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OR-02

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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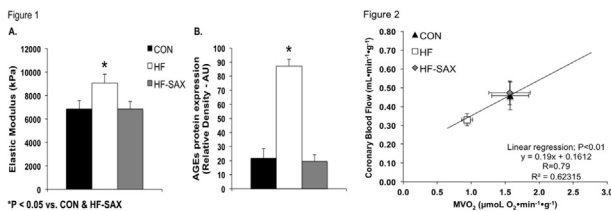
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Objective: Our lab recently reported coronary arterial dysfunction, a hallmark feature of heart failure (HF), and myocardial oxygen supply/demand imbalance in a mini-swine model of heart failure with preserved ejection fraction (HFpEF). Accumulation 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.



OR-03

CARDIO-RESPIRATORY INTERACTIONS IMMEDIATELY FOLLOWING DYNAMIC LEG CYCLING: INFLUENCES OF THE MUSCLE PUMP

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Changes in cardiorespiratory coupling during the moments immediately following prolonged exercise are not well understood and the mode of recovery during the transition to post-exercise may be important. Cardiorespiratory coupling influences the stresses put on the arterial system by oscillatory changes in cardiac output and systemic vascular resistance. We hypothesized that the cessation of muscle pump activity and the unloading of the cardiopulmonary baroreceptors during inactive recovery would allow for exacerbated oscillations in neutrally-mediated cardiovascular function and arterial control resulting in an unstable cardiorespiratory environment. To test this hypothesis, healthy subjects ($n = 13$, 3 female) performed 40 minutes high intensity two-legged cycling exercise followed by active and inactive recovery. Electrocardiogram (HR), beat-to-beat blood pressure (BP), thoracic impedance (Z_0), respiratory frequency and muscle sympathetic nerve activity (MSNA) were continuously monitored throughout the protocol. Data analysis was performed in the minute prior to cessation of pedaling and the first minute of inactive recovery. Z_0 was significantly higher during inactive vs. active recovery (57.1 vs. 55.8 units, $P = 0.02$; Fig. A). Respiratory coupling to HR, BP and MSNA was confirmed by signal coherence analysis (0.98, 0.98 and 0.86, respectively). Spontaneous baroreflex sensitivity was significantly increased during inactive recovery for the Up-Up reflex (2.58 fold, $P < 0.05$; Fig. B) and tended to be increased for the Down-Down reflex (1.53 fold, $P = .10$; Fig. B). We conclude that the magnitude of respiratory-induced oscillations in BP, HR, and MSNA during recovery from exercise is dependent on muscle pump induced changes in central blood volume. Greater cardiovascular sensitivity during inactive recovery may place a larger strain on the arterial system and may partially explain increased risk of sudden death following acute exercise.

