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Heart failure with preserved ejection fraction: future directions in medical treatment

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"The better insight we get into the distinct pathophysiological processes that underlie the heart failure with preserved ejection fraction phenotype, the higher the chances are to develop more relevant and effective therapies."

Approximately half of the heart failure population presents with preserved ejection fraction. Heart failure with preserved ejection fraction (HFpEF) is associated with high morbidity and mortality [1], which are merely attributed to the lack of universal non-invasive and invasive diagnostic criteria [2], the increased prevalence of associated comorbidities [3,4] and the lack of effective medical therapies. The latter underscores the need for development of novel, evidence-based pharmacotherapies that may alter the natural history of the disease.

Aldosterone antagonism

Aldosterone-mediated myocardial fibrosis is a key pathogenetic feature of HFpEF [5]. Aldosterone antagonism with spironolactone could potentially alleviate the increased collagen turnover, evolving to an interesting pharmacological target. A small, open-label clinical study showed that spironolactone can improve exercise tolerance and echocardiographic indices of diastolic dysfunction in elderly women with HFpEF [6]. In the Aldo-DHF [7], spironolactone treatment reduced significantly the left ventricular (LV) mass and natriuretic peptide levels; however, it had no effect on the functional capacity. A large, randomized-controlled, outcome trial (TOPCAT; ClinicalTrials.gov identifier: NCT00094302 [101]) is now underway and is expected to shed more light into the therapeutic implications of spironolactone in HFpEF.

Regulation of cyclic guanosine monophosphate–protein kinase G pathway

Upregulation of cyclic guanosine monophosphate (cGMP)–protein kinase G (PKG) pathway could theoretically be beneficial in HFpEF by exerting antihypertrophic and antifibrotic effects [8]. Stimulation of cGMP-PKG pathway can be achieved through augmentation of cGMP precursors, that is, natriuretic peptides and nitric oxide (NO) or through inhibition of cGMP catabolism with phosphodiesterase 5A inhibitors. Natriuretic peptides are degraded by a neutral endopeptidase called neprilysin. LCZ696 is a novel neprilysin inhibitor that combines angiotensin receptor blocking and neprilysin inhibiting properties. In the PARAMOUNT trial [9], LCZ696-treated patients had significantly greater reduction in NT-proBNP levels compared to valsartan with a comparable safety profile.

In HFpEF, the NO bioavailability decreases secondary to the endothelial NO synthase uncoupling from the oxidative depletion of its cofactor, tetrahydrobiopterin (BH4) [10]. That decreased NO concentration attenuates the PKG activity reinforcing the heart failure phenotype [11]. Tetrahydrobiopterin supplementation could play an important therapeutic role in HFpEF. A synthetic preparation of naturally occurring BH4

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is now available, and encouraging results have been reported in animal models of HFpEF [10,12]. Clinical validation of these experimental findings is awaited.

Phosphodiesterase 5A inhibitors are another emerging therapeutic option for HFpEF. Early clinical data supported the beneficial role of sildenafil, a potent phosphodiesterase 5A inhibitor, in HFpEF [13]; however, two recent clinical trials did not show promising results. In SIDAMI trial [14], sildenafil administration failed to demonstrate a significant reduction in LV filling pressures compared to placebo in patients with a recent myocardial infarction and preserved LV systolic function. The major caveat of this study was the inclusion of patients with ischemic heart disease who were not representative of the HFpEF population. Like SIDAMI trial, the RELAX trial [15] failed to show any significant effect of sildenafil on exercise capacity or clinical status over placebo in HFpEF patients.

Intracellular Ca^{2+} modulation

Heart failure with preserved ejection factor is associated with a prominent late Na^+ current (I_{Na}) that stimulates the sarcolemmal Na^+–Ca^{2+} exchanger entry mode, leading to intracellular Ca^{2+} overload and incomplete diastolic relaxation of sarcomeric proteins [16]. Therapies that alleviate the diastolic intracellular Ca^{2+} burden could have a role in HFpEF [17]. Ranolazine is a potent inhibitor of late I_{Na}, and its efficacy in HFpEF patients was tested in RALI-DHF trial [18]. Intravenous administration of ranolazine induced a significant decrease in pulmonary capillary wedge pressure in the acute phase, but failed to improve echocardiographic indices of diastolic dysfunction, exercise capacity and neurohormonal activation after 14 days of oral treatment. As of now, no definite conclusions about the efficacy of ranolazine in HFpEF can be drawn, as this pilot study included a limited number of patients and had a short follow-up.

SEA0400 is a potent inhibitor of Na^+–Ca^{2+} exchanger entry mode capable of reducing the intracellular Ca^{2+} overload and attenuating the LV fibrosis [19]. Despite the fact that the pharmacologic profile of this agent is appealing, there are no clinical data yet to prove its efficacy and safety in HFpEF.

Diastolic Ca^{2+} leak from the sarcoplasmic reticulum to the sarcoplasma through the ryanodine receptor complex plays a key role in diastolic dysfunction. Experimental studies showed that ryanodine receptor complex stabilizers, such as JTV519, can exert lusitropic effects improving the LV diastolic properties [20,21]. Clinical testing of the efficacy and safety of this agent in HFpEF is warranted.

Cardiac metabolism control

Heart failure with preserved ejection factor is characterized by accentuated metabolic demands [22]. Shifting myocardial energy substrate from free fatty acids to carbohydrates could improve the metabolic profile of the myocardial cells exerting a beneficial role in HFpEF. Perhexiline, thiazolidinediones and incretin-based therapies that increase insulin sensitivity and promote myocardial glucose uptake appear quite promising therapeutic options.

Perhexiline inhibits the mitochondrial transport of free fatty acids by carnitine palmitoyltransferase I and II, thereby shifting myocardial metabolism to carbohydrates. In a small, randomized controlled trial in patients with nonobstructive hypertrophic cardiomyopathy, perhexiline was associated with improved myocardial energetic status, enhanced myocardial relaxation kinetics and improved exercise capacity compared to placebo [23]. Another randomized controlled trial is currently underway (ClinicalTrials.gov Identifier: NCT00839228 [101]) aiming to evaluate the efficacy of perhexiline versus placebo on peak oxygen consumption in patients with HFpEF.

Thiazolidinediones, such as rosiglitazone and pioglitazone, are highly selective peroxisome proliferator-activated receptor-γ agonists that regulate the transcription of insulin-responsive mRNA, thereby increasing the insulin sensitivity of myocardial cells. Two randomized clinical trials in diabetic patients without overt heart disease suggested that rosiglitazone and pioglitazone can effectively increase the myocardial glucose uptake and improve the diastolic performance of myocardium [24,25]. Outcome studies are needed to further assess the role of these agents in HFpEF.

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Glucagon-like peptide-1 (GLP-1) is a hormone promoting glucose uptake over free fatty acids by the myocardial cells via the translocation of glucose transporter 1 and 4 from the sarcoplasma to the sarcolemma [26]. Glucagon-like peptide-1 stimulation through GLP-1 analogues, such as exenatide, is an emerging pharmacologic target in HFpEF, especially in the presence of diabetes. A Phase IV clinical trial (ClinicalTrials.gov Identifier: NCT00799435 [101]) is currently underway aiming to assess the role of exenatide on LV diastolic stiffness in diabetic patients with HFpEF.

Conclusions

Over the last 5 years, a wide spectrum of novel pharmacotherapies for HFpEF has emerged. Despite the fact that experimental and early clinical data have been quite promising, the majority of the large clinical trials failed to prove the efficacy of most of these medications. New clinical trials are now underway and their results are anticipated to create important new perspectives in the HFpEF pharmacotherapy. The better insight we get into the distinct pathophysiological processes that underlie the HFpEF phenotype, the higher the chances are to develop more relevant and effective therapies.

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