

# Optimizing exercise 'dose' for treating right ventricular fibrosis in a mini-swine model of heart failure

Veterinary Research Scholars Program  
University of Missouri

Whitney Davis, Evan Hayes, Melissa Cobb, Pam Thorne, Jan Ivey and Craig Enter  
Department of Biomedical Sciences, University of Missouri, Columbia, MO

College of Veterinary Medicine  
University of Missouri

## ABSTRACT

Patients with heart failure with preserved ejection fraction (HFpEF) have symptoms of heart failure, despite exhibiting a normal resting left ventricular ejection fraction. Pathological remodeling plays a role in the progression of HF and thus is a target for treatment. However, literature examining the hypertrophic response of the right ventricle (RV) to exercise, specifically fibrotic remodeling, is lacking in a setting of HFpEF. Previous studies have shown that exercise has therapeutic benefit for patients with HFpEF, but the intensity level of exercise yielding the most beneficial effects is still controversial. The purpose of this study is to investigate the effects of exercise on RV fibrosis in a mini-swine model of HFpEF. Animals performed chronic treadmill exercise training for 17 weeks under two different intensities: (1) interval training (5 min. @ 3mph interspersed with 3 min @ 4 mph intervals, repeated 5 times, total training = 45 minutes; and (2) moderate continuous training (45 min. @ 2.5mph). Pigs were divided into 4 groups: (1) control sedentary (CON, n=6); (2) aortic-banded sedentary (HF, n=7); (3) aortic-banded interval trained (HF-IT, N=7); and (4) aortic-banded moderate continuous trained (HF-MOD, N=7). Masson's trichrome stain was used to assess total fibrosis in the RV as a percent area. Expression of regulatory biomarkers including matrix metalloproteinases (MMP 2 & 9), their tissue inhibitors (TIMP 1 & 4), and collagen (type I & III) in the RV were quantified with real time PCR. We hypothesized RV fibrosis would be increased in the HF group compared to CON pigs. Further, we hypothesized chronic exercise training would attenuate increased RV fibrosis and that this therapeutic benefit would be greater in HF-IT vs. HF-MOD animals.

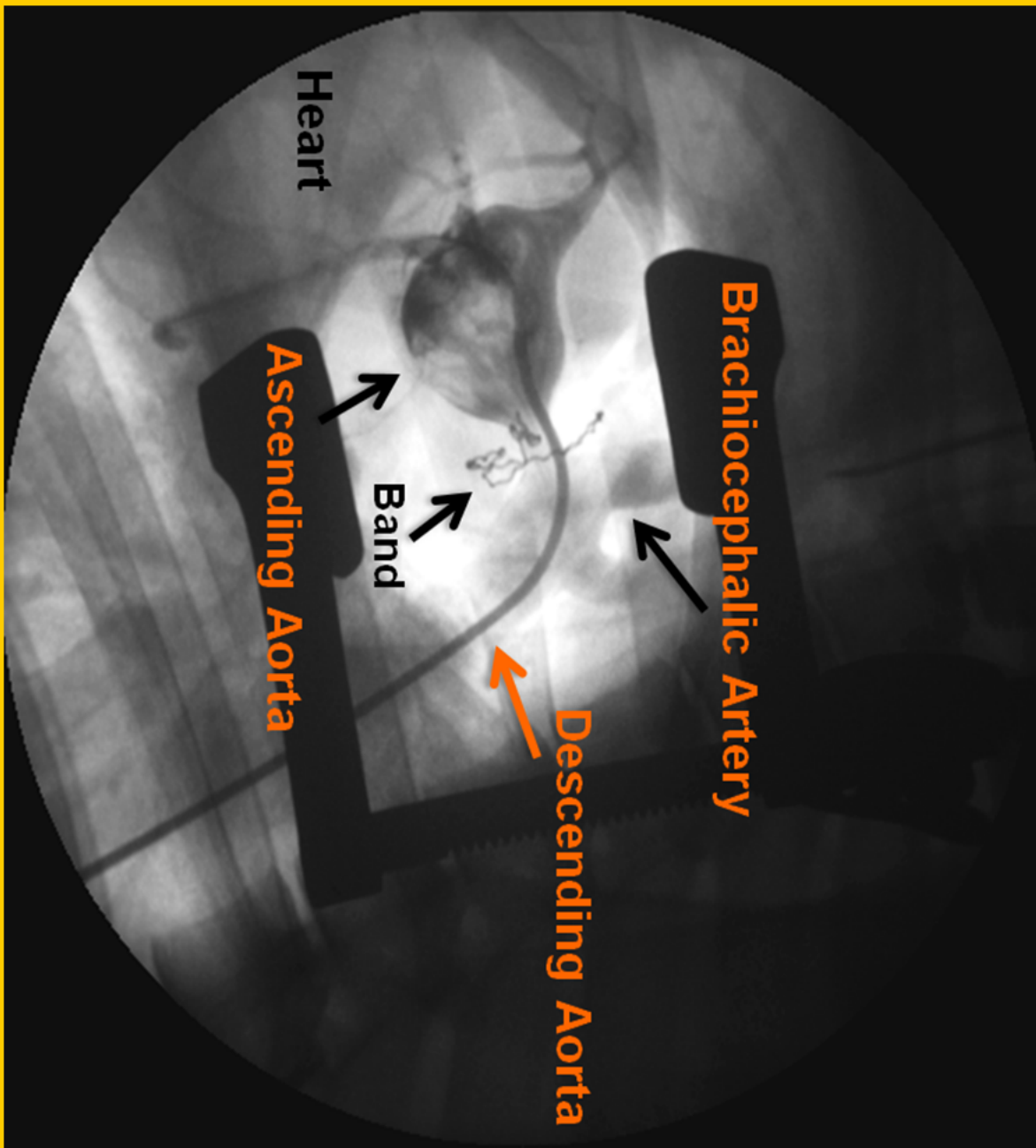
## Hypothesis

- Right ventricular fibrosis will be increased in the HF group compared to CON pigs.
- Chronic exercise training will attenuate increased right ventricular fibrosis in heart failure and the therapeutic benefit will be greater in HF-IT compared to HF-MOD animals.
- Investigate the effects of exercise on right ventricular fibrosis in a mini-swine model of HFpEF.
- Determine the optimal intensity of exercise to prevent right ventricular fibrosis in HFpEF.

## METHODS

### Aortic Banding Procedure:

Heart failure was induced by aortic banding at the ascending aorta proximal to the brachiocephalic artery. A systolic trans-stenotic pressure gradient of 70 mmHg was set at a MAP of 90 mmHg (distal to the band) and a heart rate of 100 beats/min.



- Groups:**
- Control sedentary (CON); n=4
  - Aortic-banded sedentary heart failure (HF); n=4
  - Aortic-banded interval trained (HF-IT); n=6
  - Aortic-banded moderate continuous trained (HF-MOD); n=6

### Exercise Training:

Animals performed chronic treadmill exercise training for 17 weeks using two different intensities: (1) Interval training (5 min. @ 3mph interspersed with 3 min @ 4 mph intervals, repeated 5 times, total training= 45 minutes; and (2) moderate continuous training (45 min. @ 2.5mph).

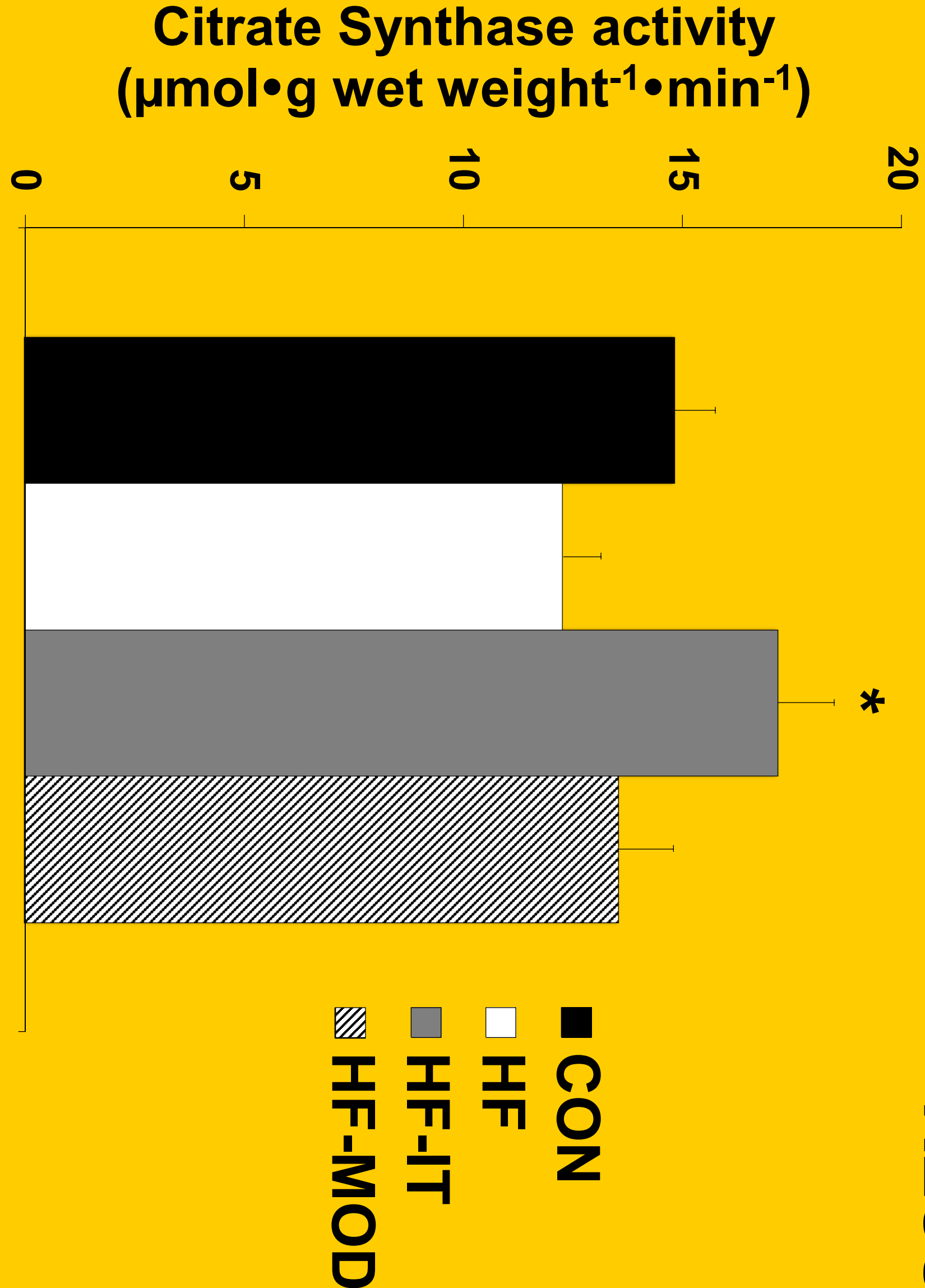


Figure 1. Citrate synthase activity. Skeletal muscle citrate synthase activity, a marker of exercise training, was decreased in the HF compared to HF-IT groups. (\*P < 0.05 vs. HF group)

## RESULTS

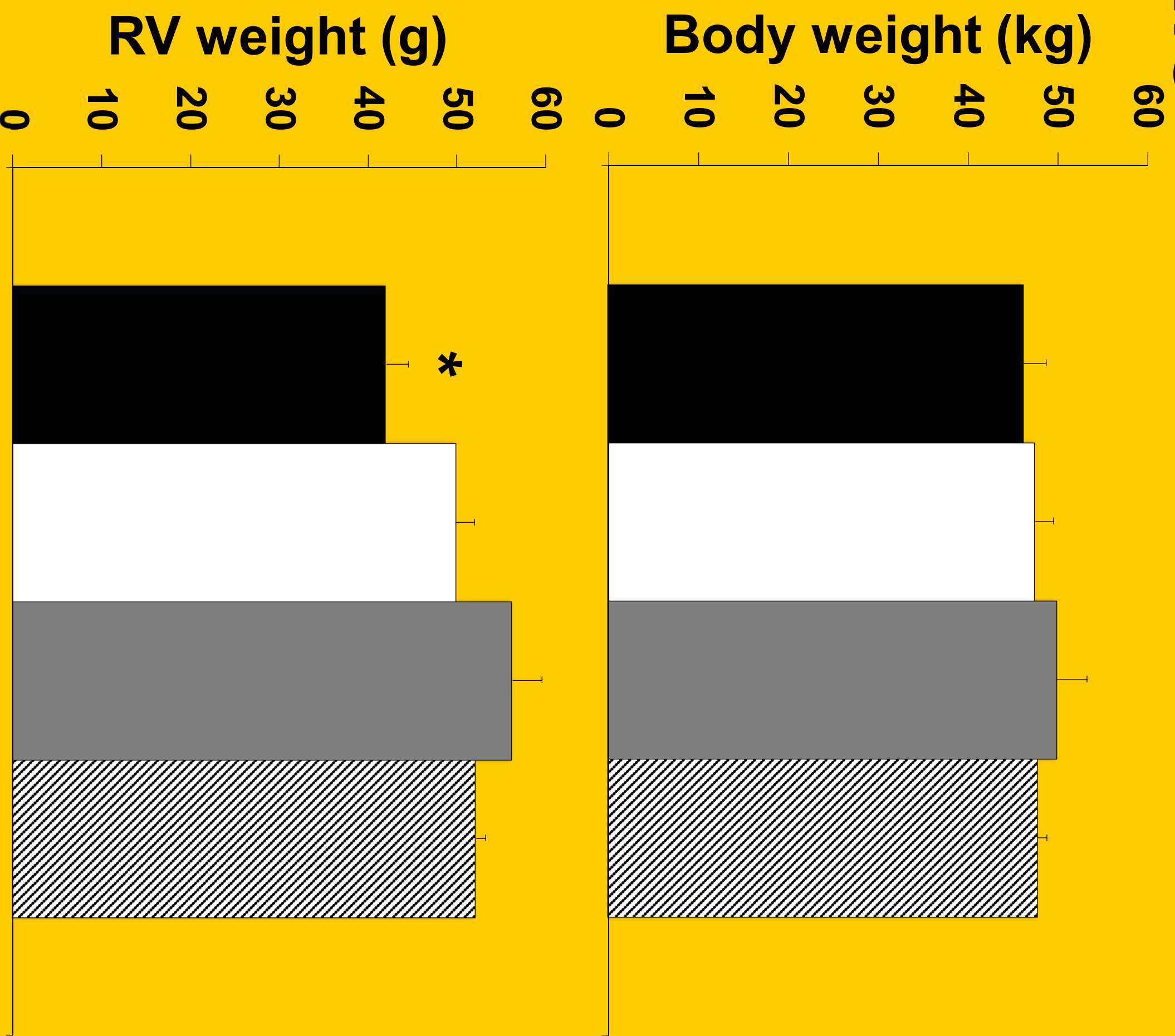


Figure 2. Right ventricular (RV) weight and body weight. Body weight was not different between groups, however, RV weight was significantly increased in all HF groups compared to the CON group independent of exercise training. (\*P < 0.05 vs. all groups)

## Right Ventricular Total Fibrosis

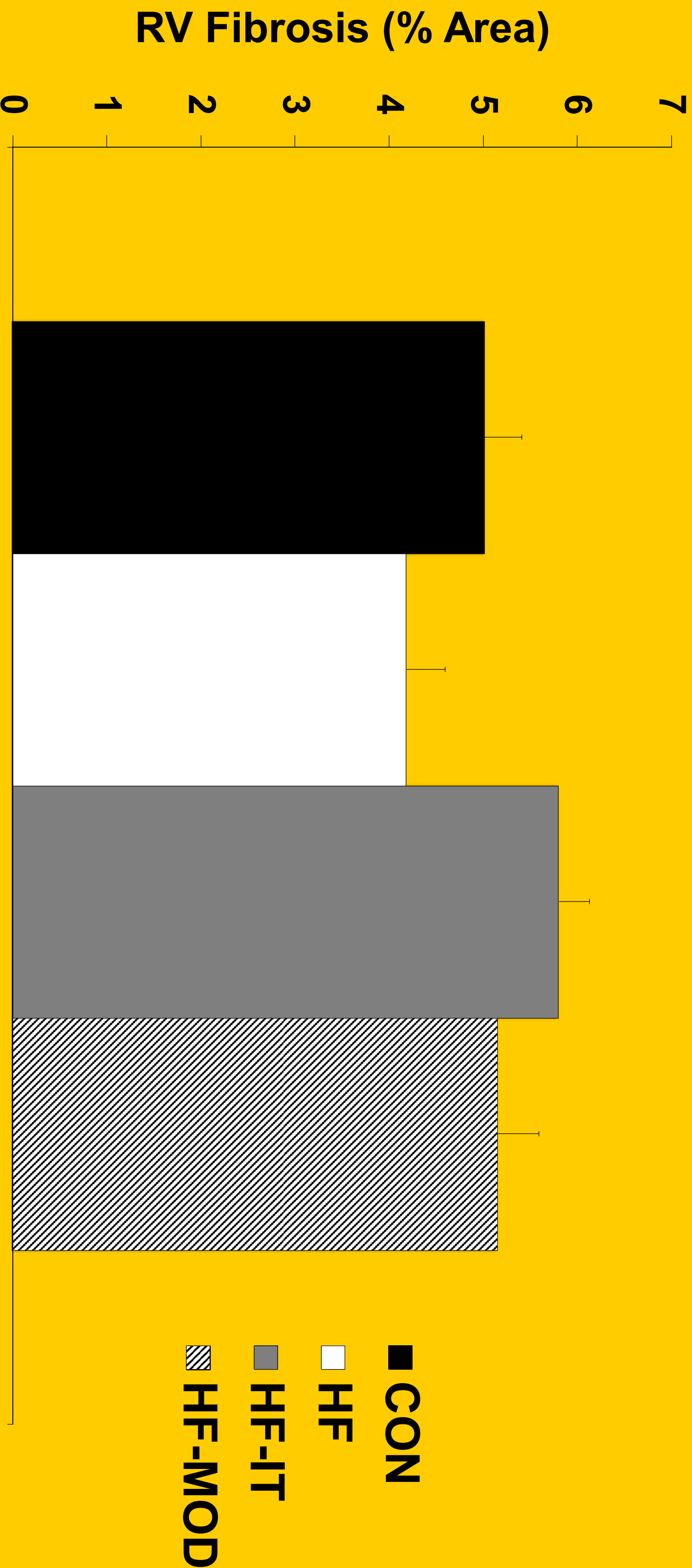
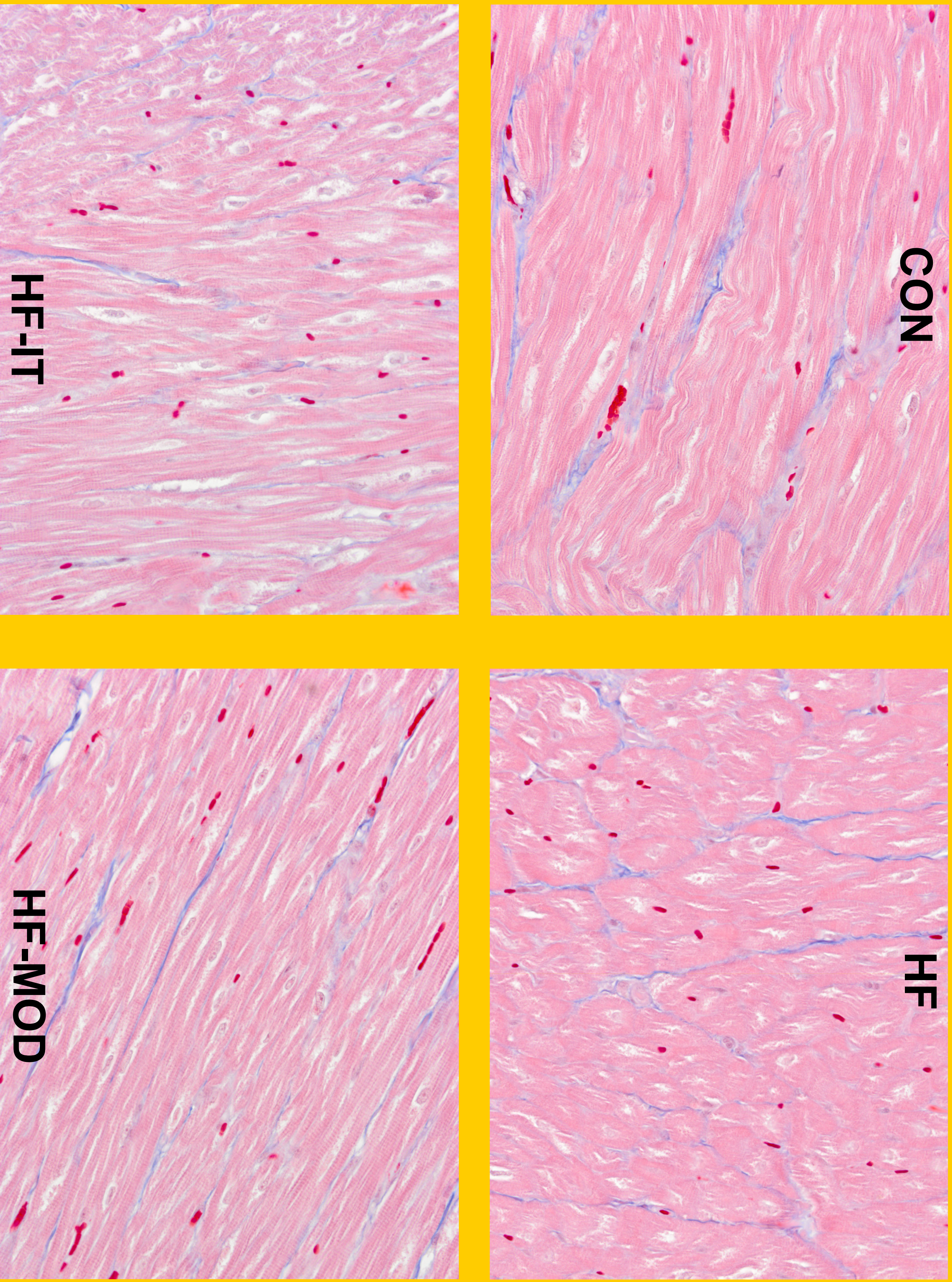


Figure 3. Total right ventricular (RV) fibrosis. There was no significant difference in total fibrosis (Masson's Trichrome stain) between groups.

## CONCLUSION

Reduced citrate synthase activity in the heart failure (HF) compared to CON group was prevented by interval exercise training. Interestingly, right ventricular (RV) hypertrophy occurred in all HF groups independent of exercise. There was no difference in total RV fibrosis between groups, disproving our hypothesis that HFpEF increases RV fibrosis in our mini-swine model. Funding: University of Missouri Veterinary Research Scholars Program – IDEXX-BioResearch endowment; NIH/NHLBI R01 HL112998 (CAE)