The Impact of DPP-4 and PDE5 Inhibition on Cardiac Fibrotic Remodeling in Mini-Swine with Heart Failure

Noelany Cruz Rivera*, Pamela J. Zgoda*, Emily G. Dehn, Melissa S. Cobb, Jessica A. Hiemstra, Jan R. Ivey, & Craig A. Emter

Biomedical Sciences, University of Missouri, Columbia, MO (*Co-first authors)

College of Veterinary Medicine, University of Missouri

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a prevalent form of heart disease impacting millions of people and associated with high morbidity and mortality. Current treatments have failed to prevent the development of the disease and as a result, there is a critical need for research examining novel treatment options for HFpEF patients. Disrupted cyclic guanosine monophosphate (cGMP) signaling, a result of impaired production or enhanced catabolism, may play a role in the development of HFpEF. Therefore, the purpose of this study was to promote cGMP signaling via two mechanisms: 1) the DPP-4 inhibitor saxagliptin (SAX); and 2) the PDE5 inhibitor tadalafil (TAD). We hypothesized preservation of cGMP signaling could prevent or decrease the accumulation of cardiac fibrosis induced by HFpEF. We assessed extracellular matrix remodeling 6 months post-aortic banding (AB) in intact, 9 month old male Yucatan mini-swine divided into four groups: control non-banded (CON; n=6), AB-control (AB; n=7), AB saxagliptin-treated (AB-SAX; n=9), and AB tadalafil-treated (AB-TAD; n=8). Treatment with TAD (2mg/kg BID) or SAX (10 mg/kg SID) began 1 week post-surgery and continued for 6 months. Tissue was isolated from the left ventricle (LV), fixed in formalin, and Picrosirius Red Stain was used to determine total LV collagen. Collagen was quantified from four separate, representative fields from each LV sample and quantified using Image-Pro Plus analysis software (MediaCybernetics, version 6.2, Bethesda, MD) and expressed as the percent area stained. The collagen percent area was significantly increased in the AB group. cGMP activity was increased in AB-TAD animals, however, increased collagen expression was prevented in both the AB-SAX and AB-TAD groups. Our results suggest manipulation of cGMP signaling is not required for saxagliptin's effect on limiting LV collagen accumulation. Future directions include correlating cardiomyocyte cGMP protein expression/activity and determining the mechanism by which saxagliptin limits cardiac fibrotic remodeling in HFpEF.

Hypothesis

Preservation of cGMP signaling will prevent or decrease the accumulation of cardiac fibrosis induced by HFpEF in aortic-banded Yucatan miniature swine.

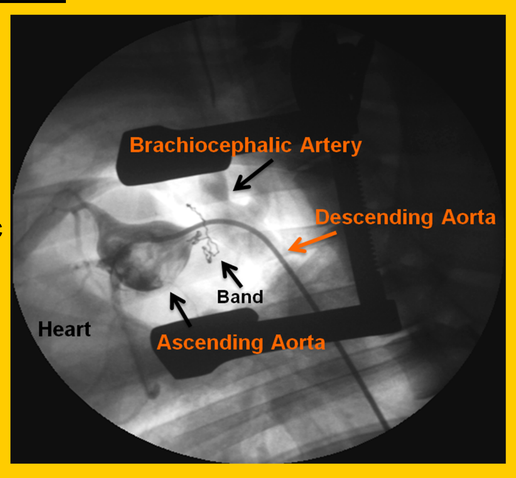
Objective

The objective of this study was to assess cardiac fibrotic remodeling while promoting cGMP signaling via two mechanisms: 1) the DPP-4 inhibitor saxagliptin (SAX); and 2) the PDE5 inhibitor tadalafil (TAD) in a Yucatan miniature swine model of HFpEF.

METHODS

Aortic Banding Procedure:

LV hypertrophy/heart failure was induced by aortic banding at the ascending aorta proximal to the brachiocephalic artery. A systolic trans-stenotic pressure gradient of 50 mmHg was set at a MAP of 90 mmHg (distal to the band) and A heart rate of 100 beats/min.



Groups:

- Control non-treated, non-banded (CON); n=6
- Aortic-Banded non-treated (AB); n=7
- Aortic-Banded tadalafil treated (AB-TAD); n=8
- Aortic-Banded saxagliptin treated (AB-SAX); n= 9

Dosing Regimen:

One after aortic-banding, animals began treatment for a period of 24 weeks with either:

1.) Saxagliptin: 10mg/kg/day

2.) Tadalafil: 2mg/kg/BID

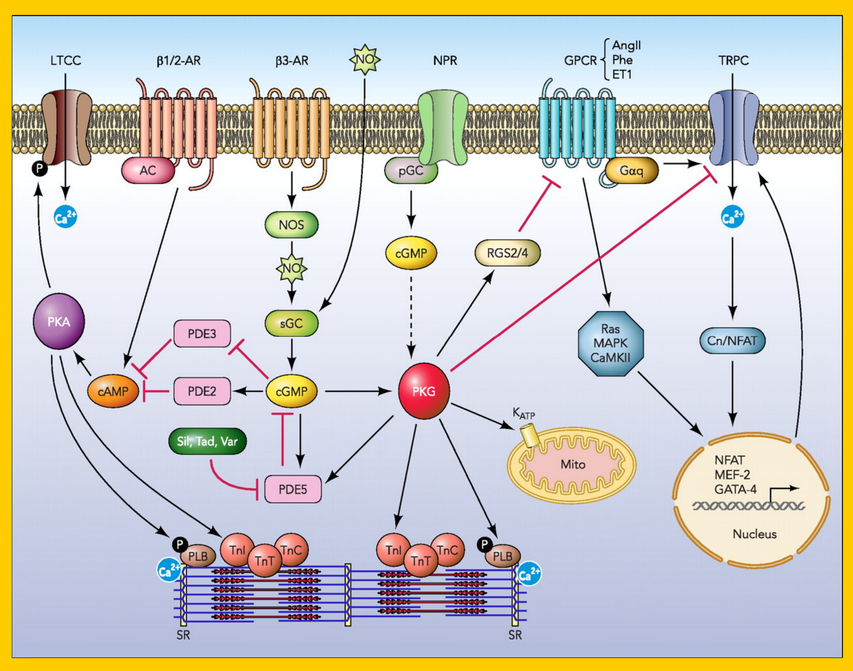


Figure 1. Regulation of myocyte stress-stimulation pathways by PKG-cGMP-PDE5. (Lee & Kass. *Physiology* 2012;27:248-258.)

RESULTS

LV cGMP and PKG Activity

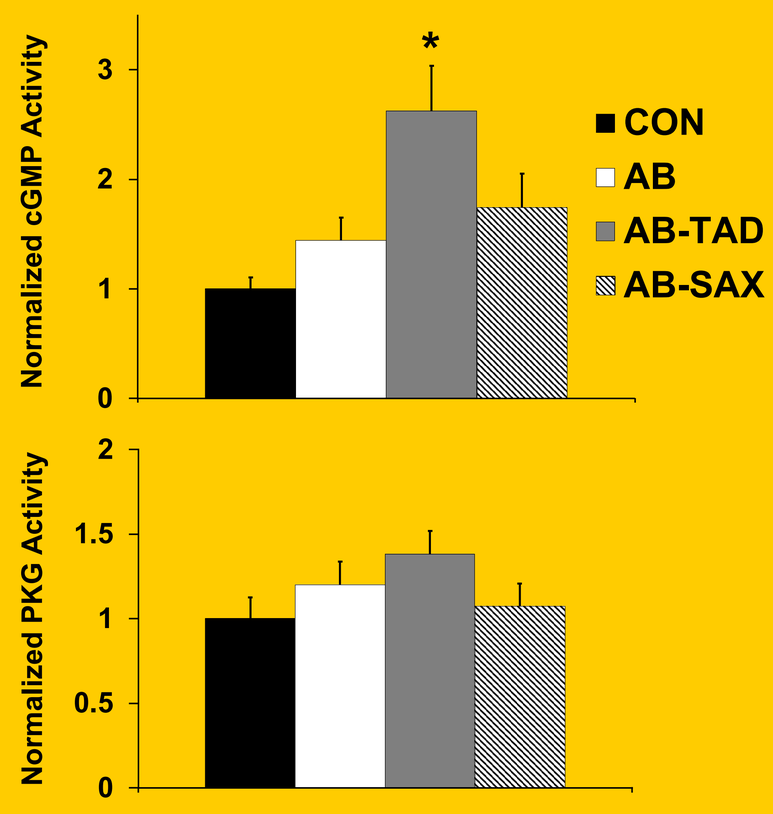
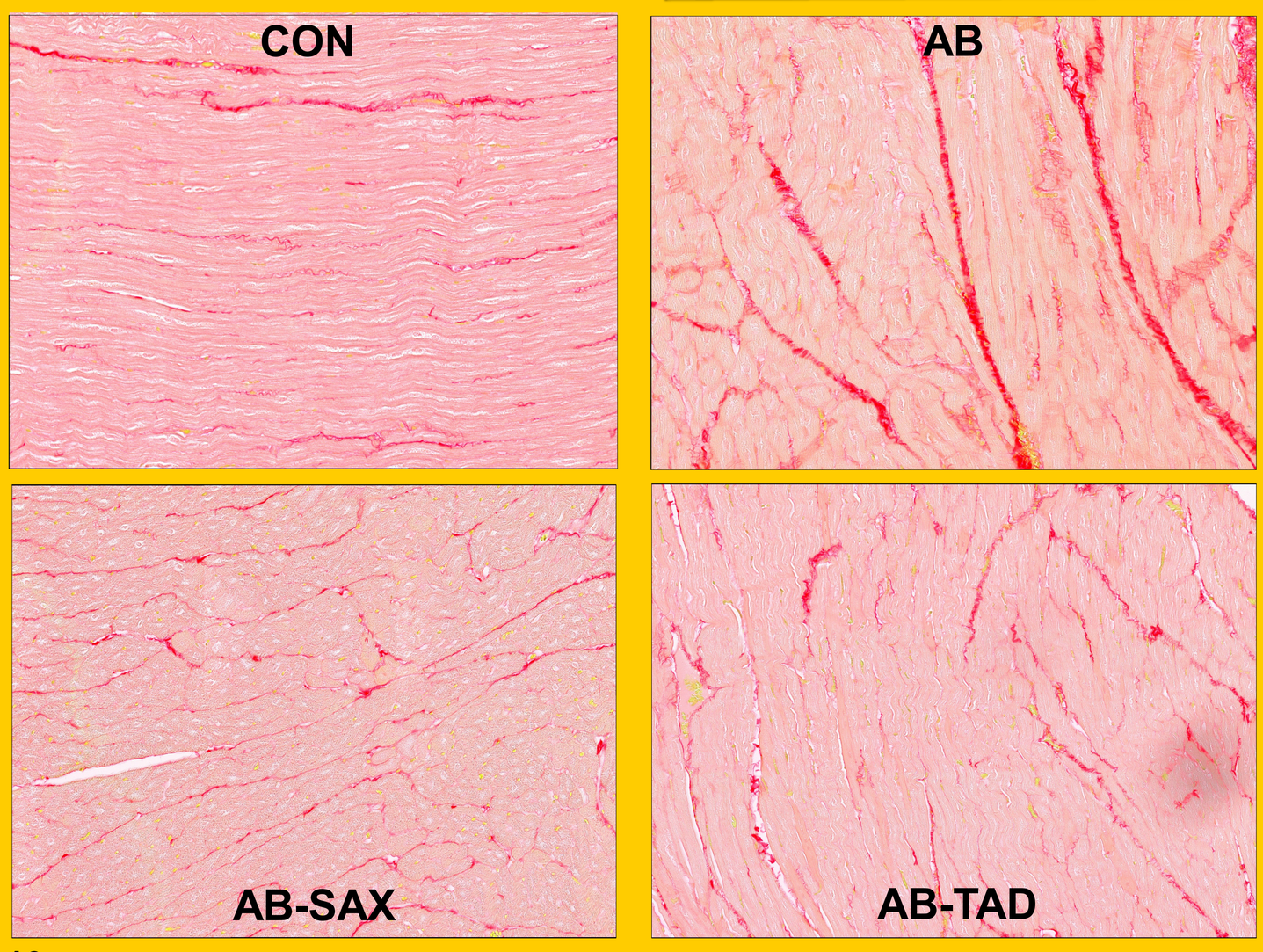


Figure 2. LV cGMP and PKG activity. cGMP activity was significantly increased following treatment with tadalafil. (*P < 0.05 vs. all groups)

LV Total Collagen



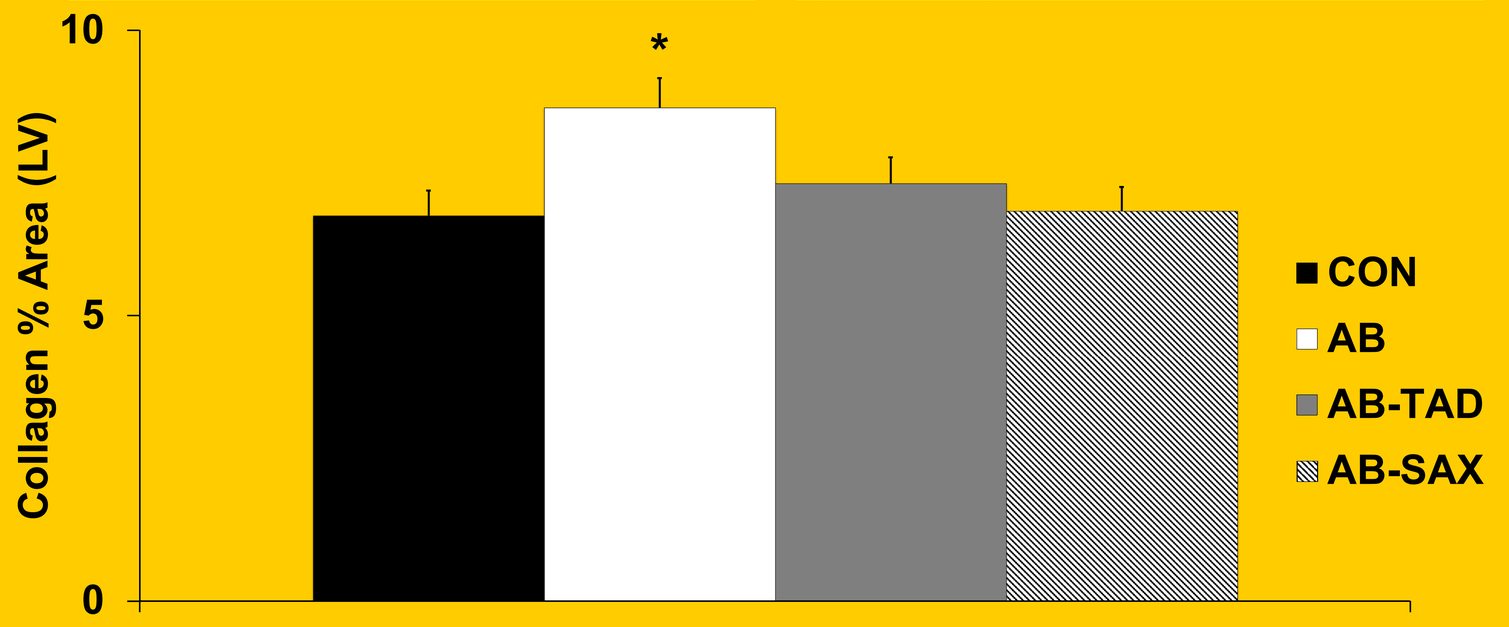


Figure 3. Total LV collagen expression. Both tadalafil and saxagliptin prevented a significant increase in LV collagen expression observed in aortic-banded animals measured as percent area. (*P<0.05 vs. all groups)

CONCLUSION

Increased LV collagen expression was prevented by both chronic saxagliptin and tadalafil therapy, with increased cGMP activity observed only following treatment with tadalafil. Our results suggest manipulation of cGMP signaling is not fundamental to saxagliptin's effects on LV fibrotic remodeling during developing HF.

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