Characterization of a cardiac phenotype in a novel cAMP reporter mouse

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Introduction:

Cyclic AMP (cAMP) is an important second messenger for intracellular signaling. In the heart, it helps control of heart rate and contractility. To investigate cAMP signaling in the heart, a new cardiac-specific cAMP-encoded reporter (*CAMPER*) mouse was developed, which reports cAMP signaling with a FRET-based biosensor. The sensor changes fluorescence upon cAMP binding. However, binding of the *CAMPER* sensor to cytosolic cAMP may cause buffering of this second messenger, which could impact cardiac function.

Hypothesis:

We hypothesize that buffering of cytosolic cAMP may lead to a baseline cardiac phenotype in the *CAMPER* mice.

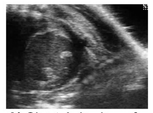
Methods:

ECHO:

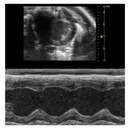
1) Mouse is placed under anesthesia using Isoflurane for 5 Minutes prior to the start of the procedure, then kept under anesthesia for the duration of the echocardiogram.

2) Once the mouse has been anesthetized, it is secured onto the stage of the echo apparatus. Next, using Nair and cotton swabs, the chest hair of the mouse is removed allowing for better contact imaging of the heart.

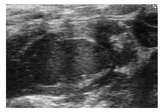
3) Using the Vevo 2100 imaging system, an echocardiogram was conducted for each mouse for ~ 15 min. Images in short-axis view and short-axis M-mode, as well as long-axis views were obtained, measured, and used for data interpretation.



A) Short-Axis view of the Left Ventricle in the Mouse Heart



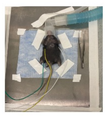
B) M-Mode image used to measure wall thickness, CO, EF, FS, SV, diastolic and systolic volume

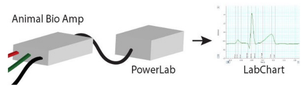


C) Long-Axis view of the Left Ventricle in the Mouse Heart

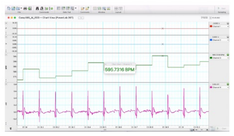
ECG:

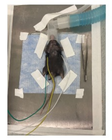
1) Mouse is weighed and placed under anesthesia using Isoflurane prior to the start of the procedure, then kept under anesthesia for the duration of the electrocardiogram (ECG). Isoflurane adjusted as needed.

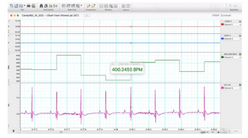




2) ECG leads are attached to the mouse, and using the Powerlab software Labchart from ADInstruments, the ECG is recorded.



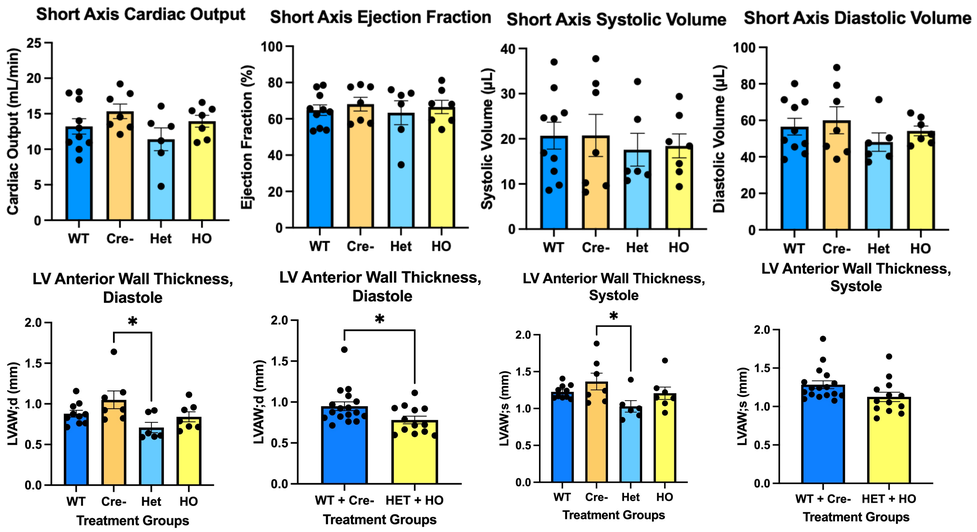




3) After the first 15 minutes of the ECG, an injection of Isoproterenol is given to the mouse IP in order to conduct a stress test. The amount of isoproterenol is determined based on the weight of the mouse.

Results:

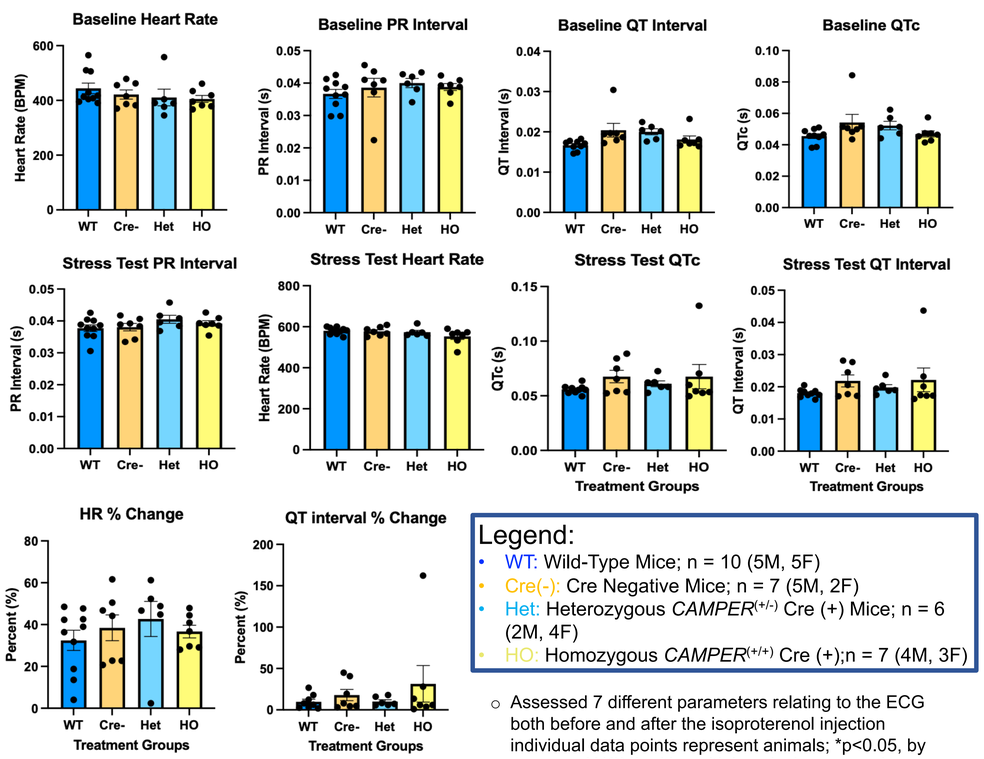
ECHO:



- Assessed 18 different parameters relating to the short axis and long axis views in echo; individual data points represent animals; *p<0.05, by one-way ANOVA with multiple pairwise comparisons.

Legend:
- WT: Wild-Type Mice; n = 10 (5M, 5F)
- Cre(-): Cre Negative Mice; n = 7 (5M, 2F)
- Het: Heterozygous *CAMPER*$^{(+/-)}$ Cre (+) Mice; n = 6 (2M, 4F)
- HO: Homozygous *CAMPER*$^{(+/+)}$ Cre (+);n = 7 (3M, 4F)

ECG:



Legend:
- WT: Wild-Type Mice; n = 10 (5M, 5F)
- Cre(-): Cre Negative Mice; n = 7 (5M, 2F)
- Het: Heterozygous *CAMPER*$^{(+/-)}$ Cre (+) Mice; n = 6 (2M, 4F)
- HO: Homozygous *CAMPER*$^{(+/+)}$ Cre (+);n = 7 (4M, 3F)

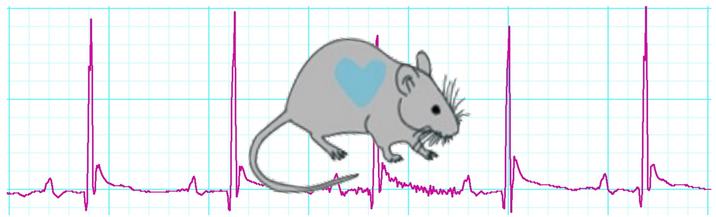
- Assessed 7 different parameters relating to the ECG both before and after the isoproterenol injection individual data points represent animals; *p<0.05, by one-way ANOVA with multiple pairwise comparisons.

Summary:

- For most parameters analyzed, no statistical significances noted between the four treatment groups, or when analyzed in two larger groups.
- Statistical significances seen with LV anterior wall thickness between Cre(-) and HET for systole and diastole, as well as for diastole in the larger two groups. This may be due to an imbalance in sexes between groups

Conclusions & Future Directions:

- Overall, we were able to characterize the electrophysiology and cardiac function of the *CAMPER* mouse heart
- A baseline cardiac phenotype that is statistically different from that of the Wild-type mouse was not determined
- The genetically encoded sensor in the *CAMPER* mouse has no discernable impact on cardiac function, and therefore can be used as a mouse model for future cardiac studies



Acknowledgements:

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