Cardio-renal positive effects of dipeptidyl peptidase 4-inhibitor sitagliptin preserve diastolic function in a model of heart failure with preserved ejection fraction

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Background: Heart failure with preserved ejection fraction (HFpEF) and chronic kidney disease (CKD) often share co-morbidities like hypertension and diabetes. Moreover, renal dysfunction in HFpEF is common and is associated with increased mortality. Co-existence of heart and kidney failure is a clinical challenge, because of diagnostic and therapeutic difficulties, since many HF medications may cause, or are contraindicated in the presence of renal failure.

Several studies suggesting that dipeptidyl peptidase 4 (DPP4) might be involved in the pathophysiology of heart failure prompted investigations of DPP4 inhibitors cardiovascular safety and potential benefits in HFpEF. In addition, DPP4 inhibitors have shown to delay CKD progression in experimental diabetic nephropathy.

Aims: To determine whether DPP4 inhibitor sitagliptin (SITA) affects the progression of HFpEF and CKD independently from the effects on glycaemia. To identify mechanisms involved in the potential cardio-renal protection.

Experimental Approach: Seven-week-old Dahl salt-sensitive (Dahl/SS) rats fed a high salt diet (8% NaCl) for 5 weeks to induce hypertension. Then, rats continued with a high salt diet and were administered with either SITA (10 mg•kg-1 by oral gavage) or vehicle for the following 8 weeks.

Key Results: Treatment with SITA attenuated diastolic dysfunction ameliorating hemodynamic indices. During 8 weeks of the treatment with SITA, blood pressure remained markedly elevated, with a slight, but significant reduction observed only at 19 weeks of age. Although such a reduction in blood pressure may have participated in functional and structural modifications, these changes cannot exclusively account for the beneficial effects of the drug. Because of a non-diabetic nature of our model and unaltered blood glucose levels, the cardio-renal protective action of SITA certainly lays beyond its effect on glycaemia.

Interestingly, SITA determined a reduction in DPP4 activity in the heart and kidney and an increase in GLP-1 levels in plasma. The link between high blood pressure and cardio-renal damage may involve high levels of oxidative stress and a low-grade systemic inflammation. In fact, levels of pro-inflammatory tumor necrosis factor-α, IL-6 and monocyte chemoattractant protein-1 were elevated in Dahl/SS rats but reduced by SITA treatment. SITA decreased the levels of eNOS monomer, responsible for reactive oxygen species generation, and elevated the amount of NO-producing dimeric form. The markers of oxidative and nitrosative stress were decreased. Oxidative stress and pro-inflammatory status observed in Dahl/SS rats contribute to activation of pro-fibrotic pathways in the myocardium and kidney. Increase of collagen deposition and activation of pro-fibrotic signalling that leads to elevated myocardial stiffness were attenuated by SITA. Moreover, a

remarkable renal tubulointerstitial fibrosis and glomerulosclerosis in high salt diet-fed rats were significantly reduced with administration of SITA.

Conclusions and Implications: SITA positively modulates active relaxation and passive diastolic compliance interfering with inflammatory-related endothelial dysfunction and fibrosis associated with HFpEF. Positive cardiac outcome and simultaneous kidney protection highlight the systemic nature of HFpEF pathophysiology and the multi-organ positive effects of SITA.