

Targeting Endothelin Receptor-1A (ET_A) in Obesity-Associated Cardiac Dysfunction



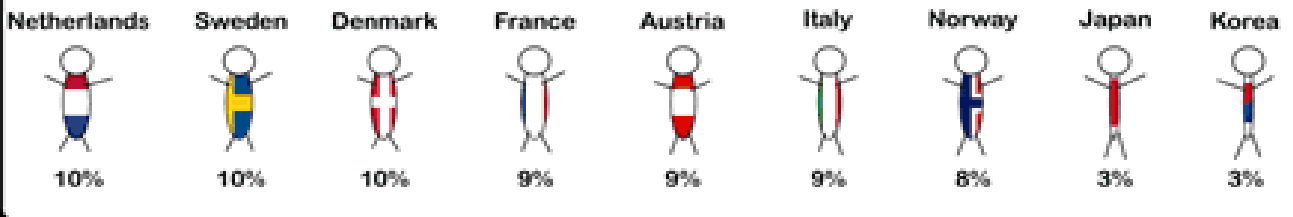
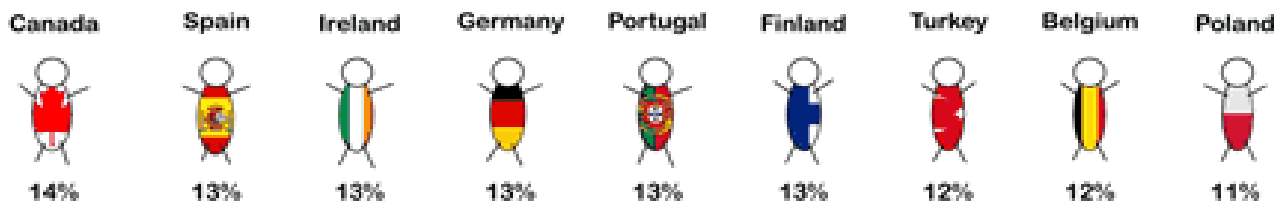
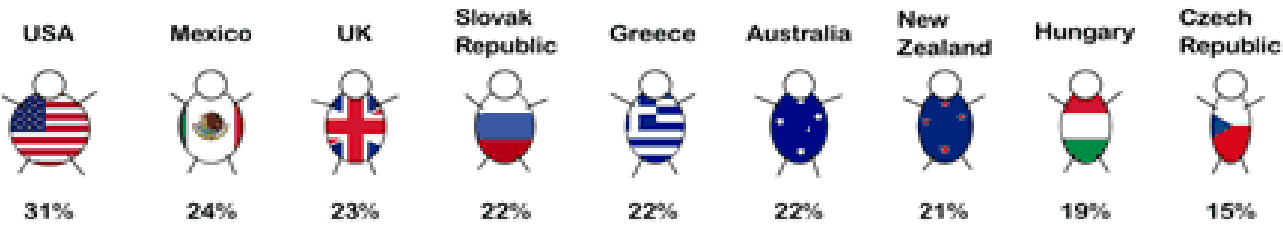
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INTRODUCTION



- Obesity: An emergent health problem world wide

OBESITY: The percentage of the population older than 15 with a body-mass index greater than 30.



INTRODUCTION



Obesity →

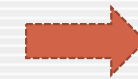
Dyslipidemia

Hypertension

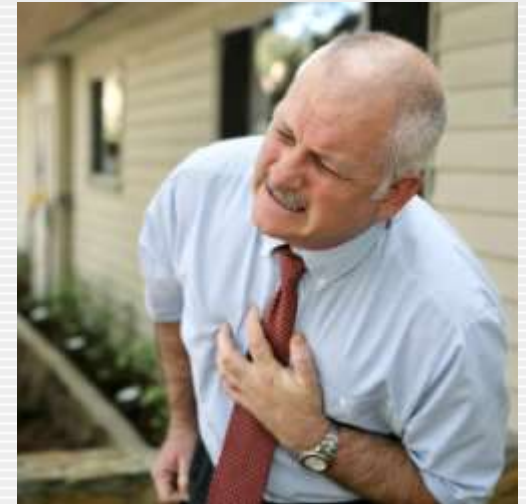
Glucose intolerance

Insulin resistance

Inflammation



**Cardiac
Dysfunction**



SIGNIFICANCE



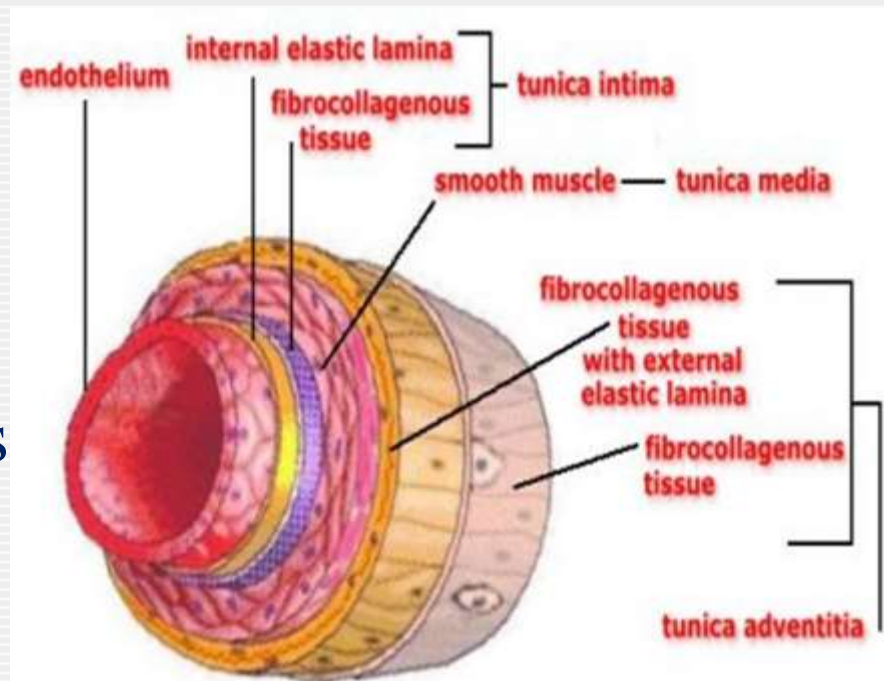
- Understanding of pathophysiology of obesity induced-heart disease
- Help us ascertain the role of endothelin receptors in obesity associated cardiac dysfunction
- Therapeutic benefit in treating heart disease



INTRODUCTION



- Endothelin-1 (ET-1)
 - A potent vasoactive peptide secreted by endothelium
 - Regulating cardiovascular functions
 - Mediates its effects on cardiovascular system through its cognate receptors ET_A (heart) and ET_B (vasculature)



HYPOTHESIS



Cardiac specific deletion of ET_A receptor prevents cardiac hypertrophy and cardiac contractile dysfunctions in high fat-diet-induced obesity



METHODS



- **Experimental animals**
- **Echocardiographic assessment**
- **Isolation of murine cardiomyocytes**
- **Cell shortening/relengthening**
- **Intracellular Ca²⁺ transients**
- **Western Blot analysis**
- **Data analysis**

METHODS



- **Experimental animals:**

4-week-old cardiac specific ET_A -receptor knockout mice

Age- and gender-matched controls (C57BL/6J mice)

Maintained on a 12:12-hour light-dark illumination cycle and allowed food and water without limitation



Randomly assigned to low-fat (10% kcal % fat) or high-fat (45% kcal % fat) diet for 6 months, high-fat diet was calorically rich due to higher fat composition

RESULTS



RESULTS



1. Effect of ETAKO on biometrics of the animals

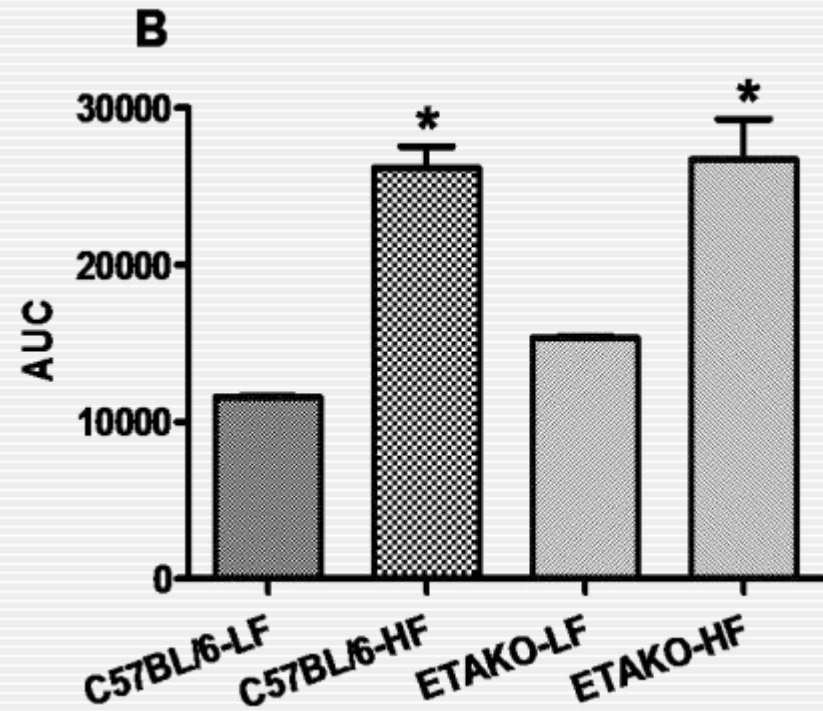
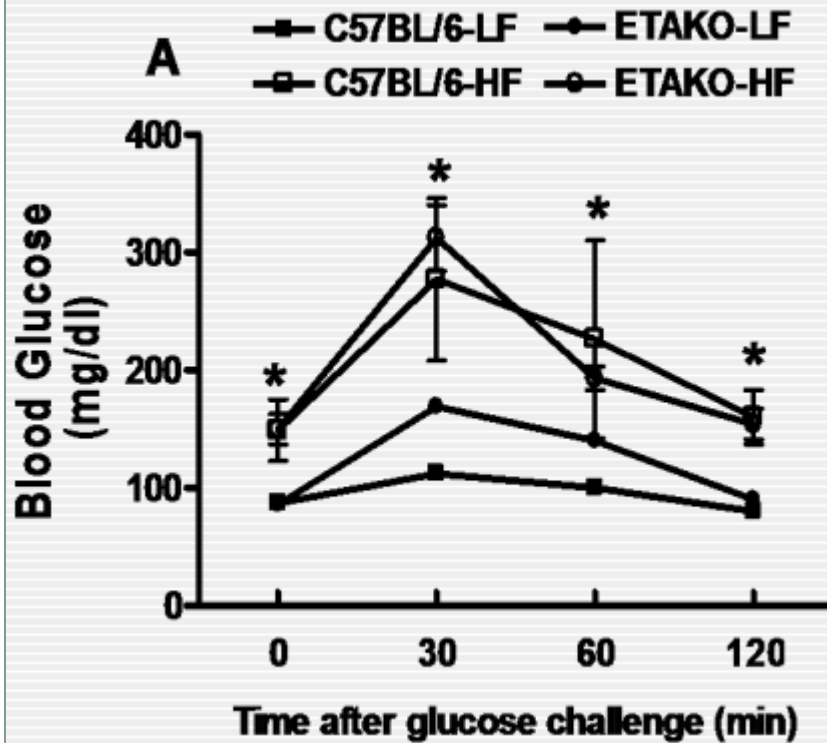
	C57BL/6J+LF (n=10)	C57BL/6J+HF (n=10)	ETAKO+LF (n=10)	ETAKO+HF (n=10)
Body Weight (g)	21±2	41±3*	22±2	36±3
Heart Weight (mg)	144±10	210±16*	142±12	150±15#
HW/BW (mg/g)	6.86±0.2	5.12±0.2	6.45±0.6	4.17±0.5
Liver Weight (g)	1.21±0.03	1.41±0.05*	1.22±0.06	1.28±0.08#
LW/BW (mg/g)	57.62±4.26	34.39±3.42	55.45±5.24	35.55±2.56
Kidney Weight (g)	0.32±0.03	0.47±0.02*	0.34±0.04	0.36±0.06#
KW/BW	15.23±1.26	11.46±2.56	15.45±3.44	10±1.57
Fasting Blood Glucose (mg/dl)	88±4	172±24*	86±4	150±28*

Mean ± SE, * p<0.05 vs. corresponding low fat-diet group; # p<0.05 vs. C57BL/BJ high fat diet group. LF= low fat-diet; HF= high fat-diet; ETAKO=Cardiac specific ET_A knockout; HW: heart weight; LW: Liver weight; KW: Kidney weight; (n) = animal numbers.

RESULTS



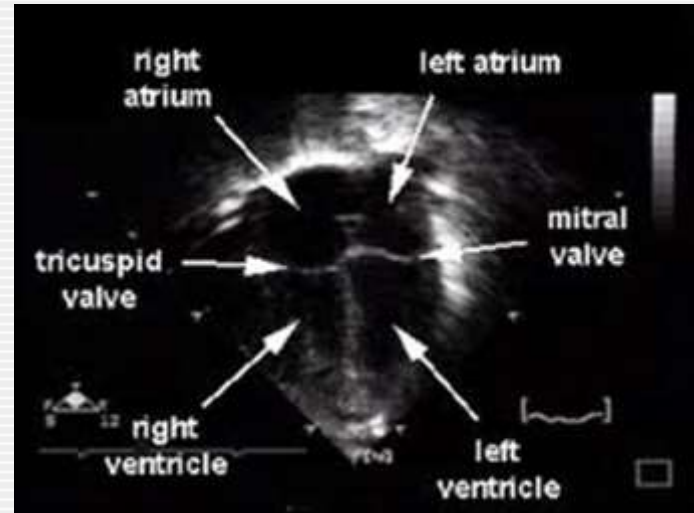
2. ETAKO has no effect on glucose tolerance



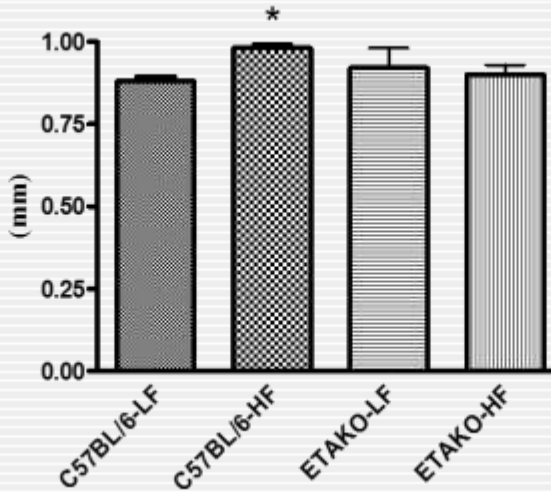
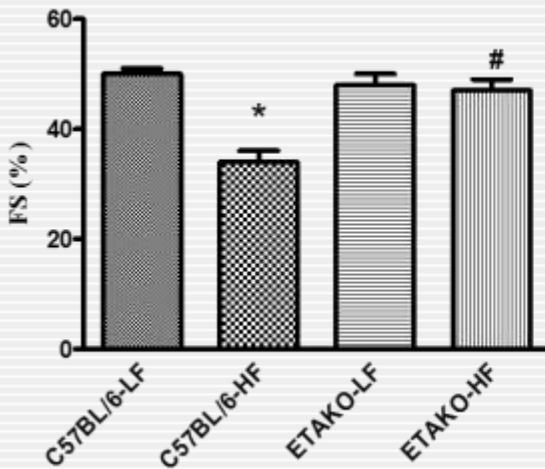
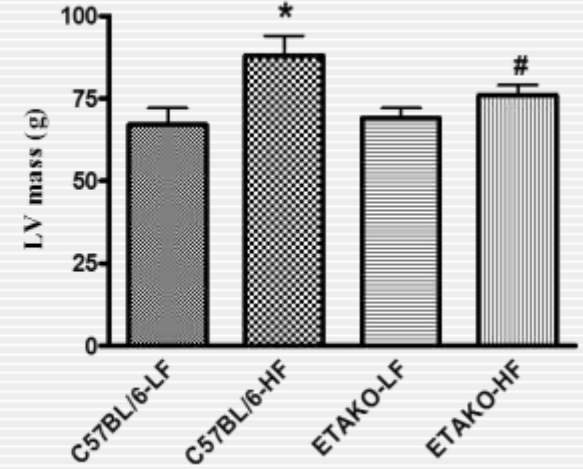
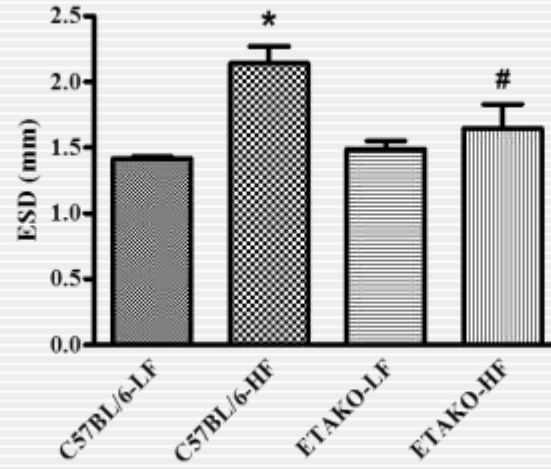
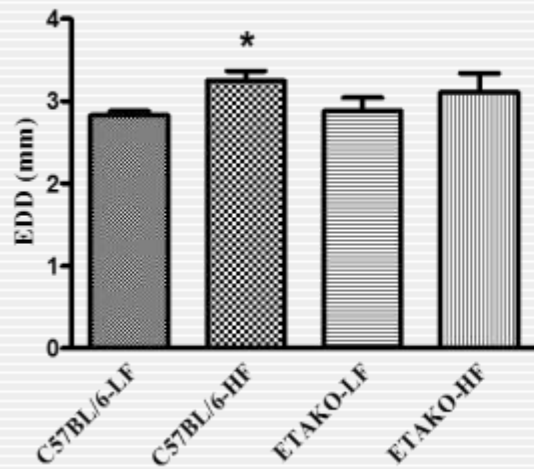
RESULTS



3. ETAKO attenuates HF-diet-induced change on echocardiography



RESULTS

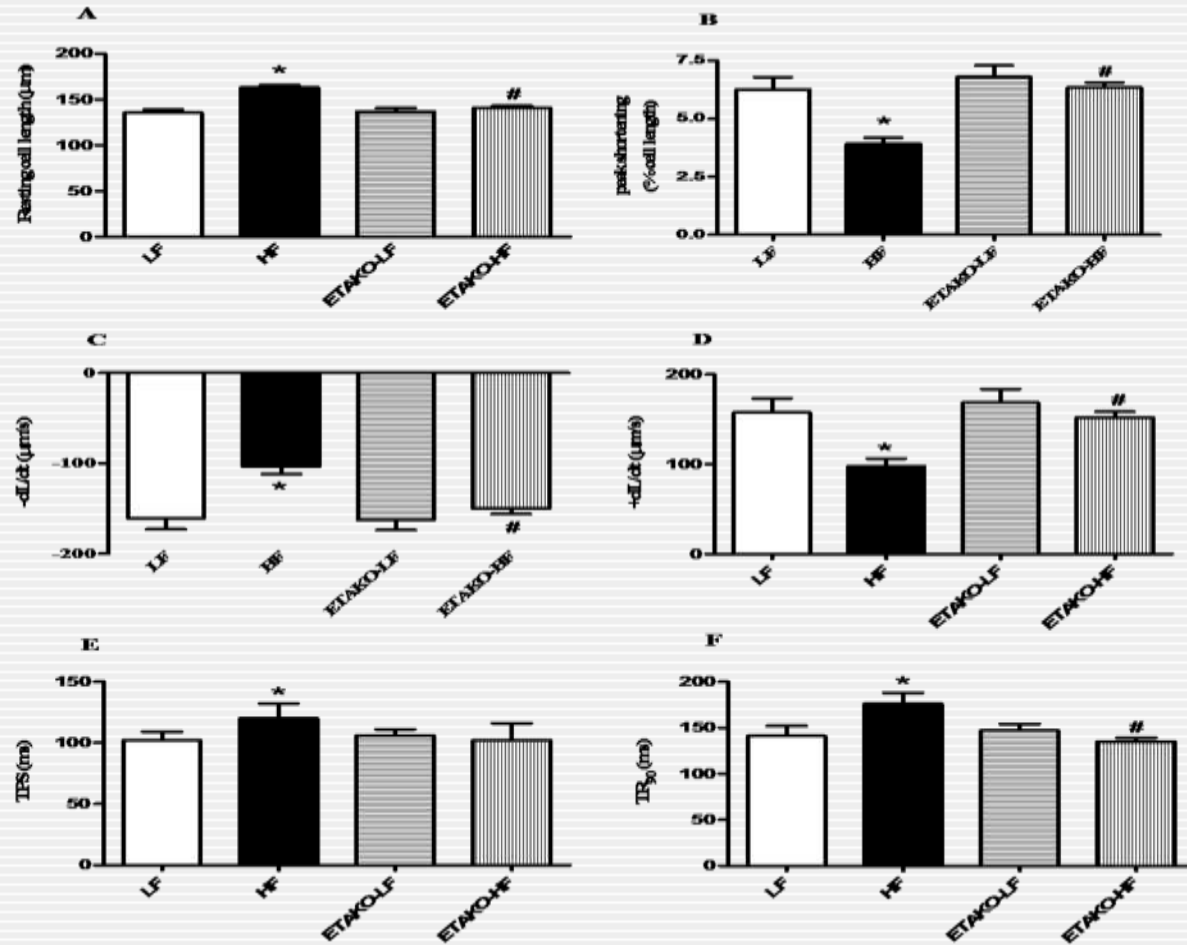


EDD:
End Diastolic Diameter
ESD:
End Systolic Diameter
LV mass:
Left Ventricular mass
FS:
Fractional Shortening

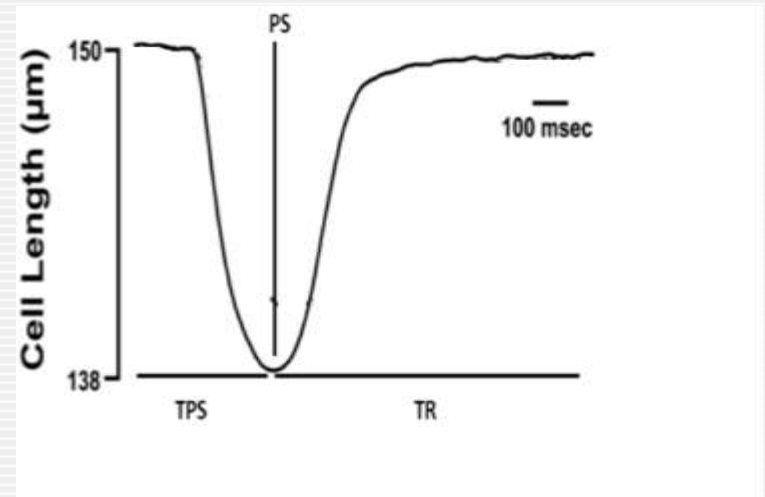
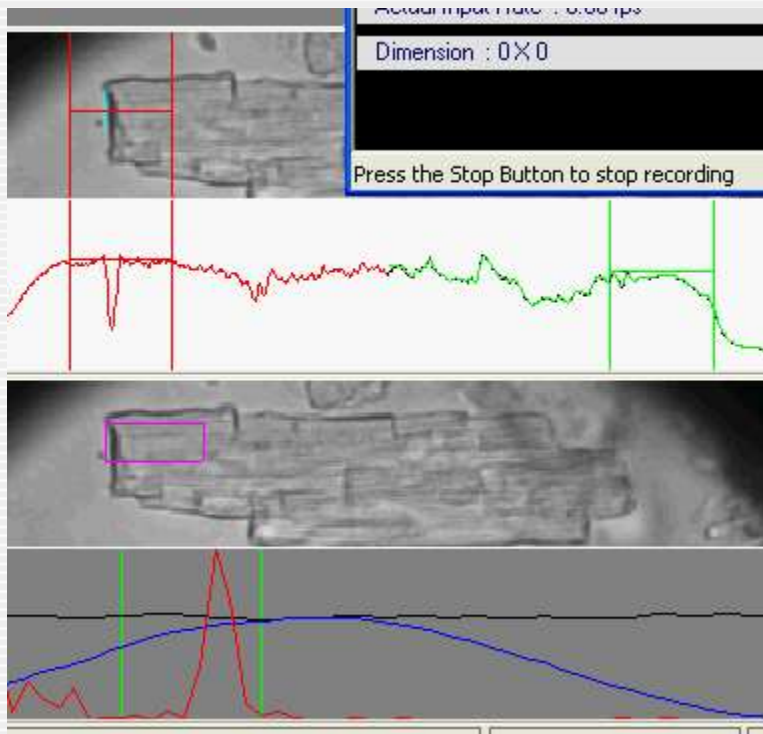
RESULTS



4. ETAKO rescues heart from HF-diet-induced cardiac dysfunction



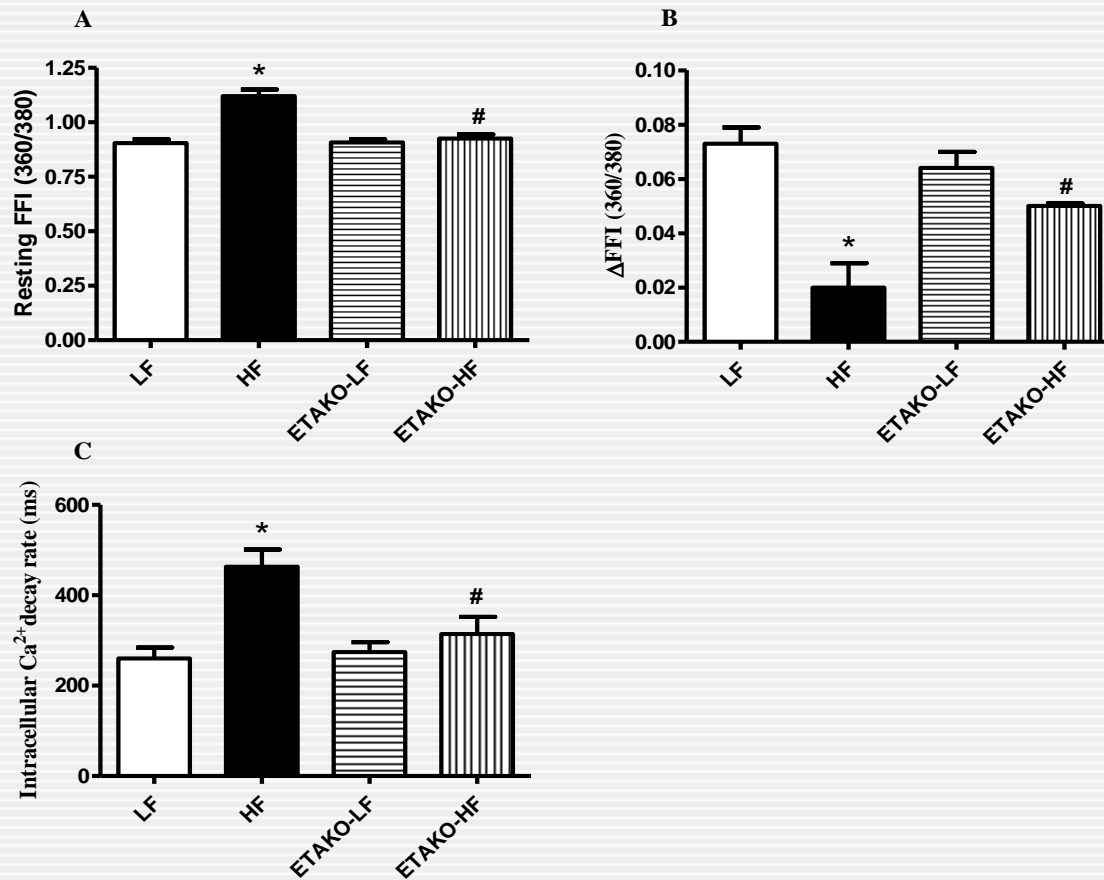
RESULTS



RESULTS



5. ETAKO rescues heart from HF-diet-induced cardiac dysfunction



RESULTS



6. ETAKO regulates HF-diet-induced hypertrophy and autophagy



CONCLUSIONS



- ETAKO attenuates HF-diet-induced cardiac dysfunction
- ETAKO reduces HF-diet-induced cardiac hypertrophy
- FUTURE STUDIES will be performed in order to show if there is any relationship between hypertrophy and autophagy in the regulatory effects of ETAKO in HF-diet-induced cardiac dysfunction

THANK YOU!



- EPSCoR and University of Wyoming
- Dr. Sreejayan Nair
- Dr. Asli Fahriye Ceylan Isik
- Dr. Yinan Hua
- Dr. Julia Mckee Dolence
- Dr. Jun Ren & C-CRAM

QUESTIONS

