

# Treatment of HFpEF: why we have no evidence

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## Abstract

The treatment of heart failure with reduced ejection fraction (HFrEF) is relatively straightforward, with guidelines from the European Society of Cardiology (ESC) and the American Heart Association (AHA)/American College of Cardiology providing numerous class 1 recommendations, supported by evidence at level A. In stark contrast, the same guidelines do not offer a single recommendation with level A evidence for management of heart failure with preserved ejection fraction (HFpEF). This difference is due to a failure of clinical trials to provide a reliable evidence base in HFpEF, for complex and multifactorial reasons. This review highlights how uncertainties surrounding the importance of left ventricular ejection fraction, the mechanisms driving HFpEF, and the burden of comorbidities have probably frustrated efforts thus far. ■  
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## Introduction

The treatment of heart failure remains one of the “wild” frontiers of cardiology, where prevalence, morbidity, and mortality are all still sufficiently high to drive academic and commercial investment. This attraction persists despite the very many successful trials in heart failure with reduced ejection fraction (HFrEF), which have clearly shown the benefit of angiotensin-converting enzyme inhibitors, 1-adrenoceptor blockers, mineralocorticoid receptor antagonists, cardiac resynchronization therapy (biventricular pacemakers), implantable cardioverter-defibrillators, and most recently, angiotensin-receptor blockers combined with neprilysin inhibitors. Furthermore, these drugs/devices seem to work irrespective of

the etiological cause of HFrEF (ischemic vs other). Many of these same therapies have been tested in studies of similar design in heart failure with preserved ejection fraction (HFpEF), but without success. The question is why?

## Selection based on left ventricular ejection fraction

Heart failure is a nebulous syndrome with nonspecific symptoms (fatigue, breathlessness, ankle edema) and signs that lack diagnostic sensitivity (elevated jugular venous pressure, lung crackles, third heart sound). For this reason, the clinical suspicion needs to be supported by investigations that have high sensitivity and specificity. The attraction of measuring left ventricular ejection fraction (LVEF) to aid di-

### Abbreviations

**CHARM-PRESERVED:** Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction; **HFpEF:** heart failure with preserved ejection fraction; **HFrEF:** heart failure with reduced ejection fraction; **J-DHF:** Japanese Diastolic Heart Failure Study; **LAP:** left atrial filling pressure; **LVEF:** left ventricular ejection fraction; **MAGGIC:** Meta-Analysis Global Group In Chronic heart failure; **NT-proBNP:** N-terminal pro-B-type natriuretic peptide; **PEP-CHF:** Perindopril in Elderly People with Chronic Heart Failure; **TOPCAT:** Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial

agnosis is that values are easily obtained by echocardiography and, although prone to measurement error, when LVEF is below 40% it is very probable that left ventricular dysfunction is the cause for the patient's symptoms. Furthermore, if doubt remains, measurement of circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) provides further diagnostic power. These simple investigations provide a stable foundation on which to make a diagnosis of HFrEF and have been the basis of enrolment into successful clinical trials. In contrast, these powerful diagnostic filters are not available in HFpEF because, by definition, LVEF is above 40% (see below) and NT-proBNP is often not markedly elevated. Consequently, there is a real danger of labeling nebulous syndromes, in which the heart may not drive symptoms or events, as HFpEF.

Furthermore, very large registries suggest that the power of LVEF to predict both total mortality and cardiovascular events is lost once it exceeds 40%,<sup>1</sup> intimating a biological boundary above which cardiovascular interventions may struggle to reduce risk, as excess risk doesn't exist! Thus, trials in HFrEF have used an LVEF of 40% as the selection cutoff, below which exists a clear inverse risk gradient between LVEF and events.<sup>1</sup>

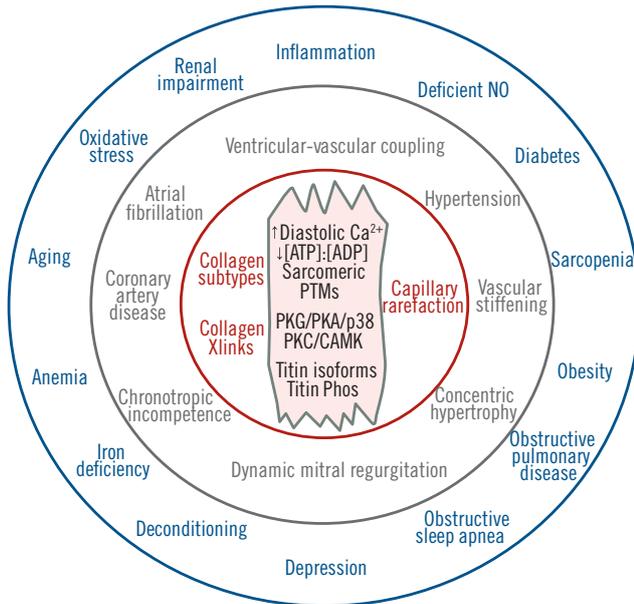
The exact LVEF cutoff value to distinguish between HFpEF and HFrEF in an individual with heart failure symptoms is controversial and has varied between trials from 40% (and greater) to 50% (and greater).<sup>2</sup> Those with an LVEF between 40% and 50% lie in a so-called gray zone between definite HFrEF and definite HFpEF. This gray zone is likely

to encompass varied pathologies, including individuals that at some point had an LVEF under 40% that has improved/recovered. Thus, one would expect interventions of proven value in HFrEF to show their greatest chance of success in trials recruiting HFpEF patients within this gray zone (trial selection criterion LVEF>40% or >45%). However, despite including patients in the gray zone, well-established HFrEF therapies have failed to have an impact on HFpEF (eg, spironolactone in TOPCAT [Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial], carvedilol in J-DHF [Japanese Diastolic Heart Failure Study], candesartan in CHARM-PRESERVED [Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction], and perindopril in PEP-CHF [Perindopril in Elderly People with Chronic Heart Failure]). These failures have occurred despite additional selection criteria designed to include patients at increased risk, such as recent hospitalization with a diagnosis of heart failure. Even when such additional selection criteria are used, the nebulous nature of HFpEF means that trials still enroll patients with poorly defined syndromes and, therefore, the study population encompasses a broad range of cardiovascular risk. This is very well illustrated by TOPCAT, where despite identical selection criteria (LVEF>45% and recent hospital admission due to "heart failure") there was a four-fold higher event rate in patients enrolled in the Americas versus those enrolled in Russia and Georgia.<sup>3</sup>

A possible solution to ensure that those with an LVEF above 40% really have HFpEF is to measure left atrial filling pressure (LAP). By definition, this is abnormally elevated in left heart failure of any cause. The difficulty is that invasive hemodynamic measurements are inappropriate for the vast majority of patients with suspected HFpEF because of their age and multiple comorbidities (see below). In addition, because symptoms occur on exertion, ideally, LAP should be acquired during exercise. Thus, invasively acquired LAP should aid HFpEF diagnosis and guide enrolment into clinical trials. However, in practice, data are difficult to interpret. For example, asymptomatic elderly patients frequently have a mean LAP above 20 mm Hg on exercise.<sup>4</sup> What is needed, therefore, is a widely accepted gold standard noninvasive measure of an elevated LAP. Unfortunately, at present, no such measure exists (see Omar et al<sup>5</sup> for recent review).

## Identifying the mechanism(s) driving HFpEF

One possible reason why therapies in HFpEF have failed is that the relatively crude way in which trials have selected patients (see above) means that the “net has been cast too wide” and that we have inadvertently captured a number of different diseases. This seems extremely probable because the comorbidities (see *Figure 1*) associated with HFpEF are un-



**Fig. 1** The complexity of heart failure with preserved ejection fraction (HFpEF). The figure depicts the processes that have been implicated in either causing HFpEF or coexisting with HFpEF and aggravating the symptom of exertional breathlessness. At the center are processes within the cardiac myocyte responsible for active (uppermost) or passive (lowermost) relaxation. Bounded by the innermost red circle are other myocardial abnormalities implicated in HFpEF that lie outside cardiac myocytes. The gray circle and text include cardiovascular pathologies that are thought to contribute to HFpEF but lie outside the myocardium. Finally, the outermost blue circle and text includes systemic changes that are thought to influence HFpEF.

**Abbreviations:** ADP, adenosine diphosphate; ATP, adenosine triphosphate; Ca<sup>2+</sup>, calcium; CAMK, calcium and calmodulin-regulated kinase; NO, nitric oxide; P38, p38 mitogen-activated protein kinase; Phos, phosphorylation; PK, protein kinase; PTMs, posttranslational modifications; Xlinks, cross-links.

likely to mediate damage through a single common pathway. Fundamentally, HFpEF is caused by a left ventricle that fails to relax normally in diastole. This can result from abnormalities within and/or outside cardiac myocytes.

Within cardiac myocytes, active relaxation requires the actin and myosin cross-bridges to detach and this in turn needs cytosolic calcium concentrations to fall, adenosine triphosphate (ATP) concentration to be high, and adenosine diphosphate (ADP) concentra-

tion to be low. Calcium and energy balance are in turn influenced by the availability of metabolic substrates, pH, and mitochondrial energetics, all of which have been reported as being perturbed in HFpEF through a variety of mechanisms. Similarly, passive relaxation needs the cytoskeletal structures that are compressed during systole to quickly decompress/relax in diastole. Abnormalities in passive relaxation have been ascribed to changes in titin isoforms and/or its phosphorylation state. These processes are in turn regulated by upstream signaling cascades, including kinases such as protein kinase G (PKG), which have also been shown to be disordered in HFpEF (as depicted in *Figure 1*).

Abnormalities outside cardiac myocytes have also been associated with the ventricular stiffening causing HFpEF. These changes include the collagen subtypes that make up the extracellular matrix, as well as abnormal cross-linking between collagen fibers. Once again, these processes are controlled by upstream signals that control fibroblast and inflammatory cell activity.

Finally, abnormalities outside the heart have been shown to contribute to HFpEF. These include abnormal coupling between the left ventricle and systemic arteries, deconditioning of skeletal muscle, and changes in heart rate associated with atrial fibrillation and chronotropic incompetence.

In summary, the processes responsible for cardiac relaxation are complex and intertwined. Generally, their individual contributions to HFpEF in a particular patient are not assessed before a treatment is started. Instead, “a one-size-fits-all” approach has been taken to HFpEF treatment. In the absence of personalized therapy, one could argue that the clinical trials conducted to date are equivalent to treating all forms of anemia with vitamin B<sub>12</sub>!

## The problem of comorbidities

It's unusual for HFpEF to occur in isolation, and commonly there are antecedent risk/causative factors (eg, diabetes, hypertension, renal disease) and other coincident conditions that may also aggravate symptoms (eg, obesity, lung disease, skeletal muscle deconditioning) (see *Figure 1*). Furthermore, HFpEF patients are older than those with HFrEF, and normal aging is associated with decrements in cardiac, skeletal, and respiratory performance that are difficult to dissociate from the HFpEF phenotype. So much so, that some

have likened HFpEF to “presbycardia.” The difficulty with the comorbidities is that they are in themselves major predictors of mortality and are unlikely to be modified by the drugs used to treat heart failure. For example, in the MAGGIC meta-registry (Meta-Analysis Global Group In Chronic heart failure), which included almost 40 000 patients with heart failure (HFpEF and HFrEF) and 16 000 deaths, the top five predictors of mortality were age, lower EF (below 40%), New York Heart Association class, serum creatinine level, and diabetes.<sup>1</sup> The predictive effect of age was even more pronounced in those with HFpEF than with HFrEF; but, unfortunately, age is not modifiable!

In common with the discussion above on the mechanisms driving HFpEF, the multiple comorbidities suggest it comprises more than one disease. In an attempt to dissect out these diseases, mathematical algorithms were applied to a cohort of extremely well-phenotyped HFpEF patients in whom 67 variables were recorded.<sup>6</sup> The result of this unbiased analysis suggested that certain characteristics tend to cosegregate more frequently than expected by chance. Features clustered into three distinct groups (phenogroups) between which existed significant differences in age and sex and prevalence of diabetes, hypertension, obesity, kidney disease, obstructive sleep apnea, and atrial fibrillation.<sup>6</sup> Although this segregation does not touch on the underlying mechanism, it may allow the recruitment of more homogeneous patient groups into future clinical trials.

## Conclusion

In conclusion, it is probable that the heterogeneous nature of the patient population with HFpEF together with the high burden of life-limiting, but noncardiac, comorbidities have frustrated clinical trials to date and diminished their chance of success. These limitations can only be overcome through a more detailed understanding of this diverse condition and more careful selection of patients to ensure they share a dominant underlying pathology that can be altered by the study intervention. ■

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