

Clinical application of personalized medicine: heart failure with preserved left ventricular ejection fraction

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KEYWORDS

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Heart failure (HF) with preserved left ventricular (LV) ejection fraction (HFpEF) represent today the largest 'unmet medical need', because none of the drugs presently available improved survival in this consistent proportion of patients with HF, ~50% of the total, who have an LV ejection fraction $\geq 50\%$. Heart failure with preserved left ventricular ejection fraction is a clinical syndrome that in its classical form, is associated to typical risk factors and comorbidities. The comorbidities represent one of the element contributing to the extreme heterogeneity which characterizes HFpEF. The pathophysiological mechanisms, as well as the clinical presentation, are multifaceted. These factors explain, by and large, the failure of a generalized therapeutic strategy, while build the argument for personalized medicine, designed to address the specific phenotypes, with therapies proven in specific subgroups of patients with HFpEF to reduce mortality and improve 'surrogate' outcomes, such as quality of life.

Introduction

Heart failure with preserved systolic ejection fraction (HFpEF) represents ~50% of all cases of heart failure, with a slightly better survival compared to patients with heart failure and reduced systolic ejection function (HFrEF), but with a constantly increasing incidence for population aging and consequently with a high socio-economic burden destined to increase over time. Heart failure and reduced systolic ejection function is still the largest 'unmet medical need', based on epidemiological data and since no drug has managed to improve the outcome of HFpEF patients to date. The extreme pathophysiological, clinical, and associated comorbidity heterogeneity that characterizes HFpEF largely explains the failure of an all-inclusive therapeutic strategy in HFpEF patients, the so-called 'one size fits all approach', and lays the foundations for personalized medicine, aimed at curing specific phenotypes, with therapies that have been shown in certain subgroups of HFpEF

patients to be able to reduce morbidity and improve surrogate outcomes, such as quality of life.¹

When the doctor approaches the patient with HFpEF and must choose a suitable therapy, it is first of all important to reach a correct diagnosis, since there are many pathologies that can mimic an HFpEF, such as constrictive pericarditis, high output heart failure, valvular, or ischaemic heart disease. Furthermore, there are rare cases in which the patient, 'labelled as HFpEF', presents a specific aetiology of the disease (e.g. infiltrative, hypertrophic, restrictive, genetic), which could be treatable and should not be overlooked.² A simplistic diagnostic approach, based on the use of a five variable clinical/echocardiographic score (H2FPEF), was recently derived and validated at the Mayo Clinic, Rochester, Minnesota, and could represent a first useful tool to be applied in clinical practice in order to diagnose HFpEF.³ Vice versa, as underlined in a recent European Consensus Document, a diagnosis of HFpEF certainty must go through the implementation of different diagnostic steps, which include first of all the assessment of the probability of disease before the test and secondly the use of natriuretic peptide levels and resting echocardiography (HFA-PEFF algorithm). If the diagnosis remains

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uncertain, the stress echocardiogram aimed at evaluating the diastole and in persistently doubtful cases, the right heart catheterization, both difficult to apply in peripheral centres, are recommended. Finally, as a last step, the aetiological diagnosis is recommended through a dedicated work-up.

Having reached the diagnosis of HFpEF, the doctor finds himself in the uncomfortable situation that occurs in all cases of illness without proven therapy. In reality, as mentioned above, in the heterogeneity of HFpEF there is a therapeutic chance. In the pathophysiological model most commonly accepted in HFpEF, the so-called 'typical garden variety' of HFpEF, cardiac and extra-cardiac comorbidities, such as arterial hypertension, diabetes mellitus, anaemia, chronic obstructive pulmonary disease, and renal failure determine remodelling and left ventricular (LV) dysfunction, according to the most accredited physiopathological hypothesis, through systemic inflammation and coronary microvascular endothelial dysfunction.⁴ Endothelial dysfunction in turn leads to diastolic dysfunction of the LV through the infiltration of macrophages, with consequent interstitial fibrosis, and to the hypertrophy of cardiomyocytes linked to low levels of nitric oxide and cyclic guanosine monophosphate. In addition to the heart, the inflammatory process underlying HFpEF affects organs, such as lungs, skeletal muscle, and kidneys which can lead to pulmonary hypertension, muscle weakness, and sodium retention, respectively. The individual steps of this cascade of events, themselves represent possible specific targets for personalized therapeutic strategies.

It is important to emphasize that once specific aetiologies have been excluded, a practical therapeutic approach that can be proposed to HFpEF patients, based on current evidence, is to provide optimal control of risk factors, ideally bringing blood pressure <130/80 mmHg, the glycated hemoglobin (HbA1c) <7 mg%, the use of statin therapy if indicated. In addition, in the presence of signs of hypervolaemia, it is recommended to start/increase the dosage of the diuretics. Likewise, it may be important to evaluate the adequacy of blood pressure control under exercise but also the heart rate during exercise, in order to evaluate whether to enhance hypotensive therapy or whether to use negative chronotropic drugs. Therapeutic customization occurs when we have to choose which drug to use in order to obtain a specific therapeutic goal. This therapy should be chosen pragmatically on the basis of the classification of our patient in specific phenotypes, for which more appropriate therapies are available and with greater evidence than others.

In recent years, various consensus documents have outlined the different modalities applicable to the phenotypes of the patient with HFpEF. The first of these documents, still extremely contemporary despite the trials conducted in these years, describes HFpEF as a syndromic disease where multiple cardiac and vascular anomalies, cardiovascular risk factors, and overlapping extra-cardiac comorbidities can be present in various combinations (Figure 1).⁵ Adapting specific treatment strategies for the dominant phenotype of a specific patient with HFpEF is a promising approach that can increase the likelihood of demonstrating clinical benefit. According to expert opinions, another

indispensable element for phenotyping patients with HFpEF is represented by the use of biomarkers, able for example to identify subgroups with prevalent myocardial fibrosis, with myocardial damage/ischaemia, or with altered inflammation markers.⁶ From the integration of these biomarkers with clinical/pathophysiological, electrocardiographic, and echocardiographic parameters different therapeutic strategies can emerge in the different patients with HFpEF. This integration is increasingly complex and difficult to implement, given the amount of data theoretically to be considered in HFpEF syndrome, which is why phenotyping methods guided by mathematical/statistical algorithms, the so-called 'machine learning', are being studied, of which the cluster analysis first proposed by Shah in 2015 represents the first example and which are certainly destined to impact in the future on our therapeutic choices, outlining phenotypes that will likely represent therapeutic targets in future randomized clinical trials.⁷ To lower the therapeutic choice to be adopted in everyday clinical practice, the therapeutic strategies will be treated with more evidence in specific macro-phenotypes on the basis of the data currently available.

Therapeutic strategies in specific phenotypes

Exercise and calorie restriction

Exercise is recommended in all HFpEF patients. The results of a multicentre trial showed an improvement in the peak of oxygen consumption, in the diastolic function, and in the quality of life in the group undergoing exercise for 3 months. On the other hand, weight loss should be recommended for all HFpEF patients with high body mass index. In fact, bariatric surgery has been shown to be associated with a reduction in LV mass and an improvement in diastolic function. In addition, it was shown that the calorie restriction at 1000 Kcal/day, in addition or not to physical exercise, for a duration of 20 weeks was able to improve the peak oxygen consumption levels (VO₂) and the symptoms.⁸

ACE inhibitors and sartans

The PEP-CHF, CHARM-Preserved, and I-Preserved studies evaluated the role of ACE inhibitors and sartans in patients with HFpEF. Although no significant improvement was found in primary clinical endpoints in these trials, a reduction in hospitalizations for heart failure (non-default endpoint) with sartanic was achieved in the CHARM-Preserved study. Furthermore, a post-hoc analysis of the study showed that in the subgroup of patients with an EF (ejection fraction) range between 40% and 50% (HFmrEF), sartans are able to significantly reduce adverse events.⁹ Finally, a meta-analysis of randomized studies conducted with these drugs shows a trend towards the reduction of hospitalizations for heart failure ($P = 0.074$).

Therapeutic use guided by the specific clinical scenario: ACE inhibitors and sartans remain indicated in patients with HFpEF as first-line drugs for high blood pressure and for the prevention of organ damage (nephro-protection in diabetics). They also appear indicated in patients with a slight reduction in the ejection fraction (HFmrEF).

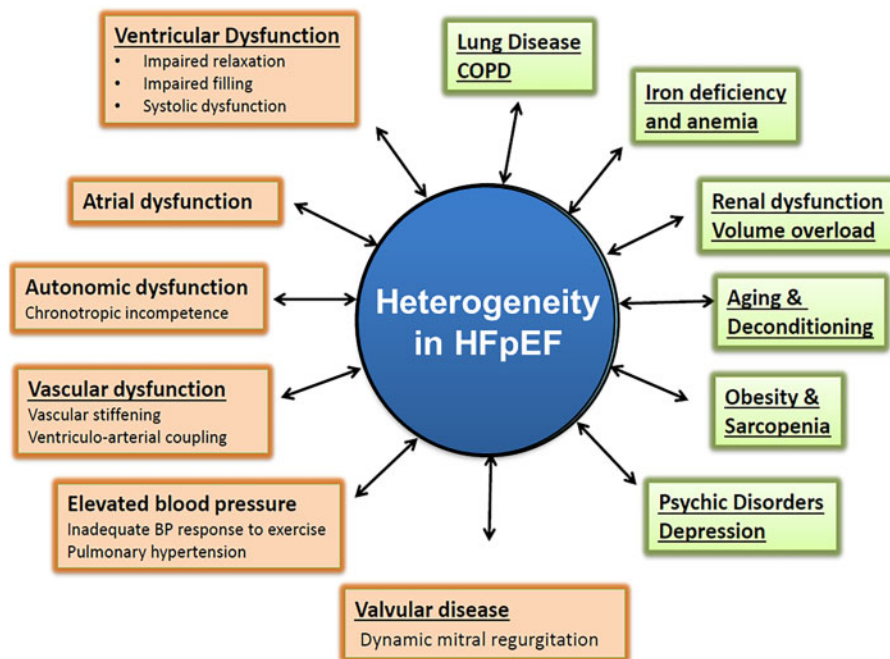


Figure 1 Pathophysiological heterogeneity in patients with HFpEF. Modified from Ref. ⁵

Beta-blockers

Two randomized trials were conducted to evaluate the role of beta-blockers compared to placebo in HFpEF, the J-DHF study, and the ELANDD study. Neither study has shown a clinical benefit from the use of beta-blockers.

Therapeutic use guided by the specific clinical scenario: in patients with atrial tachyarrhythmias, beta-blockers can be used to control heart rate. Likewise, beta-blockers can be used in HFpEF patients with associated comorbidities, such as coronary artery disease. However, after starting a beta blocker, it is important to rule out the presence of chronotropic incompetence, in which case a beta blocker could worsen the patient's symptoms.

Calcium antagonists

Numerous small studies have been conducted to evaluate the possible clinical benefit of calcium channel blockers in HFpEF; however, a clear clinical benefit has not been demonstrated. In the setting of atrial fibrillation in patients with normal EF and elevated natriuretic peptides, a small study showed an improvement in peak VO₂ with calcium antagonists compared to beta-blockers.¹⁰

Therapeutic use guided by the specific clinical scenario: refractory hypertension can benefit from the use of dihydropyridine calcium channel blockers, while atrial tachyarrhythmias can benefit from non-dihydropyridine ones.

Digoxin

The DIG-PEF study showed no long-term effects on mortality or the incidence of hospitalizations for heart failure in patients with EF >45%.

Therapeutic use guided by the specific clinical scenario: there is no evidence to support the use of digoxin in patients with HFpEF; conversely, there is growing evidence suggesting potential adverse outcomes in patients treated

with digoxin. However, digoxin may be useful in patients with right ventricular dysfunction due to its inotropic effects. In patients with atrial tachyarrhythmia, they may represent second choice drugs to achieve heart rate control.

Loop diuretics

Although there are no clinical studies on the use of loop diuretics in patients with HFpEF, they remain a mainstay of treatment for maintaining euvolemia and reducing lung congestion. Indirect evidence on the benefit of loop diuretics derives from the CHAMPION study, which used direct haemodynamic monitoring with the use of the CardioMEMS device to manage the titration of the diuretics. The study showed that treatment with loop diuretics guided by this implantable pulmonary blood pressure monitoring tool significantly reduced the frequency of hospitalizations for heart failure in patients with HFpEF.¹¹

Therapeutic use guided by the specific clinical scenario: the use of loop diuretics plays a primary role in most patients with HFpEF to lower the filling pressures of the left ventricle and reduce the symptoms of dyspnoea and exercise intolerance. They should be used as a first-line diuretic agent to achieve patient decongestion. Once a good initial diuresis is reached with the achievement of the euvolemic state, the dose of the loop diuretic must be reduced to a minimum.

Mineralocorticoid receptor antagonists

The mineralocorticoid receptor antagonist (MRA) was tested in patients with HFpEF in the TOPCAT study where no significant reduction in the primary endpoint (death from cardiovascular causes, cardiac arrest, or hospitalization from heart failure) was demonstrated in the study population. Subsequent data analyses revealed significant

disparities between patients enrolled in the Americas compared to the Russian Federation. In fact, in patients enrolled in the USA, there was a significant reduction in the primary composite outcome, suggesting the enrolment of a population of patients without heart failure in Russia and Georgia, therefore unable to benefit from the study drug.¹² In addition to the benefits of MRA's antihypertensive and diuretic properties, this class of drugs is believed to exert healthy anti-fibrotic effects in patients with collagen deposition and cardiac remodelling. However, the importance of a biomarker-based approach to phenotyping fibrosis should be stressed, as a recent study has shown that HFpEF patients with excessive elevation of myocardial fibrosis markers are resistant to MRA action.¹³

Therapeutic use guided by the specific clinical scenario: MRA must be taken into account in all patients with HFpEF and elevated BNP, previous history of hospitalization for decompensation, or evidence of volume overload. In all patients with loop diuretics where potassium supplementation is considered, MRA should be administered, unless contraindicated. A more targeted use of MRA could derive from the identification by biomarkers, such as ST2 and Galectin-3, of patients with a high degree of fibrosis.

Statins

Observational studies and small phase 2 clinical trials have suggested better results in HFpEF patients treated with statins.¹⁴ The benefits are believed to derive mainly from systemic anti-inflammatory effects resulting from the use of statins which can also improve endothelial function.

Therapeutic use guided by the specific clinical scenario: statins must be used as lipid-lowering agents in accordance with the dedicated guidelines, in particular in the setting of patients with coronary artery disease, diabetes mellitus, or chronic kidney disease. However, if a patient did not otherwise have a classic indication, statin treatment could be justified by its anti-inflammatory effects. In this context, the use of inflammation biomarkers, such as high sensitivity PCR and pentraxin, could strengthen this indication.

Angiotensin and neprilisin inhibitors

Sacubitril/valsartan, progenitor of the pharmacological class of angiotensin and neprilisin inhibitors, exerts a neurohormonal modulation action, leading to the increase of vasoactive peptides, with potential beneficial effects on diastolic function, reduction of fibrosis, vascular stiffness, increase of the diuresis and optimization of blood pressure control.¹⁵ In the PARAMOUNT study in patients with HFpEF sacubitril/valsartan improved surrogate outcomes, such as NTproBNP and left atrial size compared to valsartan. Such data and strong pathophysiological assumptions set the rationale for the PARAGON-HF study, a phase 3 clinical study, which evaluated the efficacy of sacubitril/valsartan compared to valsartan on morbidity and mortality in patients with HFpEF.¹⁶ Although the study did not demonstrate a statistically significant reduction ($P = 0.059$) of the primary outcome (cardiovascular mortality and heart failure hospitalizations), predefined subgroup analyses showed a possible benefit in patients with FE $\leq 57\%$ (value of median EF in

the trial) and in women. In addition, the study showed improvement of various secondary outcomes, such as quality of life and reduction of renal adverse events.

Therapeutic use guided by the specific clinical scenario: pending the knowledge as to how the regulatory agencies will implement the results of the PARAGON-HF trial and the possible reimbursement of the drug, it is possible to propose a targeted use of sacubitril/valsartan in decompensated patients with a range of EF from the mid-range (HFmrEF), or from 40% to 50%, up to the HFpEF patient with EF values of up to 55-60%, probably distinguished according to the sex of the patients (up to EF equal to 55% if man, up to 60% if woman).

Sodium glucose-2 transporter inhibitors

Sodium glucose-2 transporter (SGLT-2) inhibitors have reduced hospitalizations for heart failure in high-risk CV patients with diabetes mellitus (EMPAREG and DECLARE trials) and are currently under study in phase 3 trials on patients with HFpEF, with and without diabetes mellitus (EMPEROR PRESERVED with empagliflozin and DELIVER with dapagliflozin). It should be underlined that these drugs are likely to act with mechanisms of action that go beyond simple decongestion; however, actions still have to be clarified and are the subject of ongoing studies.

Therapeutic use guided by the specific clinical scenario: while awaiting the results of ongoing clinical studies, being a drug now recommended in the diabetic patient guidelines, in the diabetic patient with HFpEF the SGLT-2 inhibitors should be used as first-line drugs.

Promising drugs

Soluble Guanylate Cyclase Stimulators

A soluble guanylate cyclase (sGC) stimulator (vericiguat) was tested in patients with HFpEF in a randomized phase IIb clinical trial, the SOCRATES-PRESERVED study. The drug did not improve primary outcome, i.e. reduction of NTproBNP and left atrial volume. However, an improvement in physical activity was achieved with higher doses of vericiguat.

Therapeutic use guided by the specific clinical scenario: to date, there is no role for therapy with sGC stimulators in HFpEF. However, further ongoing Phase 2 studies, VITALITY, and CAPACITY, examine the effect of high doses of sGC stimulators on exercise tolerance in HFpEF.

Iron supplementation

The guidelines for the treatment of heart failure recommend the evaluation of ferritin and transferrin saturation in order to define the susceptibility of each patient to additional therapies. However, the reference values have been validated in patients with HFrEF and we do not yet know if these cut-offs are also applicable to those with HFpEF. Following the IRONOUT study, which showed a failure of oral polysaccharide iron therapy to increase ferritin levels and transferrin saturation in patients with HFrEF, subsequent studies (FAIR-HF2, AFFIRM-AHF, HEART FID, and FAIR-HFpEF) are in progress and use parenteral administration of iron carboxymaltose. The only one of these studies to

include patients with HFpEF is the FAIR-HFpEF, a double-blind randomized trial that is evaluating patients' exercise performance after 24 weeks of follow-up. The cut-offs used are those validated for HFREF: ferritin <100 ng/mL or ferritin values between 100 and 299 ng/mL but with transferrin saturation percentages <20%.

Therapeutic use guided by the specific clinical scenario: to date, there are no data on IV iron supplementation in the treatment of HFpEF, pending the results of the ongoing FAIR-HFpEF trial.

Conclusions

Heart failure with preserved left ventricular ejection fraction is a heterogeneous syndrome associated with comorbidity. To date there is no therapy capable of reducing mortality and morbidity in all HFpEF patients, conversely, there are effective therapies in specific phenotypes. Therefore, at present, the therapy of the HFpEF patient is a therapy aimed at its phenotypic characteristics. However, it is probable that in the future, through the use of machine learning, phenogroups capable of responding better to certain therapies can be identified, thus approaching ever more personalized medicine.

Conflict of interest: none declared.

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