Treatment of HFpEF: an unresolved enigma

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Background: Heart failure with preserved ejection fraction (HFpEF) accounts for 50% of HF cases. The growth of the HFpEF population is in part attributable to a changing demography, with HF being most prevalent in the elderly. At the same time, the pathophysiology of HFpEF is not clear. While the majority of HFpEF patients do not have a recognized primary cardiac pathology, they are of advanced age, more often female and have high prevalence of non-cardiac comorbidities, such as hypertension, obesity, diabetes, chronic obstructive pulmonary disease and chronic kidney disease. In a recently proposed paradigm, HFpEF is regarded as a systemic syndrome mediated in large part by risk factors and co-morbidities, resulting in a systemic multi-organ proinflammatory state which affects the heart, leading to myocardial remodelling and dysfunction through a signalling cascade, which begins with coronary microvascular endothelial dysfunction. It subsequently involves myocardial infiltration by activated macrophages, which induce reactive interstitial fibrosis and altered communication between endothelial cells and surrounding cardiomyocytes.

Current guidelines confirm that no treatment has been shown to reduce morbidity and mortality in patients with HFpEF and management is limited to treatment of comorbidities and administration of diuretics. While several candidates such as statins, advanced glycation end-product breaker alagebrium, soluble guanylate cyclase pathway stimulator verciguat, If inhibitor ivabradine and late INa inhibitor ranolazine await proper trials in HFpEF settings, the scientific and clinical community looks forward for the results of the ongoing phase III trial with sacubitril/valsartan (PARAGON-HF).

Despite the diversity of the HFpEF syndrome, the treatment strategy thus far has focused on a one-size-fits-all approach. However, a more tailored, personalized approach may be more appropriate for heterogeneous HFpEF patients. While waiting for the identification of better therapeutic targets, to test the potential application of old drugs can be also worth.

Aims: On these bases, our recent studies aimed to determine whether the chronic administration of sitagliptin (SITA) or ranolazine (RAN) affects the course of LV dysfunction in a Dahl salt-sensitive (Dahl/SS) rat model of HFpEF. When fed high-salt diets, Dahl/SS rats develop hypertension, renal failure, insulin resistance and dyslipidemia. The development of HF by 19 weeks is not associated with a decrease in LV systolic function or an increase in LV end-diastolic diameter, which mimics the characteristics of clinically observed HFpEF.

The widespread expression of dipeptidyl peptidase 4 (DPP4) in vasculature, myocardium and immune cells raises the possibility that this protein plays a role in cardiovascular function. In

particular, the finding that DPP4 activity is often associated with inflammation and cardiac remodelling points to an involvement of DPP4 in the pathophysiology of HF. Additionally, one of the potential mechanisms involved in HFpEF pathophysiology is an increase late Na+ current (INa) in cardiac myocytes. RAN by selectively inhibiting late INa can decrease Na+-dependent calcium accumulation and is expected to promote Ca2+ extrusion through the Na+/Ca2+ exchanger improving myocyte relaxation and diastolic tension, as shown in several preclinical and clinical settings.

Results and Conclusions: SITA positively modulated active relaxation and passive diastolic compliance interfering with inflammatory-related endothelial dysfunction and fibrosis associated with HFpEF. Because of a non-diabetic nature of our model and unaltered blood glucose levels, the cardioprotective action of SITA lays beyond its effect on glycaemia. Inhibition of late INa by administration of RAN resulted in the improvement in diastolic function without significant changes in blood pressure. In this view, the findings presented here provide insights into the role of DPP4 inhibition and a decrease of the late INa in HFpEF. Because of the pathophysiological complexity and a significant clinical heterogeneity of patients that present with an HFpEF syndrome, our results may be relevant to the specific patient subpopulation.