Heart Failure with a Preserved Ejection Fraction: From Pathophysiology to Biomarkers … and Beyond!

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ABSTRACT
Diagnosing and managing heart failure according to the left ventricle’s ejection fraction (LVEF) has become part of evidence-based medicine. Not surprisingly, LVEF - a powerful prognostic factor in heart failure - has caused a marked heterogeneity in the clinical benefit of various therapeutic interventions. From a pathophysiological point of view, however, many disease characteristics are shared among the entire heart failure spectrum (from low to high LVEF). The many functional and anatomical differences within the spectrum are merely quantitative, with an extensive overlap between the extremes of the spectrum and belonging to the same linear relation when plotted against LVEF. Therefore, although counter-intuitive from a clinical point of view, from a pathophysiological point of view heart failure seems to progress along a common disease trajectory independently of LVEF. In this review, we will scrutinise this apparent paradox, estimate how it relates to the recent biomarker-oriented (as opposed to a classic LVEF-oriented) approach to heart failure and discuss to what extent it may affect conceptual progress in chronic heart failure.

INTRODUCTION
More than thirty years ago, it was recognised that signs and symptoms of heart failure may occur in patients in whom the ejection fraction of the left ventricle (LV) is within normal limits. Although originally studied in patients with genuine hypertrophic cardiomyopathy, heart failure with “preserved” LV ejection fraction (HFPEF) has now been recognised in a more common population, which is characterised by a high prevalence of female gender, arterial hypertension, advanced age, obesity and diabetes mellitus.

Interestingly, community surveys on chronic heart failure in general have shown that the overall distribution of left ventricular ejection fraction (LVEF) among patients with heart failure is bell-shaped and that the fraction of patients with a preserved LVEF within this distribution is much larger than anticipated, currently being about 50% of patients.

Strikingly, in contrast to patients with a reduced LVEF (HFREF), no improvements in outcomes have been documented over the past twenty years.

In this paper, we will review pathophysiological insights underlying both symptoms and disease progression in HFPEF and contemplate in which direction research should develop in the next decade.

Pathophysiology
The pathophysiology of HFPEF consists of two parts. First, it explains clinical symptoms of HFPEF, Second, it clarifies its irreversible pathophysiological progression. Although these pathophysiological aspects may be related, lessons from the past should remind us that a therapeutic intervention that reduces symptoms in heart failure do not per se halt the progression of the disease, and vice versa.

Pathophysiology of HFPEF symptoms
Symptoms of HFPEF are characterised by exercise intolerance and breathlessness on exertion. These chronic symptoms may be alternated by acute episodes of lung edema or global volume overload, usually precipitated by severe hypertension, non-compliance to therapy, (pulmonary) infection, inappropriate tachycardia (usually atrial fibrillation), or a combination of two or more of these factors.

In many patients with suspected HFPEF an alternative non-cardiac explanation for symptoms can be identified (like obesity, muscular deconditioning, pulmonary disease or angina), which may lead to misdiagnosis. This is a relevant problem in clinical cardiology, which complicates the design of clinical trials in HFPEF and urges defining guidelines for diagnosis.
Nevertheless, it is now well established that patients with HFPEF also suffer from severe cardiovascular abnormalities that exacerbate exercise intolerance, which firmly increase patient’s risk for episodes of acute heart failure. These abnormalities predominantly manifest during active LV relaxation and diastolic filling, leading to so-called “diastolic dysfunction”. The entire pathophysiological picture of HFPEF as a syndrome is, however, more complex than an isolated problem of LV diastolic function. Abnormalities of LV relaxation and filling consist of impaired active LV recoil and suction, blunted LV lusitropic response to adrenergic stimulation and a steep diastolic LV pressure-volume relation. When occurring in combination and often exacerbated by deranged ventriculo-vascular coupling, these abnormalities explain the low LV preload reserve and the low pulmonary capillary wedge pressure (PCWP)/work ratio of HFPEF patients. By increasing PCWP, they may also explain the high prevalence of pulmonary arterial hypertension in HFPEF, unless other yet to be identified pathophysiological processes would lead to pre-capillary pulmonary hypertension.

Accordingly, the pathophysiology of clinical symptoms of patients with HFPEF is predominated by diastolic LV dysfunction. The subcellular processes leading to diastolic LV dysfunction are beyond scope of this review but include an abnormal inactivation of the excitation-contraction process, passive myocyte stiffness, extracellular matrix abnormalities and impaired paracrine endothelial signalling.

**Pathophysiology of HFPEF progression**

Apart from the fact that HFPEF is associated with diastolic LV dysfunction, it is also usually associated with a progressive concentric LV remodelling. Similarly, HFREF is associated with systolic dysfunction, but also with progressive eccentric LV remodelling. These associations between function and morphology of the left ventricle, together with the LVEF-based design of clinical trials, have created a tendency to dichotomise heart failure in two separate pathophysiological entities, apparently progressing along two divergent pathophysiological trajectories (Figure 1).

However, diastolic dysfunction is not unique for HFPEF; it even is the strongest determinant of symptoms in HFREF. Also, systolic dysfunction is not unique for HFREF. In addition, concentric and eccentric LV remodelling often occur in combination, independently of LVEF. These observations suggest that HFPEF and HFREF are related, overlapping entities and may progress along a common pathophysiological trajectory (Figure 1).

Consistently, there currently is not a single pathognomonic feature, at any level of biological complexity (gene, protein, cell, organ, or organ system) that distinguishes HFPEF from HFREF. Instead, HFPEF and HFREF share many pathophysiological features, such as neurohormonal abnormalities, upregulation of growth factors, volume overload, ventricular collagen turnover, titin isoform switching and titin phosphorylation deficits, endothelial dysfunction, atrial dysfunction, arterial stiffening, etc.). The genuine differences between HFPEF and HFREF, as described in literature (e.g. longitudinal contractile function, serum brain natriuretic peptide, LV end diastolic volume and cardiomyocyte diameter) are merely quantitative differences, usually presented as statistically significant different mean values, but with an extensive overlap of the individual data points. Hence, LVEF is a rather weak predictor of cardiomyocyte diameter and even of LV volumes and thus fails to capture the type of LV remodelling in a reliable fashion. When individual data points of HFPEF and HFREF are plotted against LVEF, they belong to same (sometimes weak) linear relation.

Why is it not surprising that we fail to recognise two clear-cut distinct types of structural and functional LV remodelling? LV remodelling is the product of multiple interacting and complex signalling processes. The contribution of each of these processes is linked to the patient’s biological profile and medical background. For example, some of these processes are triggered by myocardial ischemia, myocardial infection or type I diabetes; these processes seem to promote predominant eccentric remodeling. Other signalling processes are influenced by type II diabetes, obesity, arterial hypertension and female gender; these tend to promote concentric remodelling. The biochemistry of these signalling processes are under intense investigation and has been related to intermediate mediators such as leptin, oxidative stress, hyperinsulinemia, estrogen, cytokines, etc. In vivo, these mediators and their complex signalling events merge in qualitative and quantitative combinations, specific for each patient. In a population of patients with heart failure, this creates heterogeneity, leading to a continuous spectrum of overlapping phenotypes. Any attempt to dichotomising this spectrum is artificial and lacks a conceptual basis.

According to the above reasoning, HFPEF and HFREF progress along the same pathophysiological trajectory, and only vary in the quantitative contribution of numerous signalling events. So why then, one may argue, have clinical trials on the inhibition of the renal-angiotensin system, been successful in HFREF and disappointing in HFPEF? Does this not contradict the premise that HFPEF and HFREF are part of a common disease trajectory?

No, it doesn’t. Imposing an arbitrary cut-off in any of the many prognostic continuous variables of heart failure, be it LVEF or any of the other currently available biomarkers, does not necessarily signify that a novel paradigm is generated or that disease taxonomy should be introduced, even if it unveils a different clinical response to a therapeutic intervention.

**Figure 1:** Clinical versus pathophysiological interpretation of the heterogeneity heart failure.
What if a clinical trial would indicate that heart failure patients with a normal maximal oxygen consumption (VO2 max) would show less benefit to aldosteron inhibitors as compared to patients with a reduced VO2 max? Would this be a sufficient argument to claim that heart failure with a normal or reduced VO2 max progress along different disease trajectories? No, it wouldn’t. Yet, we might still consider the result of the trial as clinically relevant. The same is true for LVEF or any other (prognostic) variable, usually coined as “biomarker” of heart failure.

**“Biomarkers”: rising stars of heart failure**

There is a current trend to characterise and manage heart failure patients by the measurement of one or multiple biomarkers. New biomarkers have emerged from large-scale quantitative analyses of gene expression, including cDNA microarrays and proteomic analyses. This multi-marker strategy looks refreshing and may provide new insights. At least, it surpasses patient management based on a dogmatic cut-off of LVEF alone. It may personalise heart failure management and help to optimise current heart failure guidelines. On the other hand, one may seriously question where-to to this approach will eventually lead. It may be feared that adding still more biomarkers and other disease parameters in heart failure will never end and fail to re-launch conceptual thinking. Time has perhaps come to envisage integrative approaches, already introduced in other fields of life sciences, that encounter limits of reductionism and seek understanding out of myriad validated bits of data.

Systems biology aims to provide a framework for how structural and functional components, often known as disease biomarkers in clinical medicine, interact in self-organising modular biological networks. Networks rather than the components themselves create physiological behaviour and disease. Each node in a network represents a component (a gene, a transcript, an organelle, a cell, …) and interconnecting nodes describe a typical architecture, which is imposed by biological evolution and selection. At each level of complexity, a network obtains new properties, which are not predicted from the properties of the network at the lower level, referring to emerging properties in a dissipative structure, introduced by Prigogine. Within a network perspective to biology, a disease is defined as the failure of a biological network or as the failure to obtain a next-level emerging property.

Rather than further studying heart failure and its pathophysiology in terms of a preserved or a reduced LVEF, one might better start to begin thinking on the network failures in chronic heart failure. What are the crucial biological networks (in the network of networks) of cardiac function and heart failure, and where are the vulnerable hubs which can destabilise networks? Can network perspective to heart failure provide novel biological (organ-specific) fingerprints of failure that allow predicting a patient’s risk, early disease development or disease stage? How do these fingerprints relate to the current growing list of heart failure biomarkers? Can systems biology help to define novel surrogate endpoints for clinical trials? How can a network, if associated with a disease, be targeted pharmacologically? How does this relate to the growing list of targets, now emerging from reductionist sciences?

These are the future scientific questions of chronic heart failure, independently of whether LVEF is preserved or reduced. Hence, although relevant in daily clinical cardiology, from a conceptual and scientific perspective the value of LVEF in heart failure is becoming irrelevant.

**CONCLUSIONS**

Is it clinically relevant to distinguish HFNEF and HFREF during the clinical management of heart failure?

Yes, it does. Diagnosis of heart failure can be challenging when LVEF is normal and necessitates specific diagnostic guidelines. In addition, haemodynamic and prognostic management is different in HFNEF and HFPEF.

Does this mean that HFNEF and HFREF are different diseases?

No, it doesn’t. HFNEF and HFREF share many disease characteristics, and the observed pathophysiological differences are merely quantitative, with a large overlap between individual data points. This indicates that HFNEF and HFREF progress along the same pathophysiological disease trajectory, although the end result is a heterogeneous disease consisting of a spectrum with different (but overlapping) clinical phenotypes. This heterogeneity is caused by patient’s biological “background”, such as age, gender, metabolism, etc which influences the process of LV remodelling.

Why then do HFNEF and HFREF respond differently to ACE-inhibitors?

It is not unusual that arbitrary cut-off values of prognostic variables of a disease, such as LVEF > 50% in chronic heart failure, induce differences in the clinical response to therapy. This does not indicate, however, that this prognostic variable constitutes a good platform to introduce disease taxonomy with distinct pathophysiological entities. There is little doubt that cut-off values of many other variables in heart failure (e.g. BNP, VO2 max, etc.) would induce a similar variability in the response to therapeutic interventions.

If LV ejection fraction > 50% is not a good basis to introduce disease taxonomy in heart failure, what about biomarkers?

Biomarkers are interesting tools indeed and can be refreshing in heart failures sciences during the endeavour to optimise therapeutic guidelines and personalise medicine. On the other hand, the number of biomarkers is rapidly increasing, and the biological meaning of these biomarkers are often so obscure that a biomarker-oriented approach may soon become very confusing.

How then should we proceed? Heart failure research is stagnating, and pharmaceutical companies are discouraged by the negative results of many expensive trials.

Reductionistic and high-trough put sciences have yielded a massive amount of new and exciting data in heart failure over the past ten years. New molecular pathways, therapeutic targets and biomarkers have been defined. It is now time to seek understanding out of myriad validated bits of data. This can happen only if we embrace systems approaches to heart failure. These approaches will define biological networks and dysfunction of networks in the pathophysiology of chronic heart failure. The strategy of approaching heart failure from one arbitrary variable, like LVEF, has reached its limits.
REFERENCES


