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Editorial

Metformin and its Potential for Heart Failure with Preserved Ejection Fraction

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Introduction

The health burden of Heart Failure with Preserved Ejection Fraction (HFpEF) is substantial. In some countries, HFpEF is the leading cause of hospital admission in patients over 65 years of age and is predicted to be the leading cause of mortality within a decade [1,2]. HFpEF is characterised by reduced exercise capacity and ability to engage in activities of daily living, poor Health-Related Quality of Life (HRQoL), high rates of hospitalisation, and premature mortality [3]. In sharp contrast to the wealth of proven therapies for Heart Failure with Reduced Ejection Fraction (HFrEF) that have improved mortality and morbidity, there is a distinct lack of treatment options for HFpEF. Drugs or devices which are recommended in current HF treatment guidelines to improve outcomes in HFrEF have not been shown to have similar benefit in HFpEF patients, and to date, phase III randomised controlled trials have not consistently yielded evidence-based therapy for HFpEF [4]. The lack of treatment options in patients with HFpEF represents a significant unmet need that urgently demand new therapeutic strategies that arguably target mechanisms specific for HFpEF.

Targeting co-morbidities in HFpEF

A key feature of HFpEF patients is the presence of several comorbidities, including obesity, diabetes and hypertension, that contribute not only to the aetiology of HFpEF but also to the progression of the disease in HFpEF [5-7]. A new paradigm on the relationship between comorbidities and the development of HFpEF has been proposed [8]. This hypothesised that the high prevalence of comorbidities in HFpEF synergistically induces a systemic pro-inflammatory state, leading to coronary microvascular and generalized endothelial inflammation, which in turn results in abnormalities in ventricular and vascular function ultimately leading to increased Left Ventricular Hypertrophy (LVH), diastolic dysfunction due to LV stiffness and consequent HFpEF development. Indeed, patients with HFpEF have evidence of inflammation not only in the myocardium but also in lungs, skeletal muscles, and kidneys that contributes to pulmonary hypertension, exercise intolerance, and renal impairment in HFpEF [9,10]. In the BIOSTAT study, we recently confirmed the importance of inflammation in HFpEF patients in a network analysis of 92 biomarkers in patients with HFpEF [11]. These observations support the notion that targeting comorbidities and the consequent systemic microcirculatory dysfunction may be a strategic approach in addressing the unmet therapeutic needs of HFpEF [12].

Obesity, metabolic syndrome, insulin resistance, diabetes and HFpEF

There are several lines of evidence strongly suggesting that obesity and diabetes contributes to the risk of developing and worsening HFpEF [13]. Obesity is highly prevalent (50%) in HFpEF patients [12]. In patients with HFpEF, Body Mass Index (BMI) is strongly associated with New York Heart Association (NYHA) functional class and a predictor of poor outcome [14,15]. It is likely that obesity is more than just a co-morbidity for HFpEF and instead may be involved in its pathogenesis. Obesity has been identified as a risk factor for HFpEF [16,17]. Increased adiposity promotes hypertension, systemic inflammation and insulin resistance, all of which are commonly observed in patients with HFpEF [18]. Obesity also impairs cardiac, vascular, and skeletal muscle function [19]. Adipose tissue is metabolically active and produces cardiovascular active substances such as inflammatory cytokines and adipokines. In addition, increased visceral adiposity on multi-slice imaging has been shown to be associated with a higher risk of HFpEF events [20].

With respect to diabetes and HFpEF, there is evidence suggesting that there are two distinct Heart Failure (HF) phenotypes associated with diabetic cardiomyopathy. The first is of Type 1 Diabetes (T1D) that leads to HFrEF with a dilated left ventricular phenotype and the second is of Type 2 Diabetes (T2D)

associated with obesity that leads to a HFpEF phenotype with concentric remodelling of the Left Ventricle (LV) [21]. Seferović and Paulus recently presented evidence attributing the aetiology of the two phenotypes to the differential principal involvement of either microvascular endothelial cells (HFpEF) or cardiac myocytes (HFrEF) in the remodelling process [22]. In post-hoc analyses of both the I-PRESERVE trial as well as in CHARM-Preserved, HFpEF patients with T2D had more fluid congestion and worse quality of life and prognosis [23,24]. Thus, obesity and diabetes are not only risk factors for the development of HFpEF but also have a significant impact on its symptoms and outcome. Obesity and T2D (or diabesity) are therefore attractive potential therapeutic targets in HFpEF. Supportive evidence that obesity contributes to exercise intolerance in HFpEF through systemic inflammation has come from a 20-week caloric restriction diet in obese HFpEF that demonstrated an improvement in peak VO2 that strongly correlated with reduced body fat mass and hs-CRP, a biomarker of inflammation [25].

Targeting Obesity in HFpEF

Recognising the importance of comorbidities (that include obesity and insulin resistance), our collaborator, CSL and key investigators in the field have proposed six plausible mechanisms of potential translational significance: 3 haemodynamic mechanisms (left atrial hypertension, pulmonary hypertension, and volume overload) and 3 cellular/molecular mechanisms (microvascular inflammation, cardio-metabolic abnormalities, and cellular/extracellular structural changes) [3]. The first three haemodynamic mechanisms (left atrial hypertension, pulmonary hypertension, and volume overload) are currently being targeted with devices (interatrial septal device) and drugs in on going trials with endothelin antagonists, guanylate cyclase modulators, ARNI (in the PARAGON study) and SGLT2 inhibitors (EMPEROR-PRESERVED) [3,26] Of note, inter-atrial septal device intervention that reduces Pulmonary Capillary Wedge Pressure (PCWP) was shown to be safe and potentially beneficial at 1-year although its impact on hard outcomes remains unclear [27,28]. We also recognise the intense interest around SGLT2 inhibitors in HFpEF with at least 2 multi-centre international trials exploring this, EMPEROR-PRESERVED (with empagliflozin) and PRESERVED-HF (with dapagliflozin). However, we believe that there is a need to explore other potential therapeutic interventions. In this respect, the diabetic drug, metformin, may have potential in the setting of HFpEF.

Metformin and Its Potential in HFpEF

There are plausible reasons why metformin may be useful in HFpEF (Figure 1). Systemic inflammation is a key pathophysiological process in many of the comorbidities associated with HFpEF. There is evidence that metformin may have anti-inflammatory effects. In a translational study, we have shown that metformin inhibited tumour necrosis factor-α–dependent IκB degradation and the expression of pro-inflammatory mediators' interleukin-6, interleukin-1β, and CXCL1/2 in primary hepatocytes of healthy animals [29]. These in-vitro findings were validated in a large population cohort study of treatment naïve T2D patients and also in a subset of non-diabetic HF patients from a double blind randomized controlled trial [29]. Second, metformin has the potential to regress the adverse ventricular remodelling in non-diabetic patients with coronary artery disease as observed in the MET-REMODEL trial, a consistent finding with preclinical evidence [30]. Third, metformin's ability to reduce weight is a consideration for its potential therapeutic benefits in HFpEF. In the MET-REMODEL trial, metformin reduced weight (by 4 kg), a consistent finding with metformin use [30] . This reduction in weight could be beneficial in HFpEF. Fourth, metformin can also reduce blood pressure that could also potentially benefit HFpEF. Fifth, a recent study reported that metformin offers therapeutic benefit in mice models with HFpEF–like phenotype by reducing LV diastolic stiffness, an effect explained by metformin induced reduction in titin-based passive stiffness [31]. Finally, metformin has also been shown to improve pulmonary hypertension related to HFpEF, at least in animal models [32,33]. Although metformin has not been examined in patients with HFpEF, It is noteworthy that in patients with HFrEF and insulin resistance, metformin improved the VE/VCO2 slope in patients with HFrEF and insulin resistance [34]. In that study, there was also a non-statistical marginal reduction of NTproBNP in the metformin arm.

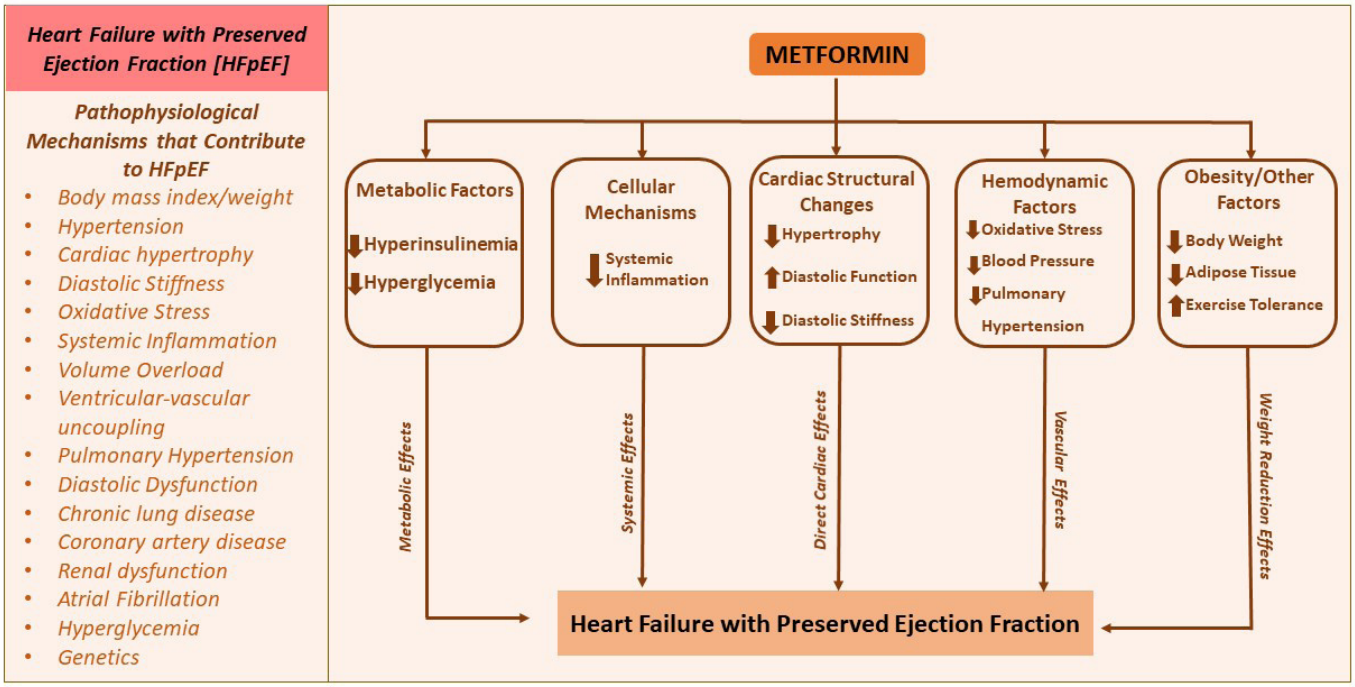

Figure 1: Plausible reasons why Metformin may be useful in HFpEF.

Taking into account all of the above therapeutic benefits observed in clinical and preclinical studies, it is clear that there is a need to explore the magnitude of the pleotropic effects of metformin, particularly in patients with HFpEF. Future studies exploring the beneficial effects of metformin in HFpEF patients are warranted (https://clinicaltrials.gov/ct2/show/NCT03629340).

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