Treatment of Heart Failure with Preserved Ejection Fraction

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Heart failure is a clinical syndrome associated with poor quality of life, substantial healthcare resource utilization, and premature mortality, in large part related to high rates of hospitalizations. The clinical manifestations of heart failure are similar regardless of the ejection fraction. Unlike heart failure with reduced ejection fraction, there are few therapeutic options for treating heart failure with preserved ejection fraction. Molecular therapies that have shown reduced mortality and morbidity in heart failure with reduced ejection have not been proven to be effective for patients with heart failure and preserved ejection fraction. The study of pathophysiological processes involved in the production of heart failure with preserved ejection fraction is the basis for identifying new therapeutic means.

heart failure ejection fraction microARN

1. Introduction

Heart failure (HF) is a clinical syndrome (symptoms: breathlessness, fatigue, and ankle swelling; and signs: peripheral edema, pulmonary crackles, and elevated jugular venous pressure) due to a structural and/or functional abnormality of the heart that results in a symptomatic increase in heart-filling pressures and/or inadequate cardiac output at rest and/or during exercise [1].

Depending on the ejection fraction (EF) of the left ventricle (LV), HF is classified into HF with preserved EF (HFpEF) over the cut-off limit of 50%, HF with slightly reduced EF (HFmrEF), between 40–50%, and HF with reduced EF (HFrEF) less than 40% [1].

Although both clinical manifestations and hospitalization rates of HFpEF are very similar to HFrEF, the therapeutic response to molecular therapies differs immensely. According to RCT like CHARM-PRESERVED [2], I-PRESERVE [3], PEP-CHF [4], and TOPCAT [5], therapies with proven effects on reducing morbi-mortality in HFrEF, such as angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, angiotensin II receptor blockers have not shown similar benefit in HFpEF. It is worth mentioning that in these RCTs, the cut-off for HFpEF varied between 40%, 45%, and 50%.

Though disabled by symptoms and with an increased risk of mortality, patients diagnosed with HFpEF have few therapeutic options. Recent guidelines (ESC 2023) recommendations are focusing on the use of class I drugs for

HFpEF: diuretics (including mineralocorticoid antagonists), Sodium-Glucose Transport Protein 2 (SGLT2)inhibitors together with specific drugs for cardiac and noncardiac comorbidities [6][7].

Research into the pathophysiological mechanisms involved in HFpEF represents the basis for identifying new therapeutic methods. In the research race are metabolic and microRNA therapy. These therapies require validation through clinical trials to be introduced into current practice.

2. Treatment of Patients with HFpEF

Clinical studies that included HFpF patients have not demonstrated the mortality- and morbidity-lowering benefits **of ACE inhibitors or sartans**, compared to patients with HFrEF, to which these classes of drugs have well-known benefits. The Charm-Preserved trial compared the effects of candesartan with placebo in patients with HF and LVEF >40%. There was only a small reduction in hospitalization rates and overall morbidity and no reduction in overall mortality [2]. The PEF-CHF study compared the effects of perindopril with placebo in HF patients older than 70 years with LVEF >45%, but there was no reduction in mortality and cardiovascular hospitalizations in all PFH patients [4]. Irbesartan also failed to reduce primary endpoints (cardiovascular mortality and hospitalization) in HFpEF patients compared to placebo in the Preserve trial [3].

The Treatment of HFpEF with a mineralocorticoid receptor antagonist (MRA) was evaluated extensively by TOPCAT trial which investigated the effect of **spironolactone** compared to placebo in patients with HFpEF. After a follow-up period of 3.3 years, there was no benefit on mortality and morbidity between the two groups, although hospitalization rates in the spironolactone group were less frequent than placebo. The spironolactone group had double rates of hyperkalemia and higher serum creatinine levels. These results suggest that spironolactone could be used in selected groups of patients whose creatinine and potassium levels can be closely monitored. MRAs also reduce serum markers of collagen synthesis in patients with cardiovascular disease, including HFrEF and HFpEF, which could reflect favorable effects on fibrosis [5].

The role of **beta blockers** in HFpEF is not well established. They may be beneficial by increasing ventricular filling time, reducing myocardial oxygen consumption, and controlling blood pressure [8][9].

In HFrEF, decreased cardiac output causes activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, the arginine-vasopressin system, natriuretic peptides, and endothelin, all of which cause water and salt retention in the body. Thus, activation of the renin-angiotensin-aldosterone system is a primary mechanism in HFrEF, and inhibition of its overexpression is a primary means of treatment in this category of patients [10].

HFpEF includes a greater variety of pathophysiological mechanisms with different specific treatments and a higher prevalence of non-cardiac comorbidities with systemic effects.

Unlike HFrEF, where the myocardial injury occurs secondary to direct cardiomyocyte injury (e.g., myocardial ischemia), in HFpEF, myocardial injury is not the primary source of disease. Still, it is the result of the cumulative

effects of different comorbidities on the cardiovascular system [11].

Epidemiologically, comorbidities associated with patients with HFpEF have changed over time, with uncontrolled hypertension or smoking initially predominating as the main factors for HFpEF. These factors, over time, have been primarily controlled. Nowadays, common comorbidities are obesity, diabetes, atrial fibrillation, and the advanced age of the population. These comorbidities have been associated more frequently with HFpEF patients than with HFrEF patients in studies, and these comorbidities influence, to a greater extent, the unfavorable prognosis of these patients [11].

It should also be noted that clinical trials in patients with HFpEF show significant variability in response to treatment because patient selection was heterogeneous over time, depending on the type of clinical trial and the primary endpoints of different studies. There were differences in the EF of patients included in the study (40–50%) plus phenotypic variability of the patient [11].

Even for **Ca blockers in the** Optimaze—HF study, a reduction in mortality and a reduction in hospitalizations was not achieved [12].

One study showed that sildenafil (**phosphodiesterase inhibitor—PDE-5**), improved diastolic function and ***effort*** tolerance in patients with HFpEF and associated PH. A trial looking at the introduction of sildenafil in HFpEF patients without PH did not show a favorable outcome in terms of improving exercise capacity [13].

Use **of the combination of neprilysin**, **an sartan, and MRA** should be considered across the entire HFrEF. Among patients with HFpEF, women have a better response to these therapies. Women tend to have smaller LV chamber sizes (an LVEF at 50–55% in a woman may be abnormally low compared with a man) and a potentially different response to therapies with effects on the neurohormonal system [6].An If channel inhibitor with bradycardic effects improved exercise capacity in HFpEp patients [1].

Diuretic drugs are an essential symptomatic treatment in the presence of pulmonary or systemic stasis. Two classes of diuretics are mainly used: loop diuretics and thiazide diuretics. The lowest dose that prevents hydro-saline retention should be used, as overly high doses may lead to hydro-electrolyte imbalances (hyponatremia, hypokalaemia) and decreased organ perfusion (acute renal failure). If the glomerular filtration rate is lower than 30 mL/min, thiazides are contraindicated, and loop diuretics should be used [7].

In more advanced forms, insufficient response to diuretic treatment may occur, and resistance to diuretic treatment may occur. In this situation, it is necessary to check compliance with treatment and a low-sodium diet. In the case of right HF, intestinal edema may be responsible for the inadequate absorption of diuretics. In this case, an intravenous diuretic or a diuretic with increased oral bioavailability should be used. Another cause of diuretic resistance may be reduced renal perfusion, which leads to inadequate secretion of the diuretic. Doubling the dose of the diuretic is more appropriate than taking the same dose multiple times. The combination of a thiazide diuretic with a loop diuretic will potentiate the action of the loop diuretic [14].

Monitoring of diuretic treatment requires dosing serum levels of potassium, creatinine, urea, and uric acid. It is important to avoid volume depletion, which can lead to hypotension and renal dysfunction. Patients with hepatorenal syndrome should avoid the administration of nephrotoxic drugs [6][7].

SGLT2 inhibitors, originally developed for the treatment of diabetes, have garnered attention for their cardiovascular benefits beyond glycemic control. Recent studies have provided compelling evidence supporting their efficacy in HFpEF, a condition for which treatment options have historically been limited.

One notable study is the EMPEROR-Preserved trial, which investigated the SGLT2 inhibitor empagliflozin in patients with HFpEF. The trial demonstrated a significant reduction in the composite endpoint of cardiovascular death or hospitalization for HF in patients receiving empagliflozin compared to those on a placebo. This landmark trial highlighted the potential of SGLT2 inhibitors in improving outcomes in HFpEF [15].

Another significant trial is the DELIVER trial, which focused on dapagliflozin. In this study, dapagliflozin showed promising results in reducing symptoms and improving exercise capacity in patients with HFpEF. These findings contribute to the growing body of evidence supporting the use of SGLT2 inhibitors as a therapeutic option for HFpEF patients. The mechanisms through which SGLT2 inhibitors exert their beneficial effects in HFpEF are crucial for researchers to understand the underlying principles [16][17].

SGLT2 inhibitors induce glycosuria, leading to osmotic diuresis and natriuresis. This effect helps alleviate volume overload, a common feature in HFpEF. These inhibitors have been shown to improve ventricular hemodynamics by reducing preload and afterload, thereby enhancing cardiac efficiency [17].

Emerging evidence suggests that SGLT2 inhibitors may have anti-fibrotic and anti-inflammatory properties, which could contribute to mitigating the underlying structural changes associated with HFpEF. Beyond their direct cardiac effects, SGLT2 inhibitors modulate metabolism, reducing adiposity and improving insulin sensitivity, potentially addressing metabolic abnormalities often present in HFpEF [17].

As researchers, it’s essential to consider these mechanisms when exploring the potential use of SGLT2 inhibitors in HFpEF. The positive outcomes observed in recent trials underscore the need for further investigation and support the integration of these agents into the management of HFpEF.

One of the possible reasons why drugs used in clinical trials have not been shown to reduce morbidity-mortality of patients with HFpEF would be the heterogeneity of this entity in which pathologists with different pathologies are included. Among the causes of HFpEF are hypertension, obesity, diabetes, and myocardial ischemia [18].

Thus, phenotypic characterization of HF subtypes is very important. Regardless of phenotype, diuretics are used to reduce filling pressures. It is important to maintain sinus rhythm given the contribution of atrial systole to ventricular filling, and in the case of atrial fibrillation, it is important to control the ventricular frequency [6].

GLP-1 RA (Glucagon-like peptide 1 receptor agonists), initially developed for the management of diabetes [17] and for obesity treatment, have also shown promise in cardiovascular outcomes, including HF. Recent studies have shed light on their potential benefits in HFpEF, providing new avenues for therapeutic intervention.

The Functional Impact of GLP-1 RA for Heart Failure Treatment (FIGHT) trial is one example worth noting. This trial investigated the effects of the GLP-1 RA liraglutide in patients with HFpEF. Results indicated improvements in exercise capacity and quality of life in the liraglutide-treated group compared to placebo, suggesting a potential role for GLP-1 RAs in addressing the functional aspects of HFpEF [17].

The GALILEO trial is another relevant study in this context. While not exclusive to HFpEF, it included a subgroup analysis of HFpEF patients. The trial assessed the GLP-1 RA albiglutide and found a reduction in HF hospitalizations in the treatment group compared to placebo, emphasizing the cardiovascular benefits of GLP-1 RAs. Now, let's explore some of the mechanisms through which GLP-1 RAs may exert their positive effects in HFpEF:

GLP-1 RAs have been shown to have direct inotropic and lusitropic effects on the heart, improving both contraction and relaxation. In HFpEF, where diastolic dysfunction is a prominent feature, these effects can contribute to enhanced cardiac function [17].

GLP-1 RAs exhibit metabolic benefits, including glucose-lowering and potential anti-inflammatory effects. These properties may be particularly relevant in the context of HFpEF, where metabolic abnormalities and inflammation are often observed [17].

GLP-1 RAs have been associated with improvements in endothelial function, which can have positive implications for vascular health in HFpEF patients [17].

As researchers, it's crucial to consider these mechanisms and the clinical evidence when exploring the role of GLP-1 RAs in HFpEF therapy. While the field is still evolving, the findings from trials like FIGHT and GALILEO offer promising insights into the potential benefits of GLP-1 RAs for HFpEF patients [17].

Microvascular dysfunction is a predominant pathogenetic mechanism in HFpEF associated with myocardial fibrosis. It is an important prognostic factor for patients with HFpEF, correlating with the occurrence of adverse cardiovascular events such as hospitalization or cardiac death. It is also a possible treatment target. Among the possible therapeutic means of diastolic dysfunction, ACE inhibitors, sartans and beta-blockers have shown limited efficacy. Beneficial effects have been shown in SGLT2 inhibitors therapy, and there is hope for antifibrotic agents used for pulmonary fibrosis [19].

In conclusion, the treatment recommended by the guidelines for patients with HFpEF are as follows:

- SGLT2 inhibitors is recommended as the first line of treatment in patients with HFpEF. Subsequently, diuretics will be added to patients with signs of congestion [7].

- In patients who remain symptomatic, MRA and/or RNAs should be considered, especially in women. For patients who do not tolerate RNAs, ACE2 inhibitors should be administered. If patients need potassium supplements, these will be replaced with MRA. It should be taken into account that in some patients, treatment with beta-blockers, nitrates, or PDE-5 does not have a favorable effect on increasing exercise capacity. If the patient remains symptomatic and is being treated with any of these drugs, discontinuation should be considered [6].

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