HDAC modification improves cardiomyocyte function via modulation of the myofilament

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Background

Heart Failure with preserved Ejection Fraction (HFpEF) represents a growing public health problem with no proven effective treatments.

- HDAC inhibitors are FDA approved anti-cancer drugs and previously shown to be beneficial in rodent models of HF.
- Previously reported enhanced myofibril relaxation → restored linear relaxation duration with SAHA treatment in a large animal model of HFpEF *(Wallner, Eaton et al. 2020).*

Aim: Evaluate the effects of SAHA on cardiac function at the level of the cardiomyocyte and contractile protein function.

Study Design

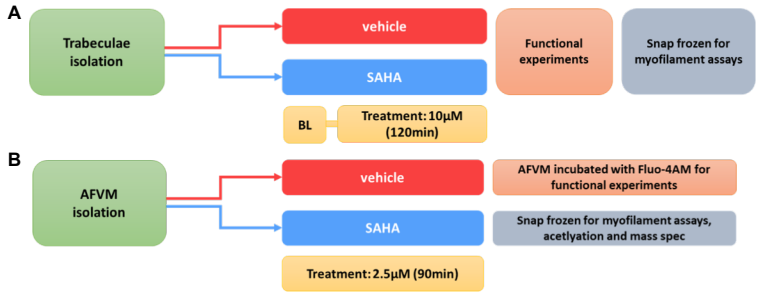

Figure 1. (A) Left ventricle trabeculae were isolated from non-failing human hearts (n=7) and (B) cardiomyocytes were isolated from adult male felines (n=4).

Non-Failing Human Trabeculae Function

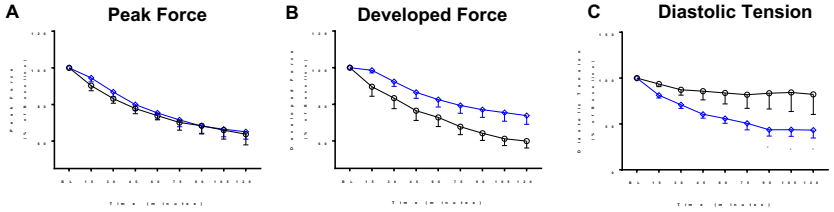

Figure 2. SAHA treated trabeculae isolated from biopsies of non-failing human LV had an increase in (A) developed force and decreased (B) diastolic tension, with a similar (C) peak systolic force. Data shown are means ± SEM.

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Non-Failing Human Myofilament Function

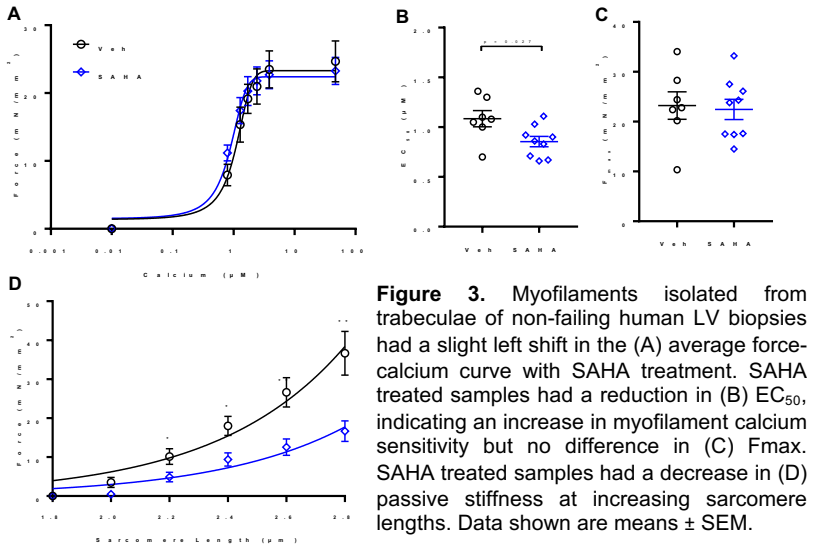

Figure 3. Myofilaments isolated from trabeculae of non-failing human LV biopsies had a slight left shift in the (A) average force-calcium curve with SAHA treatment. SAHA treated samples had a reduction in (B) EC_{50}, indicating an increase in myofilament calcium sensitivity but no difference in (C) Fmax. SAHA treated samples had a decrease in (D) passive stiffness at increasing sarcomere lengths. Data shown are means ± SEM.

AFVM Function

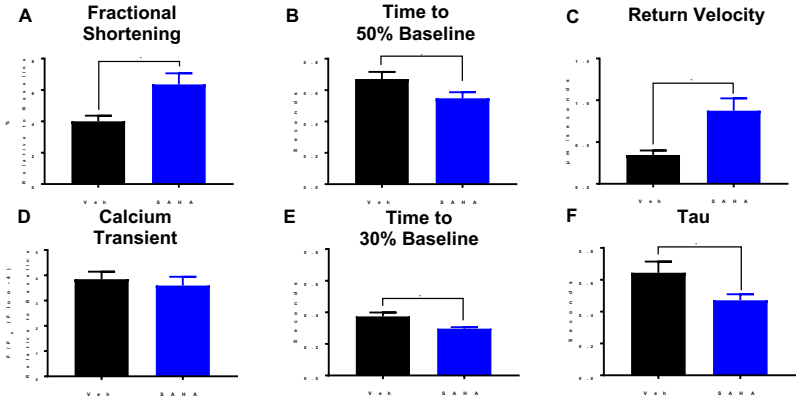

Figure 4. SAHA treated AFVM had an improvement in (A) fractional shortening, (B) time to 50% baseline of contraction and (B) return velocity. There was no difference between SAHA, and vehicle treated AFVM (D) calcium transients, but there was a decrease in (E) time to 30% baseline and (F) tau. Data shown are means ± SEM.

AFVM Myofilament Function & Acetylation

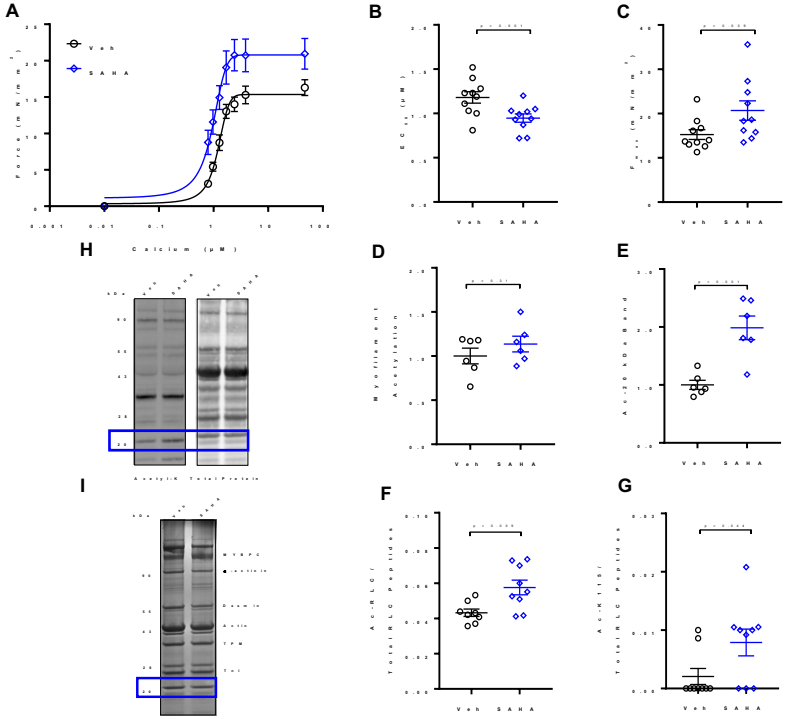

Figure 4. Myofilament (A) average force-calcium curve had a left-hand shift with SAHA treatment, with a decrease in the (B) EC50 (increase in myofilament calcium sensitivity) and increase in (C) maximum force. (H) Western Blot analysis revealed no increase in (D) global myofilament acetylation but significant increase (C) at an unknown 20kDa band. (D) Coomassie staining was performed, and mass spec revealed that this 20kDa band with (E) was the myosin regulatory light chain with one (F) specific residue (lysine 115) driving the increase in acetylation. Data shown are means ± SEM.

Conclusions

SAHA modulates cardiac function at the level of the cardiomyocyte and myofilament in human and feline myocardium:

- Increases contractility (increased fractional shortening and developed force)
- Improves relaxation (decreased time to 50% BL and increased return velocity)
- Decreases passive tension (decreased diastolic tension)

Substrate: Acetylation of myosin regulatory chain at lysine 115