

MARTÍN DONATO ^{MTSAC}**The role of incretins in diastolic heart failure associated with diabetes mellitus**

Hamdani N, Hervent AS, Vandekerckhove L, Matheussen V, Demolder M, Baerts L, De Meester I, Linke WA, Paulus WJ, De Keulenaer GW. Left ventricular diastolic dysfunction and myocardial stiffness in diabetic mice is attenuated by inhibition of dipeptidyl peptidase 4. **Cardiovasc Res** Oct 23. doi:10.1093/cvr/cvu223

Type 2 diabetes mellitus (DM-2) is an important risk factor for the development of heart failure. There are multiple and complex DM mechanisms inducing left ventricular failure. Diastolic disorders are one of its earliest manifestations, characterized by ventricular stiffness associated with the interstitial fibrosis displayed by this disease.

Dipeptidylpeptidase-4 (DPP-4) inhibitors are a new generation of drugs used for the treatment of DM-2. These agents inhibit incretin degradation, such as glucagon-like peptide-1 (GLP-1) which stimulates insulin secretion from pancreatic β -cells and also has a direct effect on other organs through the GLP-1 receptor (GLP-1R).

The aim of this study was to evaluate the effect of a DPP-4 inhibitor on left ventricular structure and function of leptin receptor-deficient mice that develop obesity and DM-2 as a side effect (Leprdb/db). Treatment with sitagliptin (SITA, a DPP-4 inhibitor)

for 8 weeks produced 85% reduction of plasma DPP-4 without evidence of hypoglycemic effects. Analysis of ventricular function from pressure curves obtained by cardiac catheterization showed that SITA treatment does not affect contractility; however, it reduces ventricular stiffness, increases arterial elastance and consequently increases systolic volume. In addition, SITA reduces slightly the increase of interstitial fibrosis.

As there is no significant effect of SITA on fibrosis or the collagen type, the improved distensibility must be explained by an extracellular matrix-independent mechanism. For this reason, the authors assessed the passive force/sarcomere length relationship of isolated Leprdb/db myocytes treated with SITA, and compared it with a group not receiving the drug. SITA-treated myocytes significantly reduced stiffness, and significantly increased titin phosphorylation, a sarcomeric protein which participates directly in myocyte stiffness regulation.

Thus, 8-week treatment with SITA decreased myocardial stiffness in a DM-2 mouse model and increased systolic output, without modifying blood glucose levels.

The mechanism by which DPP-4 inhibition improves diastolic function is still unclear; however, it seems to be mediated by activation of the cGMP-PKG pathway. This novel SITA effect could give rise to new strategies for the treatment of diastolic dysfunction associated with diabetes.