Saxagliptin Prevents Increased Coronary Arterial Stiffness and Advanced Glycation End Product Expression in a Miniature Swine Model of Heart Failure with Preserved Ejection Fraction

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Objective: Our lab recently reported coronary arterial dysfunction, a hallmark feature of heart failure (HF), and myocardial oxygen supply/demand imbalance in a mini-swine model of heart failure with preserved ejection fraction (HFpEF). Accumulation of advanced glycation end products (AGEs) may play a role in this process by increasing vascular mechanical stiffness. Dipeptidyl-peptidase 4 (DPP4) inhibitors have been shown to inhibit AGEs in diabetes, however, their impact on coronary fibrotic remodeling in HFpEF is unknown. We hypothesized chronic treatment with the DPP4 inhibitor saxagliptin would prevent enhanced mechanical stiffness and AGEs accumulation in coronaries from HFpEF swine.

Methods: Yucatan mini-swine (3-months old) were aortic-banded (AB) and divided into 3 groups: control (CON; n=6), HF-control (HF; n=7), and HF saxagliptin-treated (HF-SAX; n=9). Coronary blood flow (CBF), myocardial oxygen consumption (MVO_2), ex vivo mechanical stiffness, AGEs protein, and mRNA expression of stiffness-related genes were assessed on the left circumflex (LCX) and right coronary artery (RCA) 6 months post-AB and 23-weeks post-saxagliptin treatment (started 1-week post-AB).

Results: A significant increase in the elastic modulus of the RCA and LCX in HF animals was associated with increased vascular medial AGEs protein expression compared to CON. Increased mechanical stiffness and AGEs expression was prevented in HF-SAX animals. Increased AGEs expression in the HF group occurred independent of changes in plasma glucose concentration. Parallel trends in the mRNA expression of several extracellular matrix components and regulatory biomarkers were observed in HF animals, including increased collagen I/III, TIMP-1, and decreased MMP-9. Increased mechanical stiffness in HF animals was associated with a leftward shift in the CBF:MVO_2 relationship that was prevented by saxagliptin.

Conclusion: Saxagliptin prevented increases in coronary mechanical stiffness and AGEs expression independent of glucose regulation, suggesting DPP4 inhibition may be a viable therapeutic option for limiting vascular fibrosis and related coronary arterial dysfunction during developing HFpEF.

Figure 1

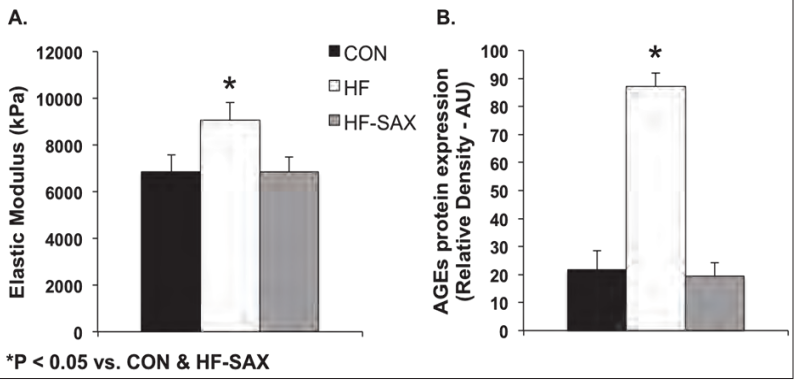

Figure 2