses of data from large groups of heterogeneous LVEF-clustered populations to a more personalized and mechanistic approach based on smaller studies with homogeneous patient populations (Figure 4).

Conflict of interest: J.Bu. reports to be consultant for Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, StealthPeptide, SC Pharma, Vifor, ZS Pharma, outside the submitted work. J.Ba. reports personal fees from Novartis, grants and personal fees from Bayer, personal fees from Servier, personal fees from Orion, grants and personal fees from Abiomed, grants and personal fees from CVRx, grants and personal fees from Medtronic, grants from Zoll, grants and personal fees from Vifor, personal fees from Abbott, personal fees from AstraZeneca, outside the submitted work; R.D.B. reports grants from AstraZeneca, grants from Bristol Myers Squibb, grants from Trevena, grants from Novo Nordisk, personal fees from AstraZeneca, personal fees from Novartis, personal fees from Vifor, personal fees from MandalMed, Inc, and other types of support from scPharmaceuticals, Inc, other from ThermoFisher, other from Roche, all outside the submitted work; L.D.W. reports to be co-founder and stockholder of Mirabilis Therapeutics BV, a spin-off Biotech aimed to develop new therapeutics for heart failure; G.H. reports personal fees from Corvia Medical, Servier, Impulse Dynamics, Novartis, AstraZeneca, Vifor Pharma, and Springer all outside the submitted work; J.-S.H. reports personal fees from Servier and Novartis, outside the submitted work; M.K. reports personal fees from Amgen, BMS, Boehringer-Ingelheim, Novartis and grants and personal fees from Ironwood, LivaNova, SCPharma, outside the submitted work; R.L. reports to be a founder of a startup biotechnology company named Elevian, Inc., which has heart failure as one of its target diseases; A.L. reports personal fees from Servier, grants and personal fees from Pfizer, personal fees from Novartis, personal fees from Roche, personal fees from Takeda, personal fees from Boehringer Ingelheim,

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