

The Role of **SK Channel** in **Metabolic Syndrome** Related **Atrial Myopathy**



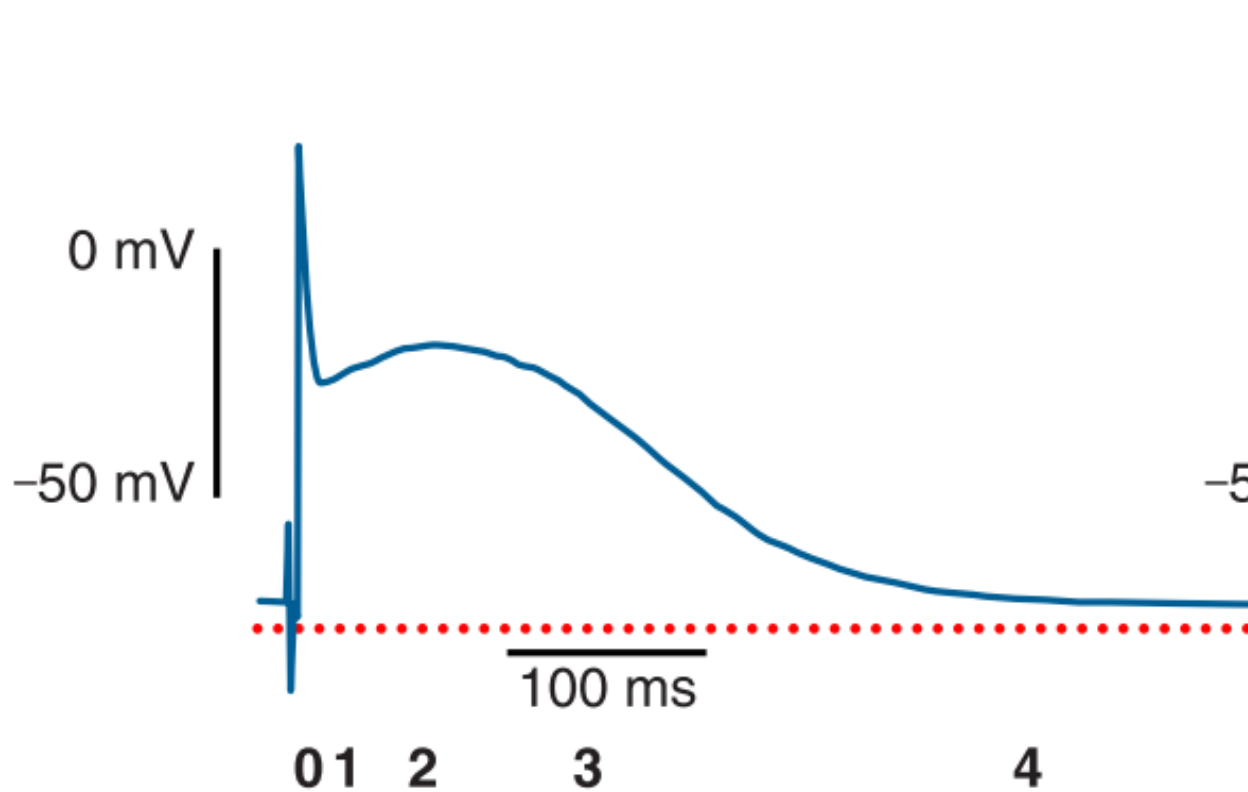
蔡維中.高醫心臟內科.
Wei-Chung Tsai, MD, FHRS
Kaohsiung Medical University, Taiwan
2021.06 @ KHRS

Disclosures

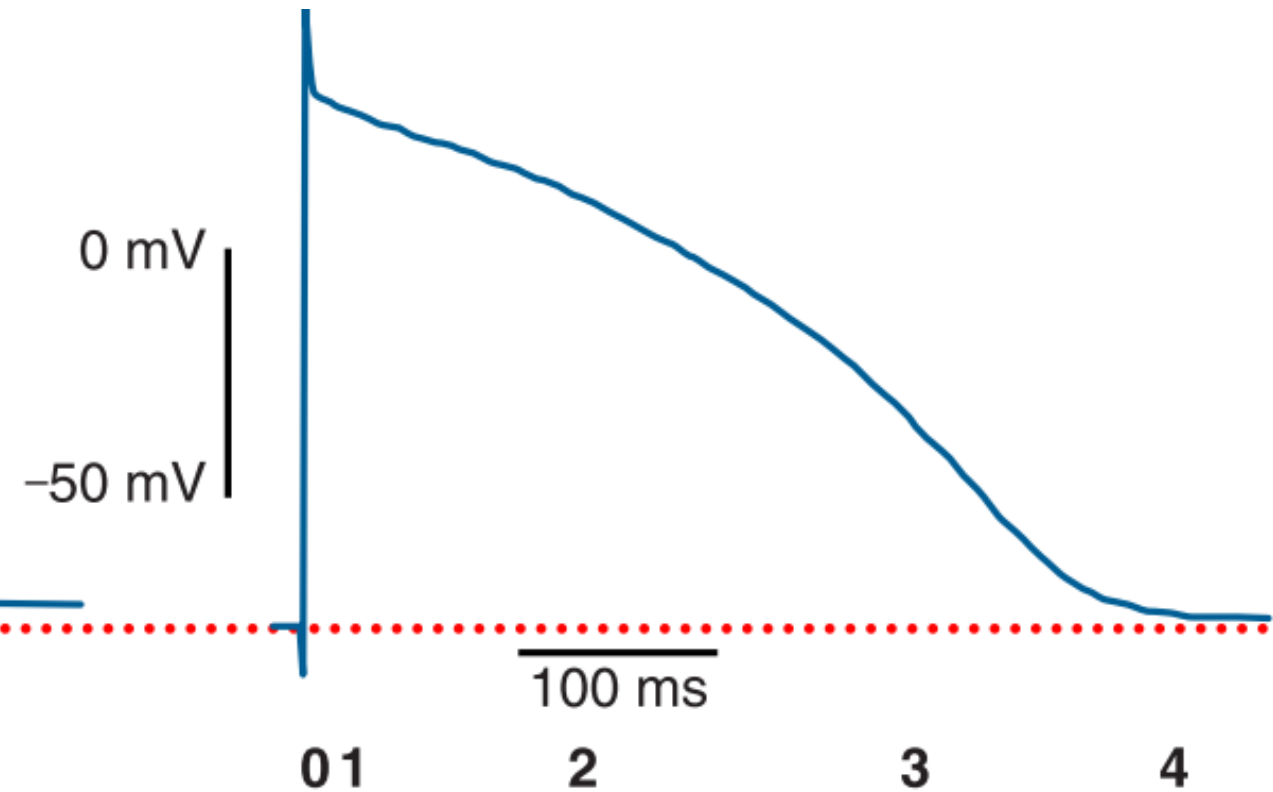
- **WC. Tsai:** None

Background

Human atria



Human ventricle



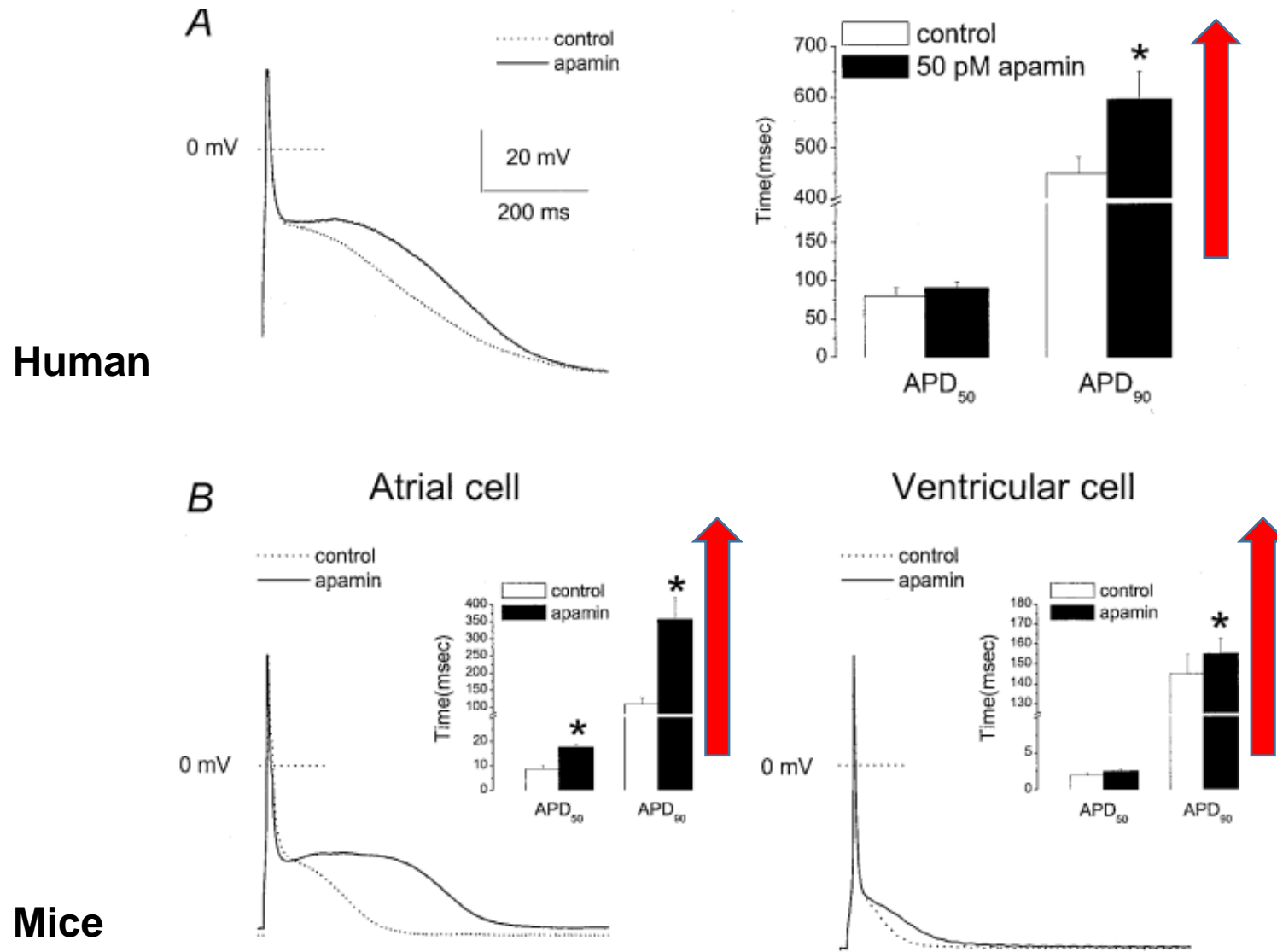
$I_{K.Ca}$



Small conductance , Ca^{2+} activated K^+ (SK) channels

Physiol Rev. 2014;94(2):609-53.

Apamin effect in human & mice



SK in human (GWAS)

- Association on chromosome 1q21 to lone AF ((rs13376333 (intronic to *KCNN3*), aOR = 1.56)).

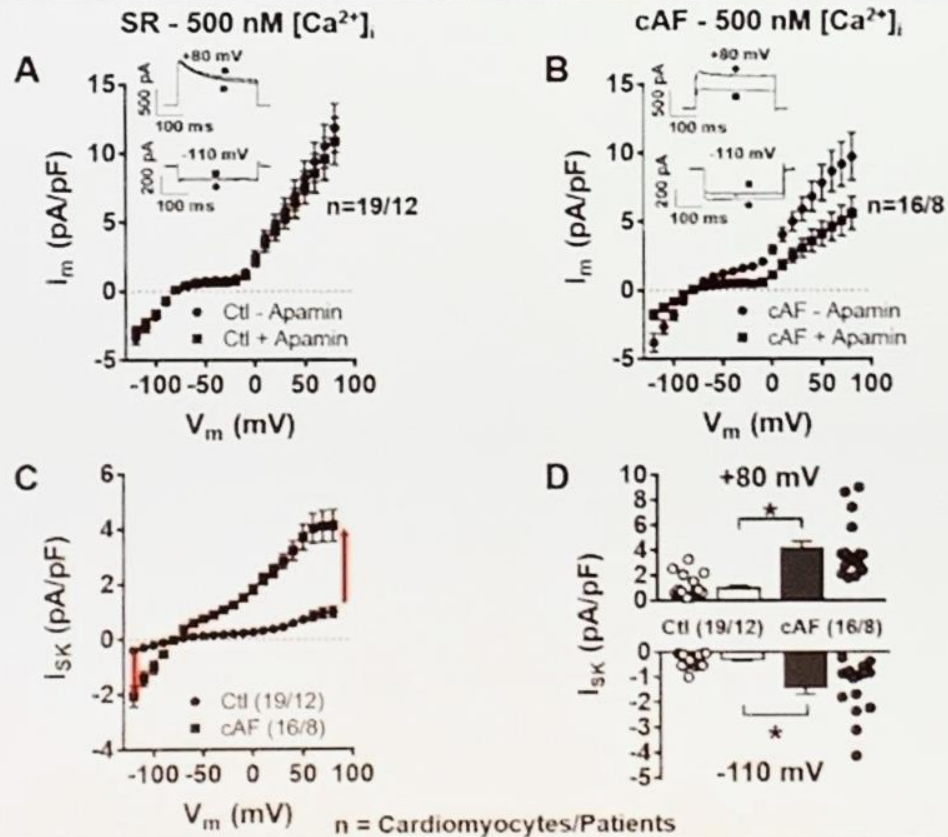
Table 2 Summary of GWAS meta-analysis results with $P < 5 \times 10^{-8}$

SNP	Locus		Closest gene	Cohort specific					Meta-analysis association signal						
	Chr.	Position ^a		AFNET & KORA S4 ^b	HVH & CHS ^b	ARIC ^b	CCF ^b	MGH & FHS ^b	Minor/major allele	MAF (%)	Meta-analysis ^a	OR	95% CI	Meta <i>P</i> value	Corroborating SNPs ^c
rs6843082	4	111,937,516	<i>PITX2</i>	0.77 (0.13)	0.43 (0.13)	0.55 (0.15)	0.87 (0.19)	0.91 (0.12)	G/A	25.8	0.71 (0.06)	2.03	1.79–2.30	2.5×10^{-28}	77
rs13376333	1	153,080,977	<i>KCNN3</i>	0.30 (0.13)	0.54 (0.13)	0.32 (0.14)	0.66 (0.20)	0.52 (0.12)	T/C	29.5	0.45 (0.06)	1.56	1.38–1.77	6.3×10^{-12}	6
rs13038095	20	45,858,983	<i>SULF2</i>	0.28 (0.20)	0.45 (0.10)	0.61 (0.19)	0.85 (0.29)	N/A ^d	T/G	10.2	0.48 (0.08)	1.61	1.37–1.91	1.1×10^{-8}	0

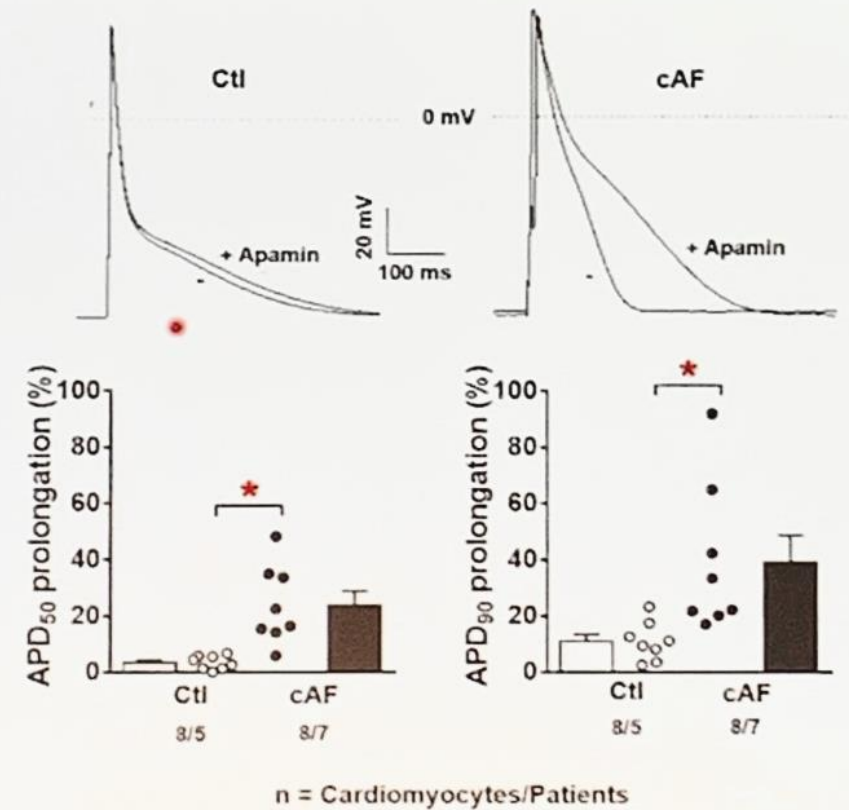
^aGenomic position from NCBI Build 36. ^b β (s.e.m.). ^cHaving $P < 5 \times 10^{-8}$. ^dMGH/FHS did not contribute to the meta-analysis of this SNP due to poor quality imputation. Chr., chromosome; MAF, minor allele frequency; OR, odds ratio, CI, confidence interval; N/A, not available. β is the regression parameter estimate (the log-odds ratio) and OR is the odds ratio of lone AF for each additional minor allele.

SK in chronic AF patients

Apamin (100 nM) Sensitive SK Currents are Increased in Atrial Cardiomyocytes of cAF Patients



SK Channel Block with 100 nM Apamin Strongly Prolongs APD_{90} in Cardiomyocytes of cAF Patients



SK in animal models

- SK currents play a role in canine atrial repolarization, are larger in PVs than LA, are enhanced by atrial tachycardia remodeling, and appear to participate in promoting AF maintenance.

Circulation. 2014 28;129(4):430-40.

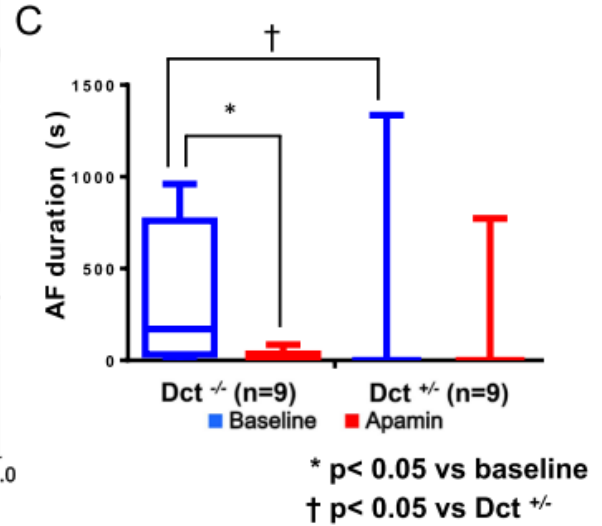
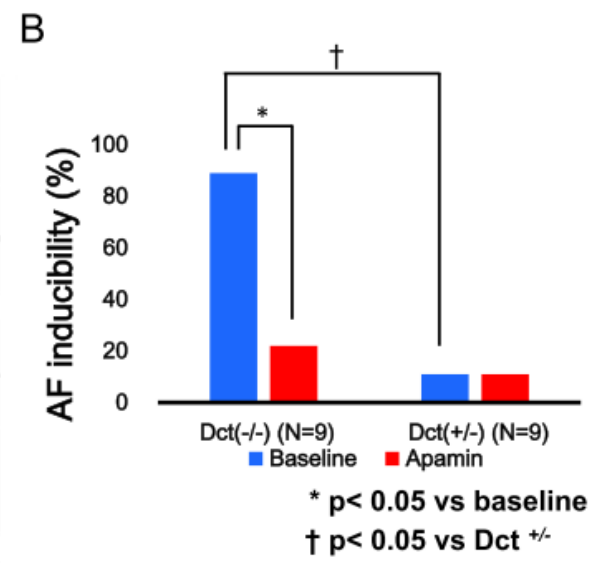
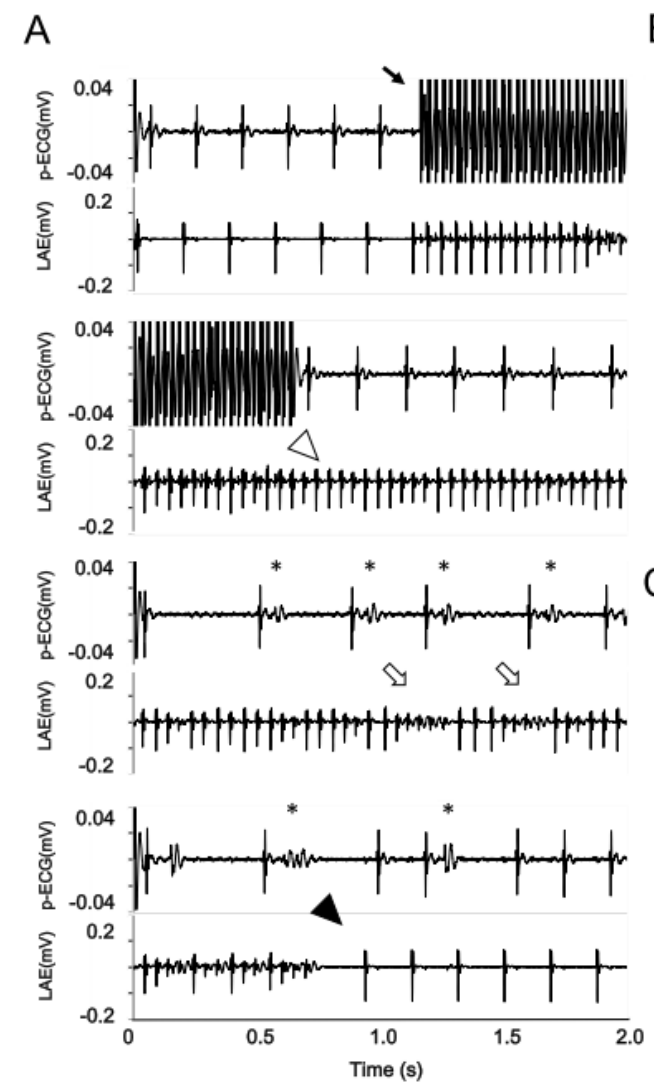
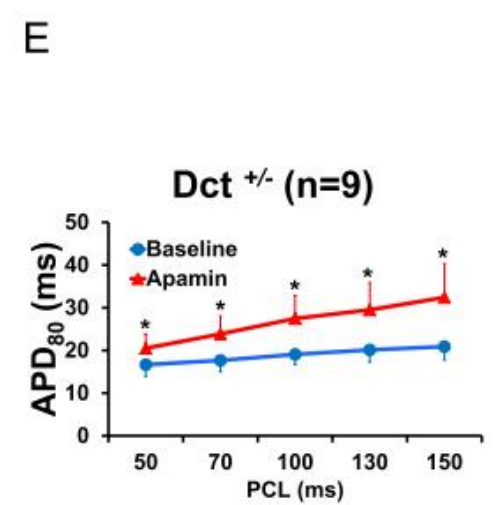
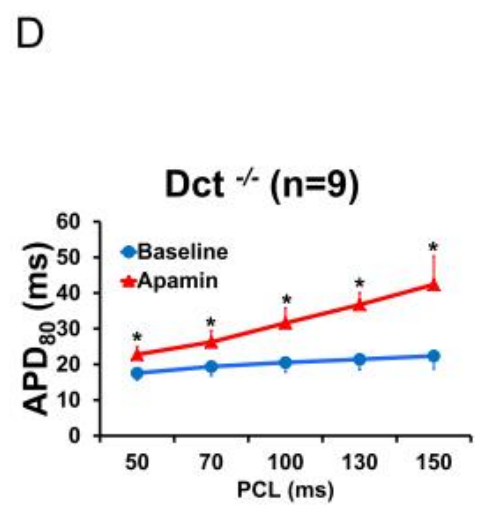
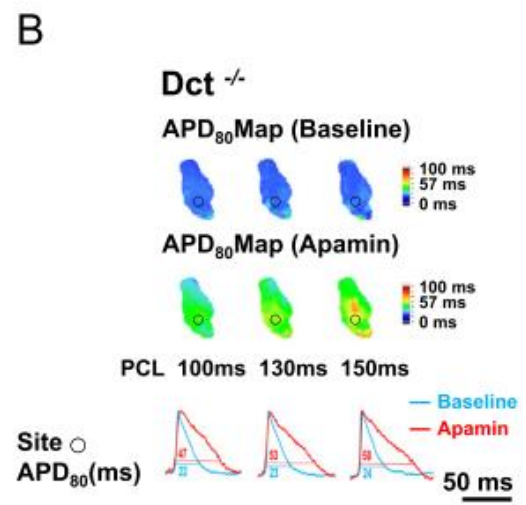
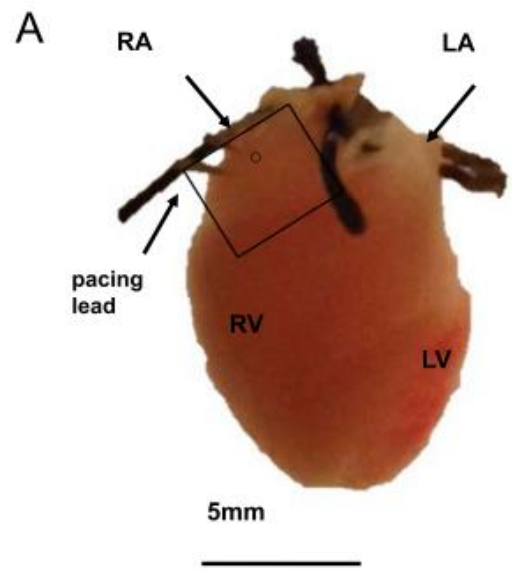
- SK channel inhibition possesses antiarrhythmic properties in a rat in vivo model of PAF with hypertension-induced atrial remodeling.

Hypertension. 2011;57:1129-1135.

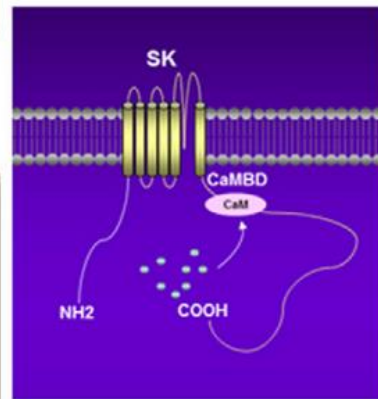
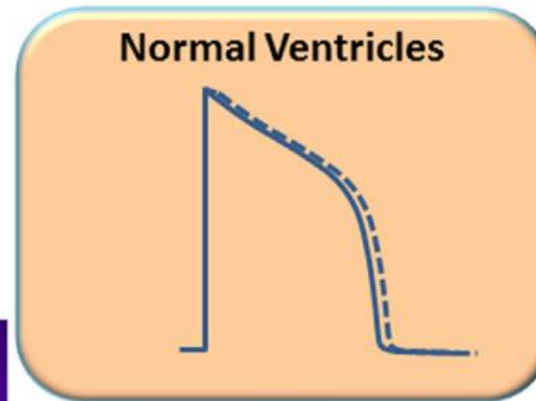
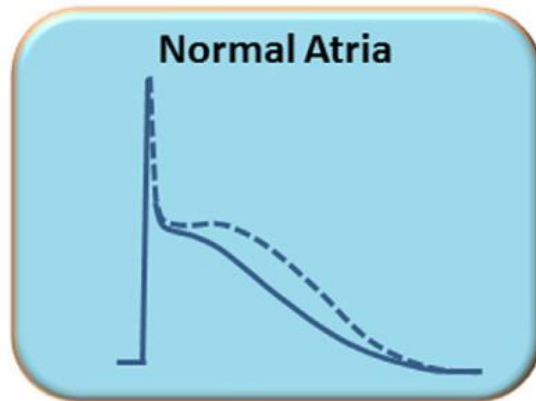
- Inhibition of SK channels prolongs atrial ERP without affecting QT and prevents/terminates AF in rat/rabbit/guinea pig models.

Circ Arrhythm Electrophysiol. 2010;3:380-390

SK in melanocyte-like cells



Functional roles of SK channels⁹



AF

SK Channel Remodeling

- ↑ Trafficking
- ↑ Expression in PV

SK channel blockers

- ↓ AF

Null deletion of SK channel

- EAD → AF

— Control
- - - SK Blocker

HF

SK channel Remodeling

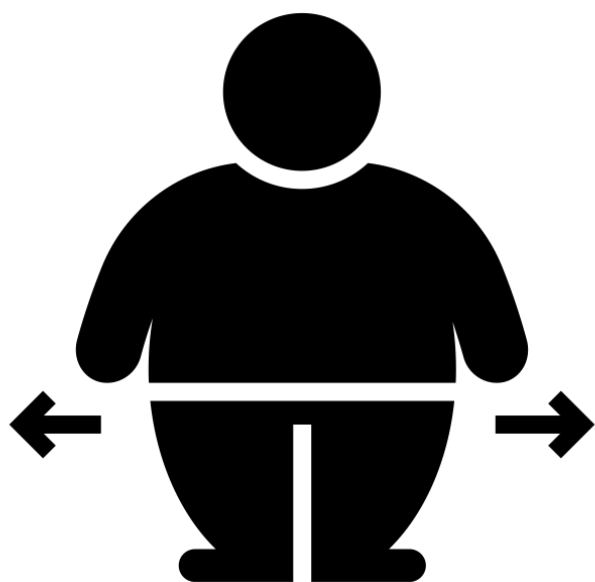
- ↑ expression in HF & post MI

SK channel blockers

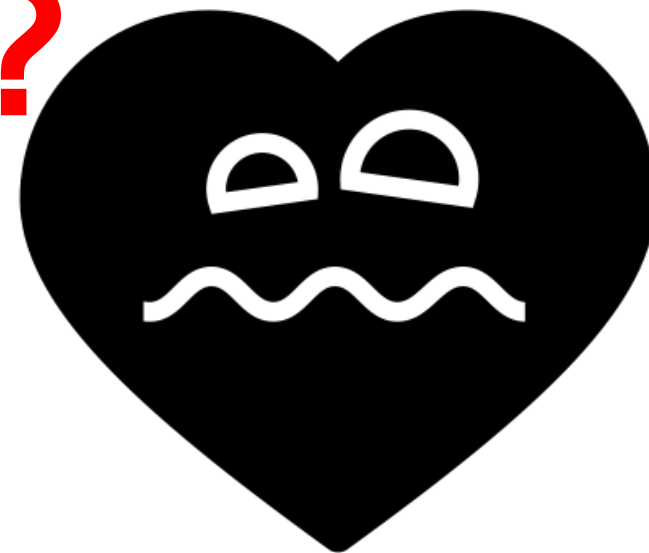
- ↑ polymorphic VT in HF
- ↓ Recurrent VF post shock

— Control
- - - SK Blocker

Atrial myopathy in Metabolic syndrome ?

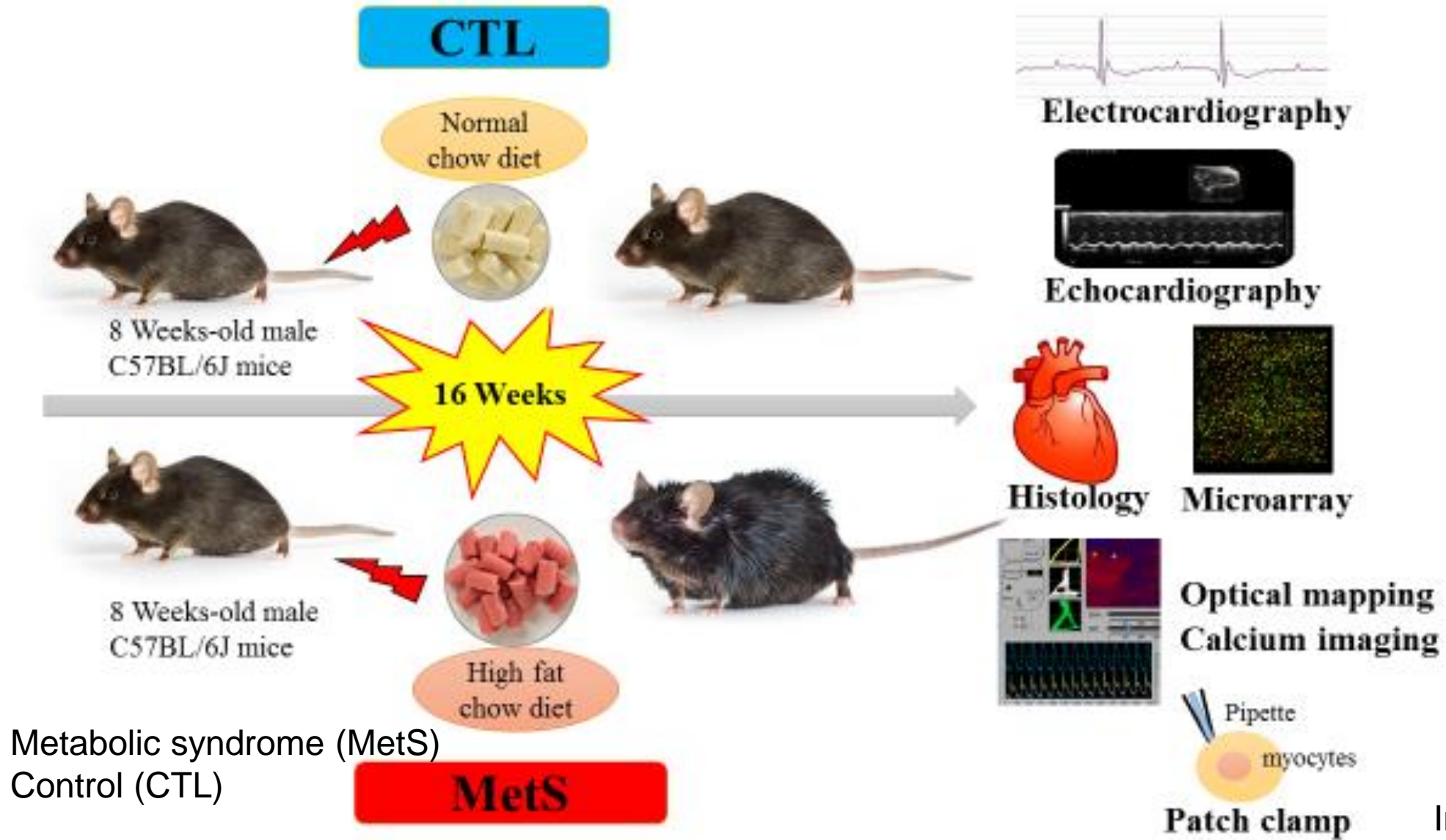


SK?



Methods and Results

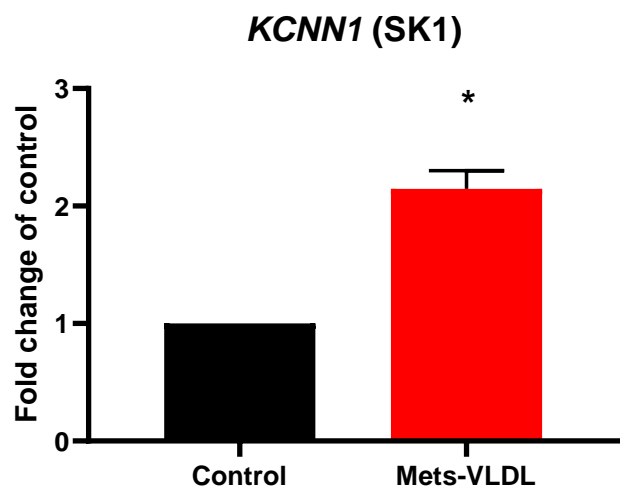
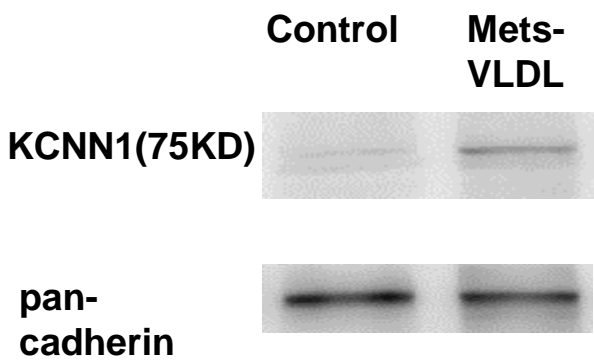
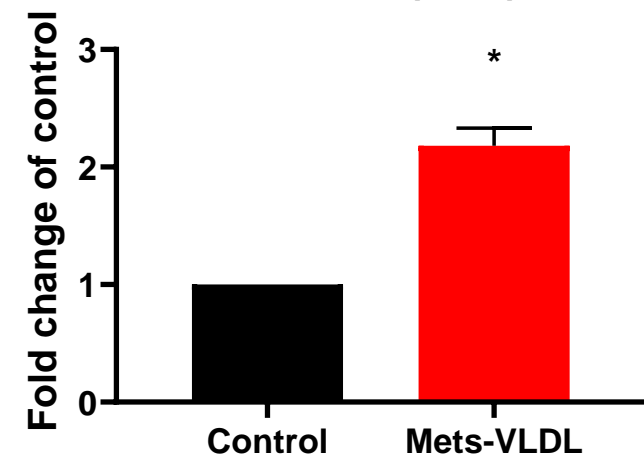
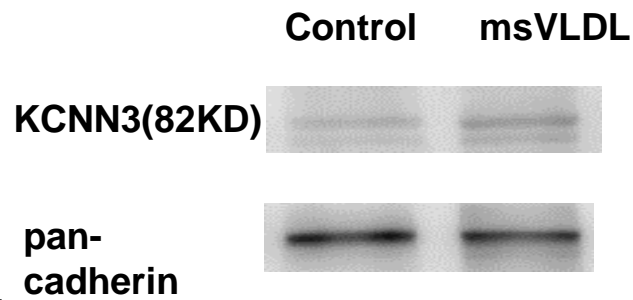
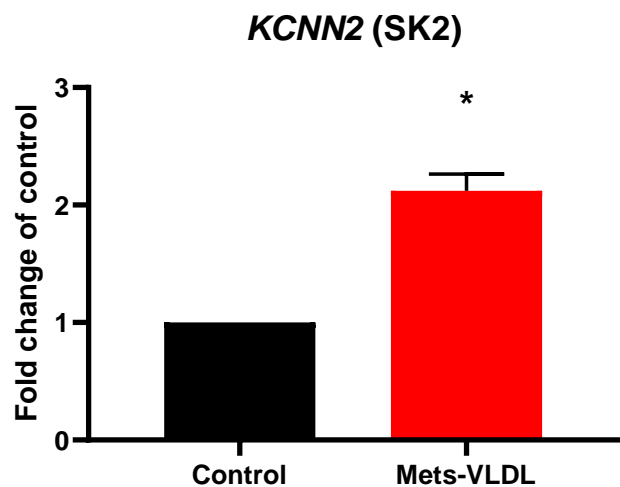
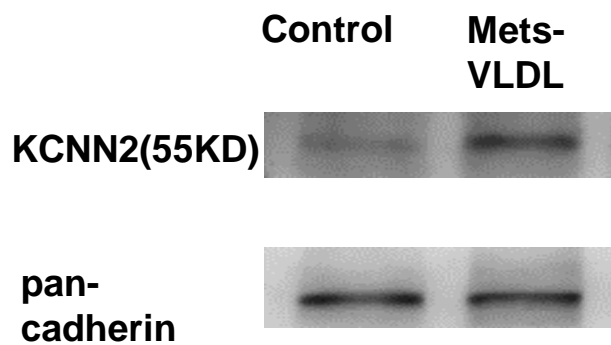
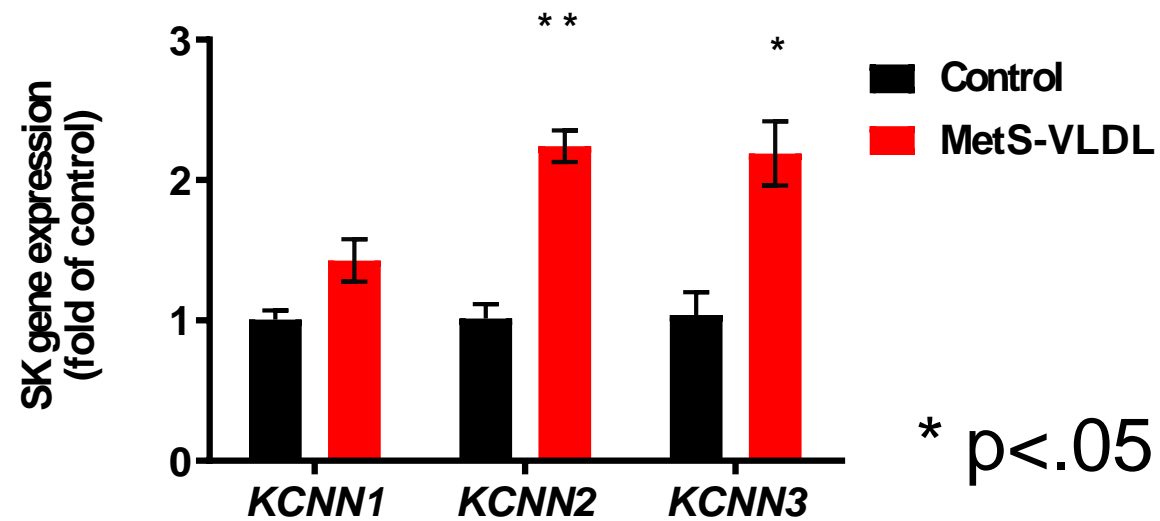
Scheme of the model and investigations



Metabolic syndrome (MetS)
Control (CTL)

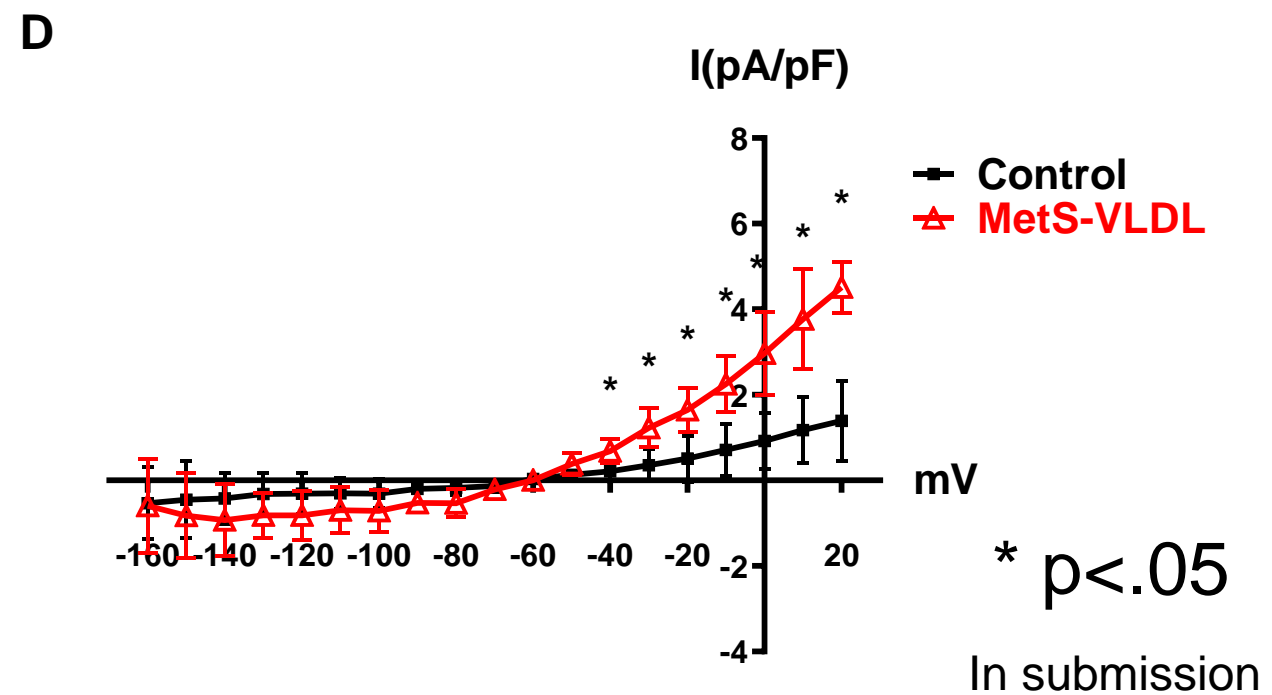
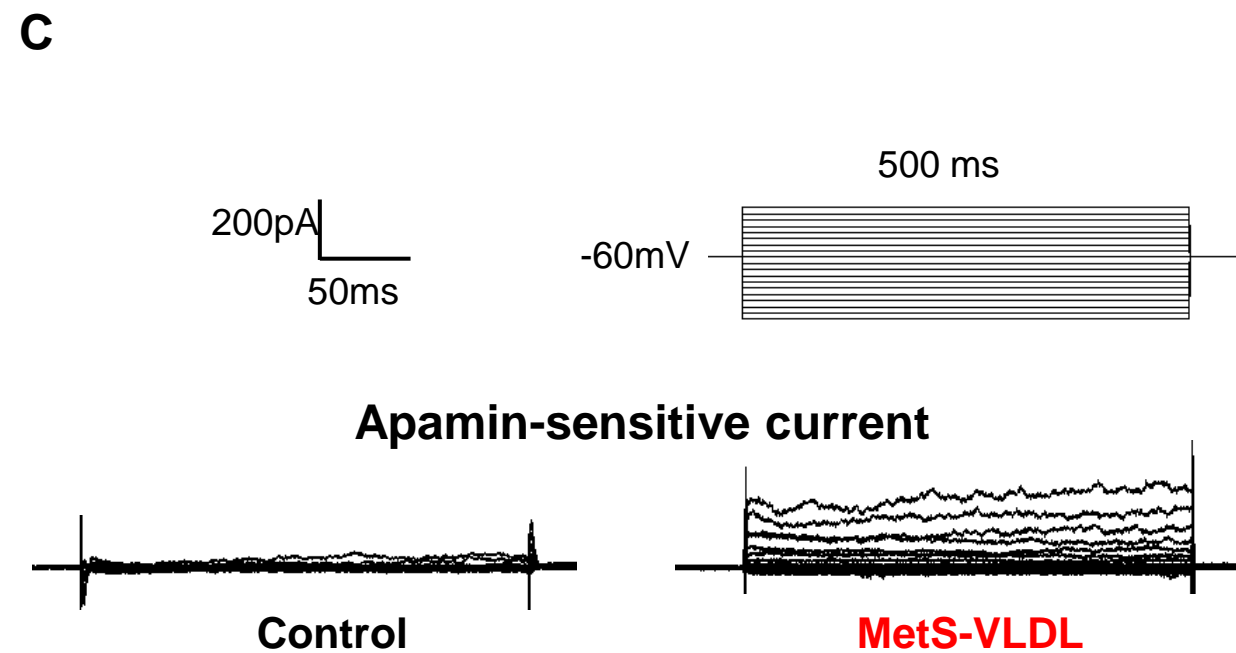
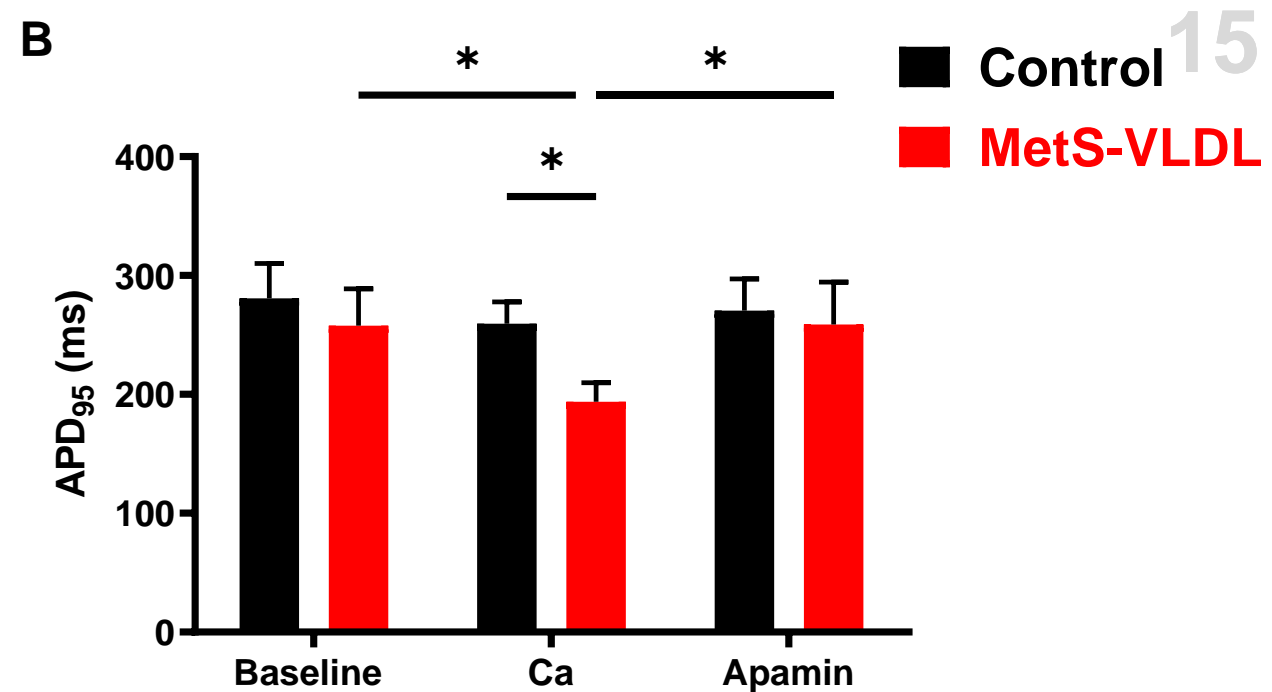
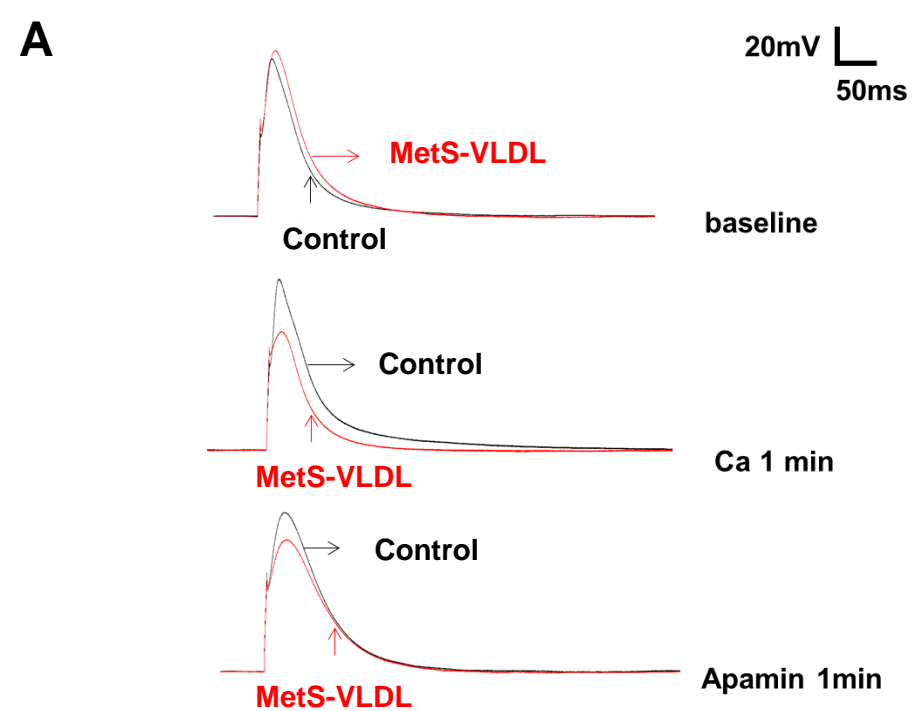
Cell data

1. mRNA, protein
2. Patch clamp

A**B****C****D*** $p < .05$

In submission

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In submission

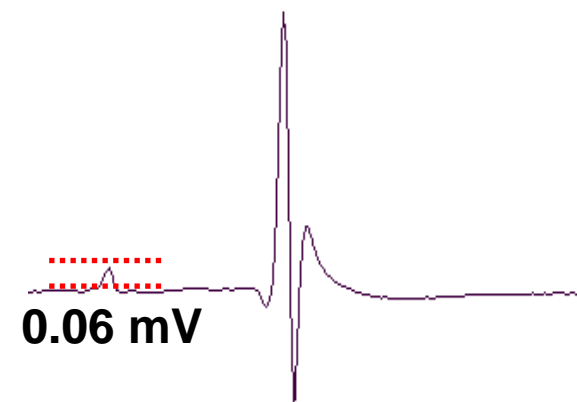
Animal data

1. ECG, UCG
2. Optical Mapping
3. mRNA
4. Histology

ECG

Electrocardiography	CTL	MetS	P value
Heart rate (bpm)	387.89±85.56	366.90±94.20	0.41
P width (ms)	15.88±2.56	15.75±5.17	0.85
P voltage (mV)	0.06±0.02	0.08±0.03*	0.01
PR (ms)	58.41±14.59	49.56±14.48	0.16
QRS duration (ms)	35.50±7.45	32.71±9.72	0.49
R voltage (mV)	0.90±0.23	0.73±0.24*	0.01
QT (ms)	73.64±15.95	75.41±35.33	0.61
RR (ms)	162.21±36.78	175.95±48.45	0.36
QTc (ms)	57.95±9.88	56.90±22.66	0.61
PWA (ms x mV)	0.48±0.16	0.66±0.35*	0.03
PWAc (ms x mV)	0.39±0.14	0.51±0.27	0.11
PWc (ms)	12.70±2.54	12.14±3.73	0.56

CTL



MetS



* $p < 0.05$

Both group $n \geq 10$

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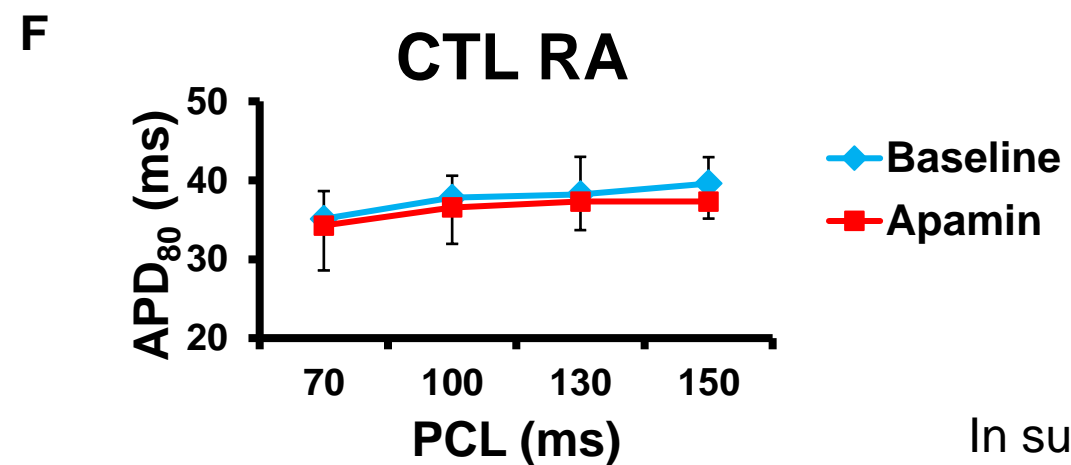
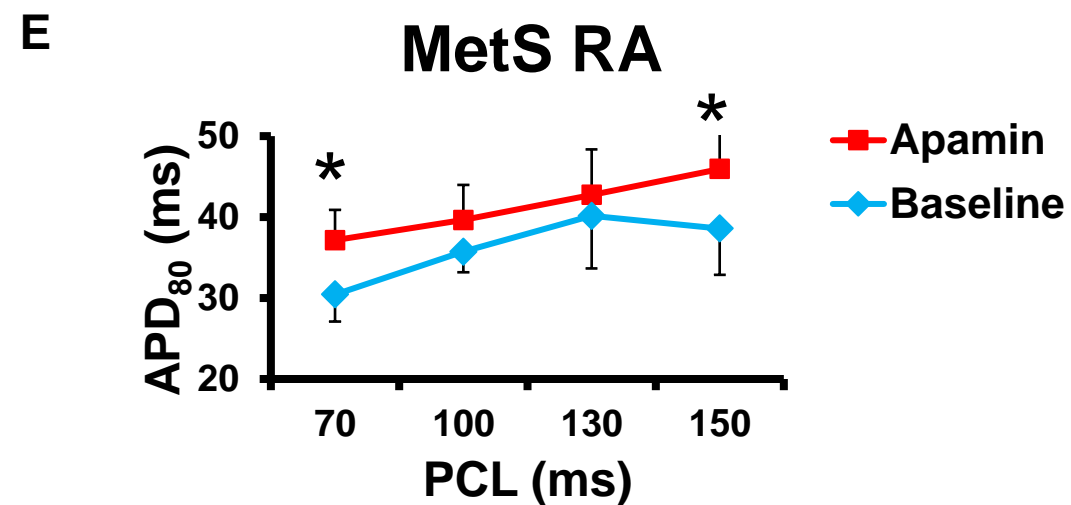
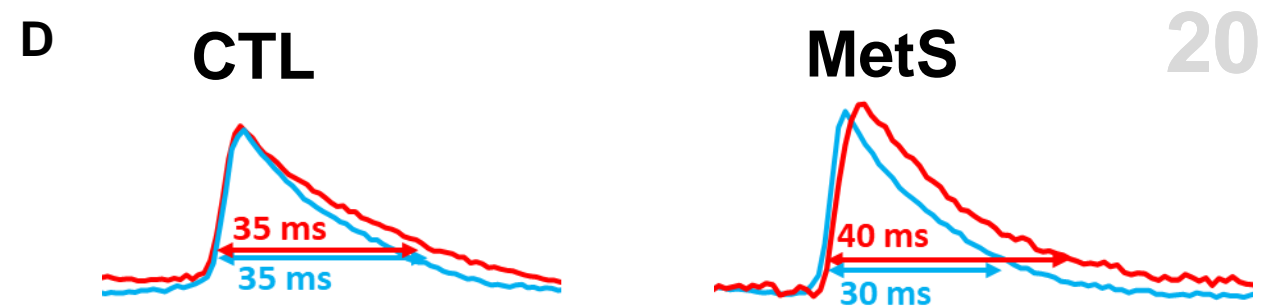
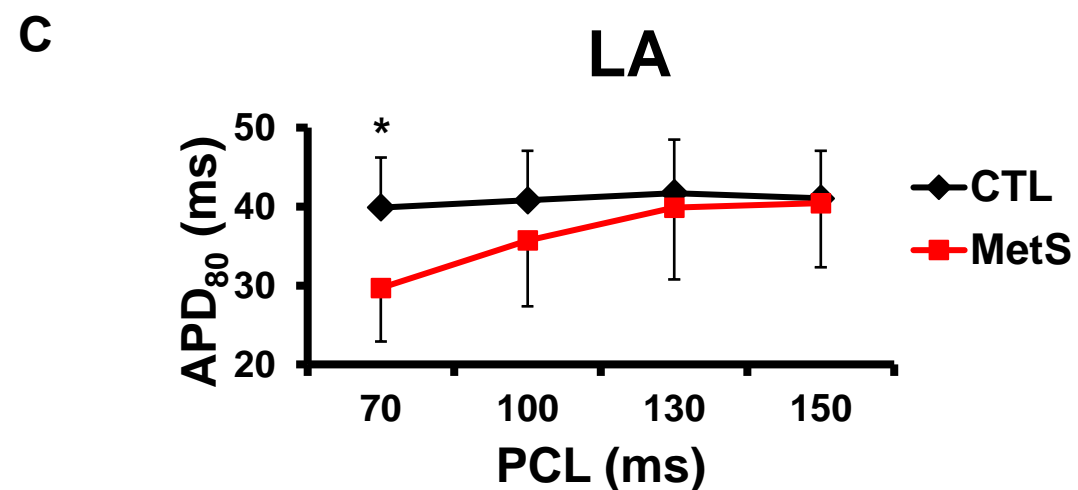
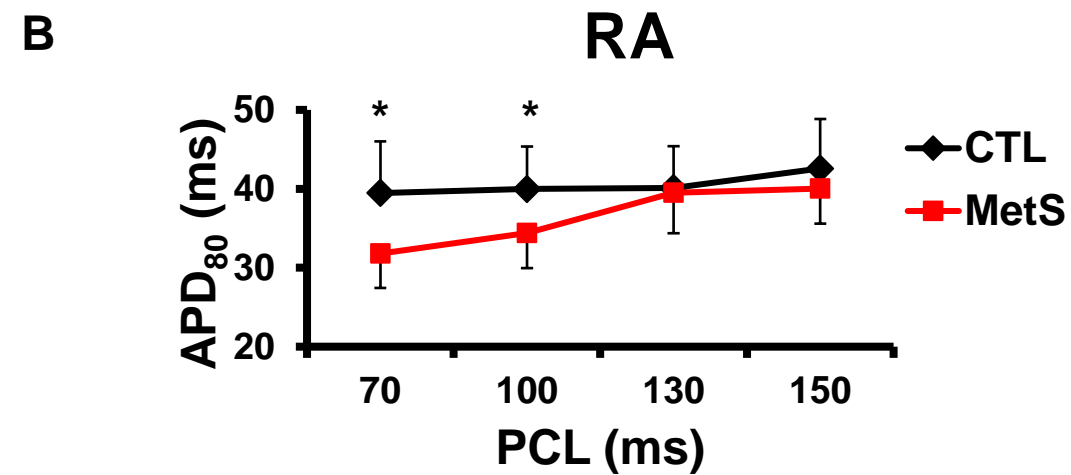
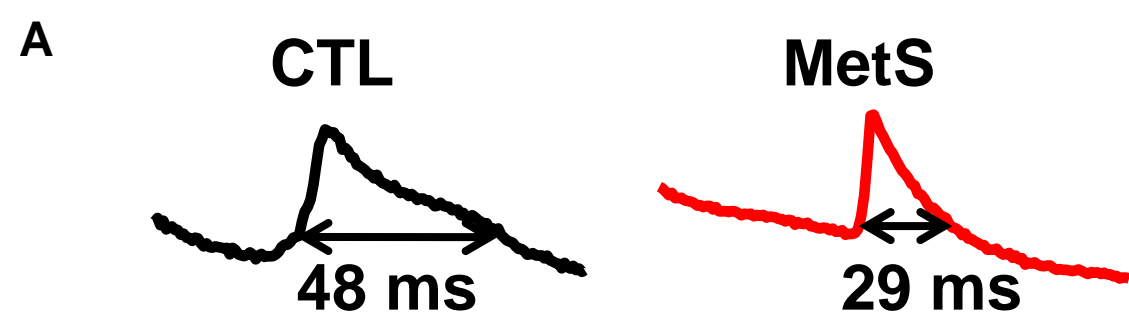
Echocardiography	CTL	MetS	P value
Ao Root (mm)	1.92±0.18	1.98±0.14	0.25
IVSd (mm)	1.06±0.14	0.96±0.08*	0.04
IVSs (mm)	1.49±0.27	1.39±0.17	0.48
LA (mm)	2.31±0.35	2.55±0.53	0.14
LVIDd (mm)	3.91±0.46	4.15±0.36	0.19
LVIDs (mm)	2.63±0.49	2.86±0.46	0.28
LVPWd (mm)	0.90±0.09	0.93±0.07	0.39
LVPWs (mm)	1.29±0.14	1.33±0.15	0.63
FS (%)	33.13±6.35	31.56±6.67	0.74
EF (%)	61.68±7.13	59.85±7.35	0.74

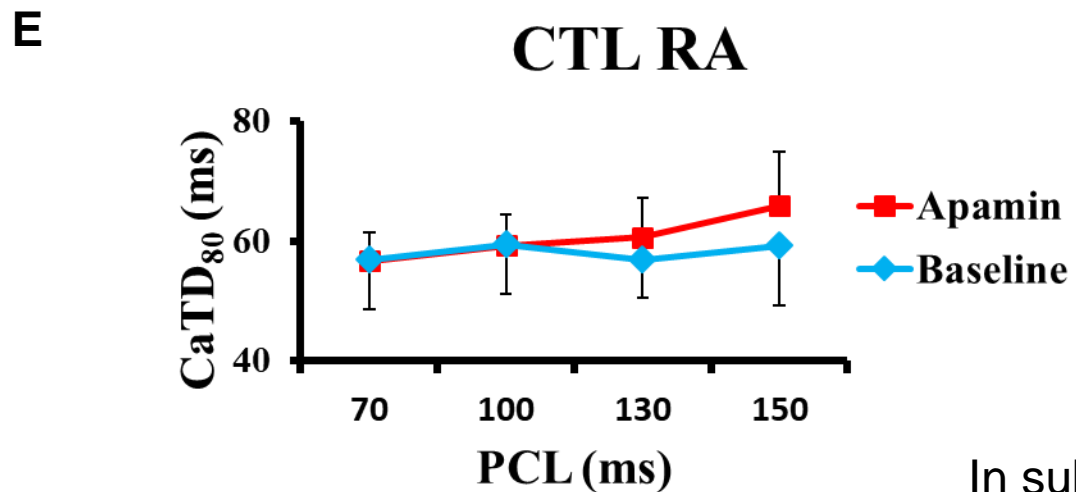
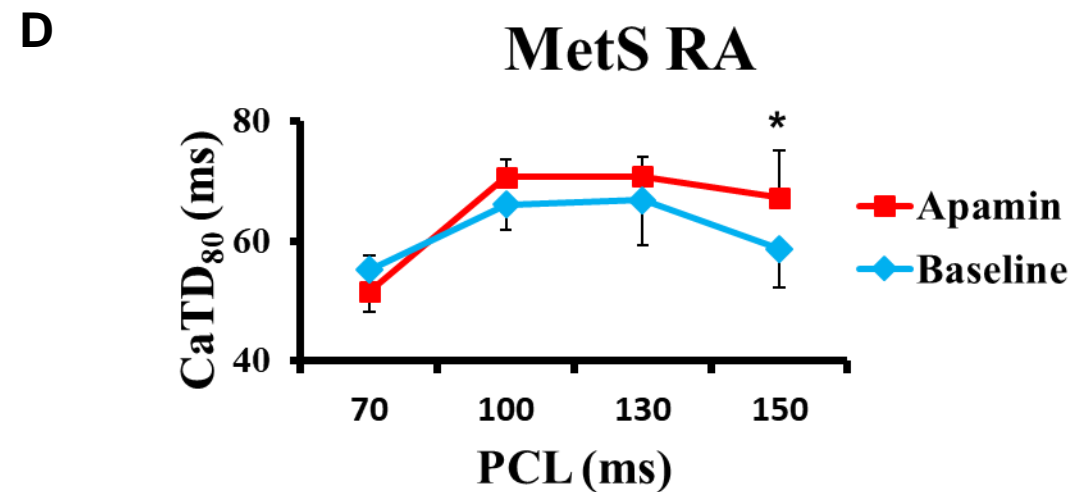
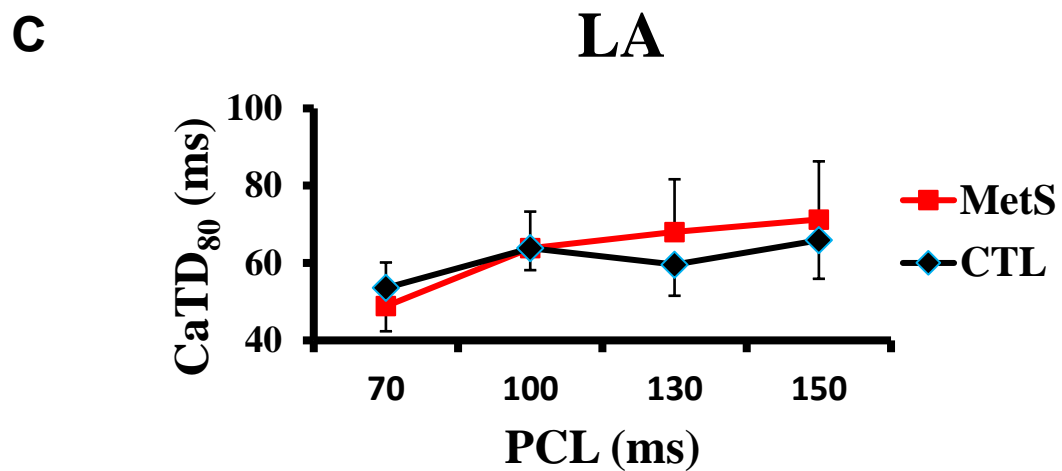
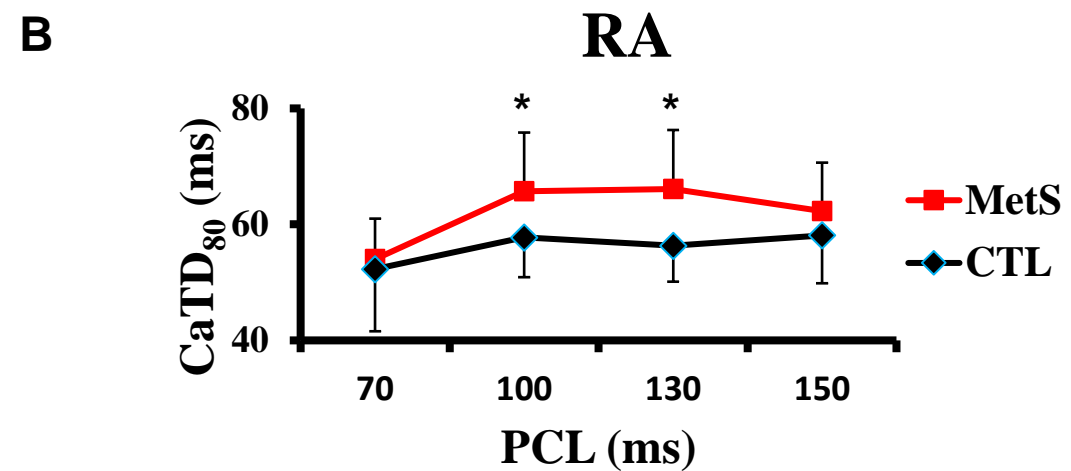
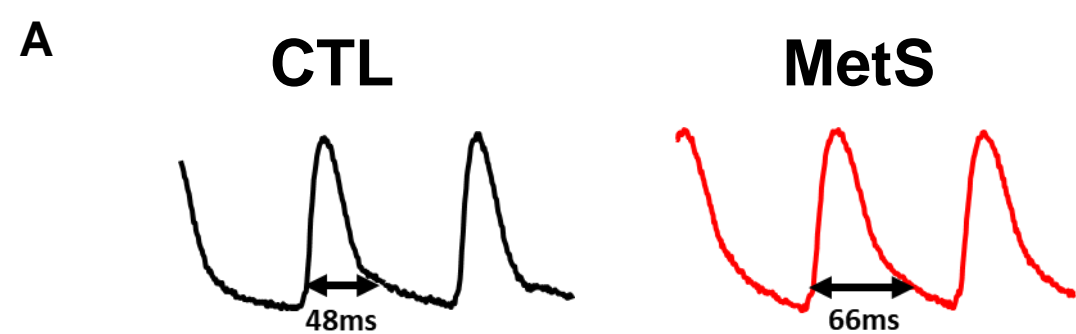
* p<.05

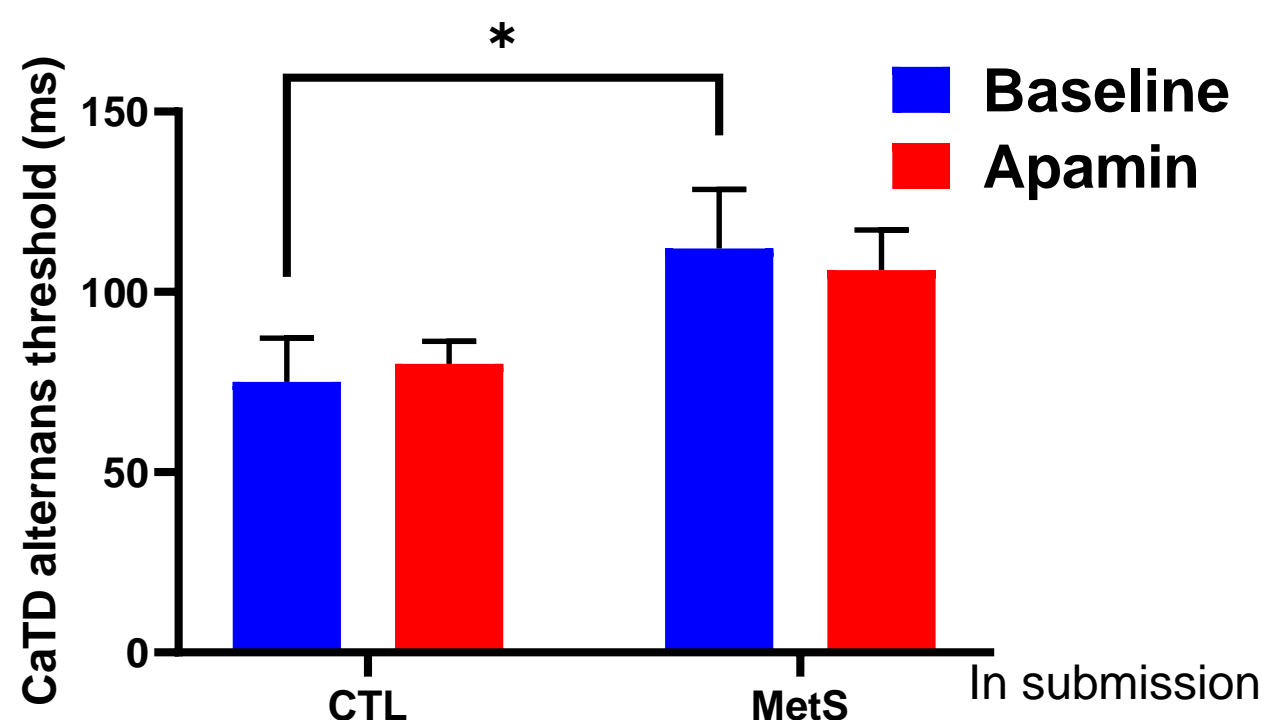
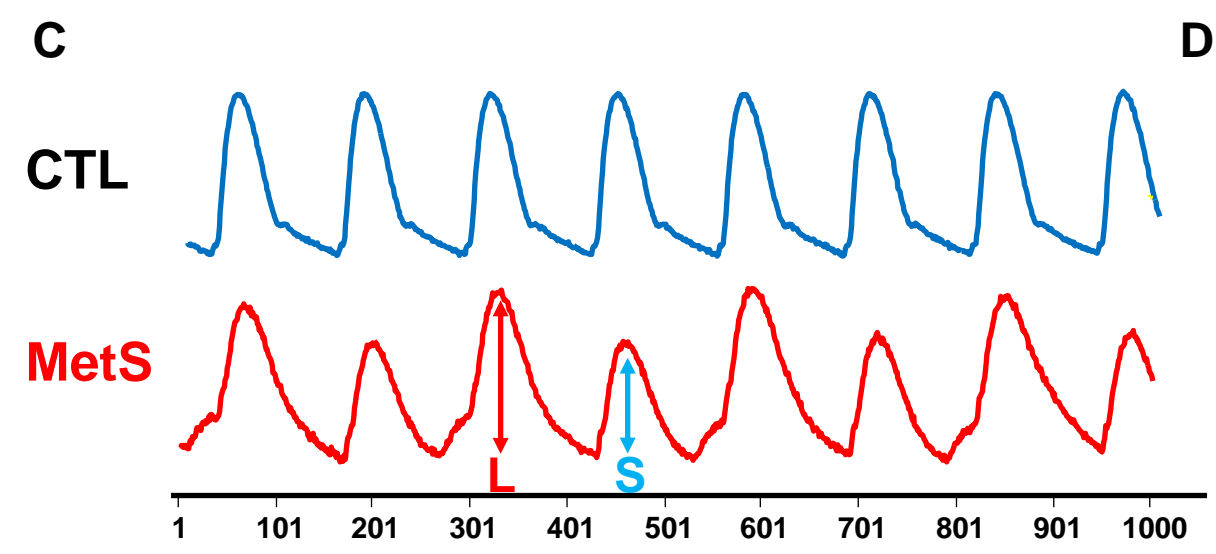
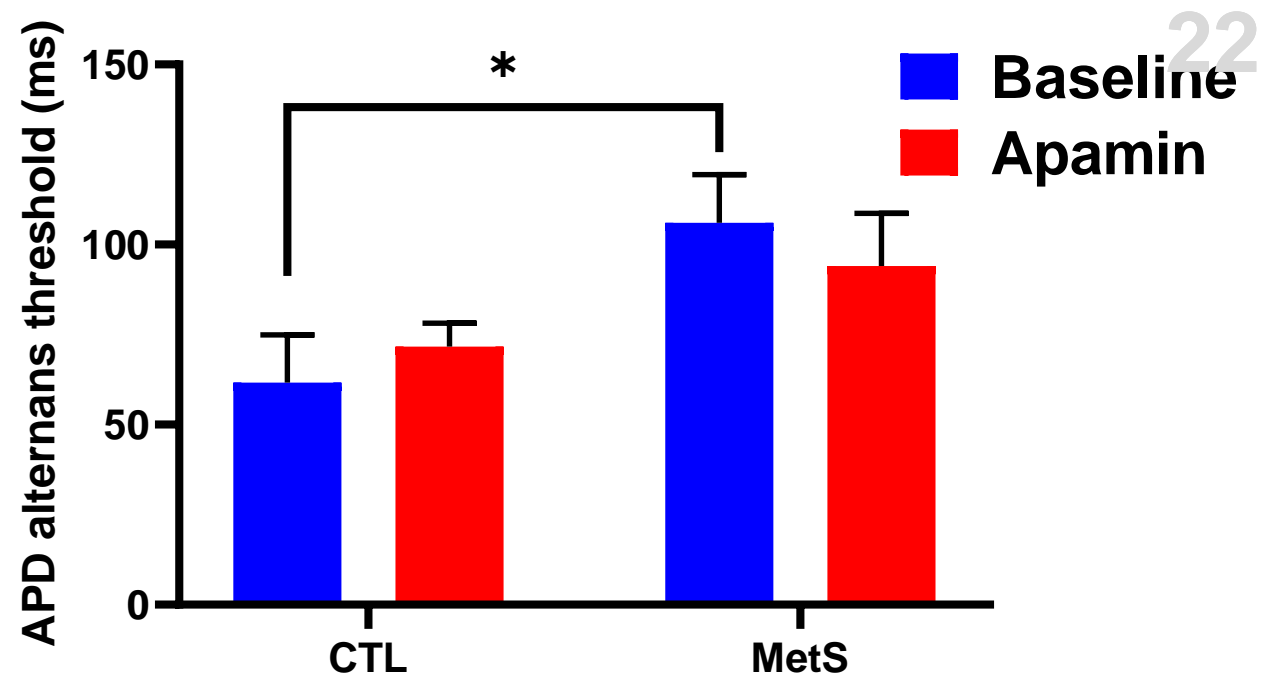
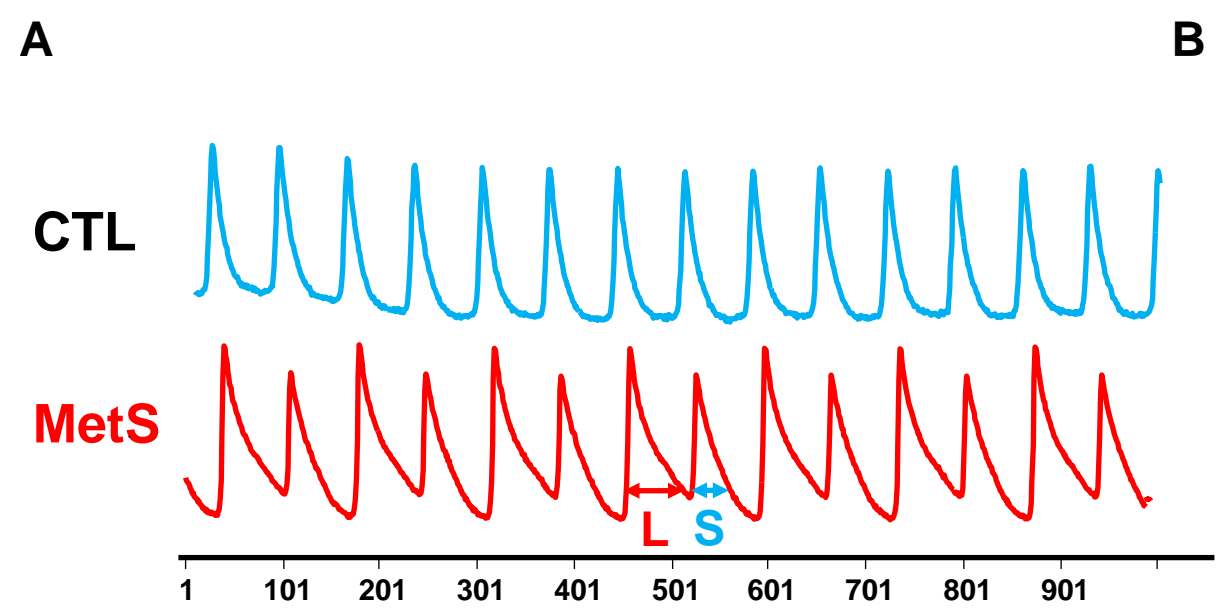
Both group n ≥ 10

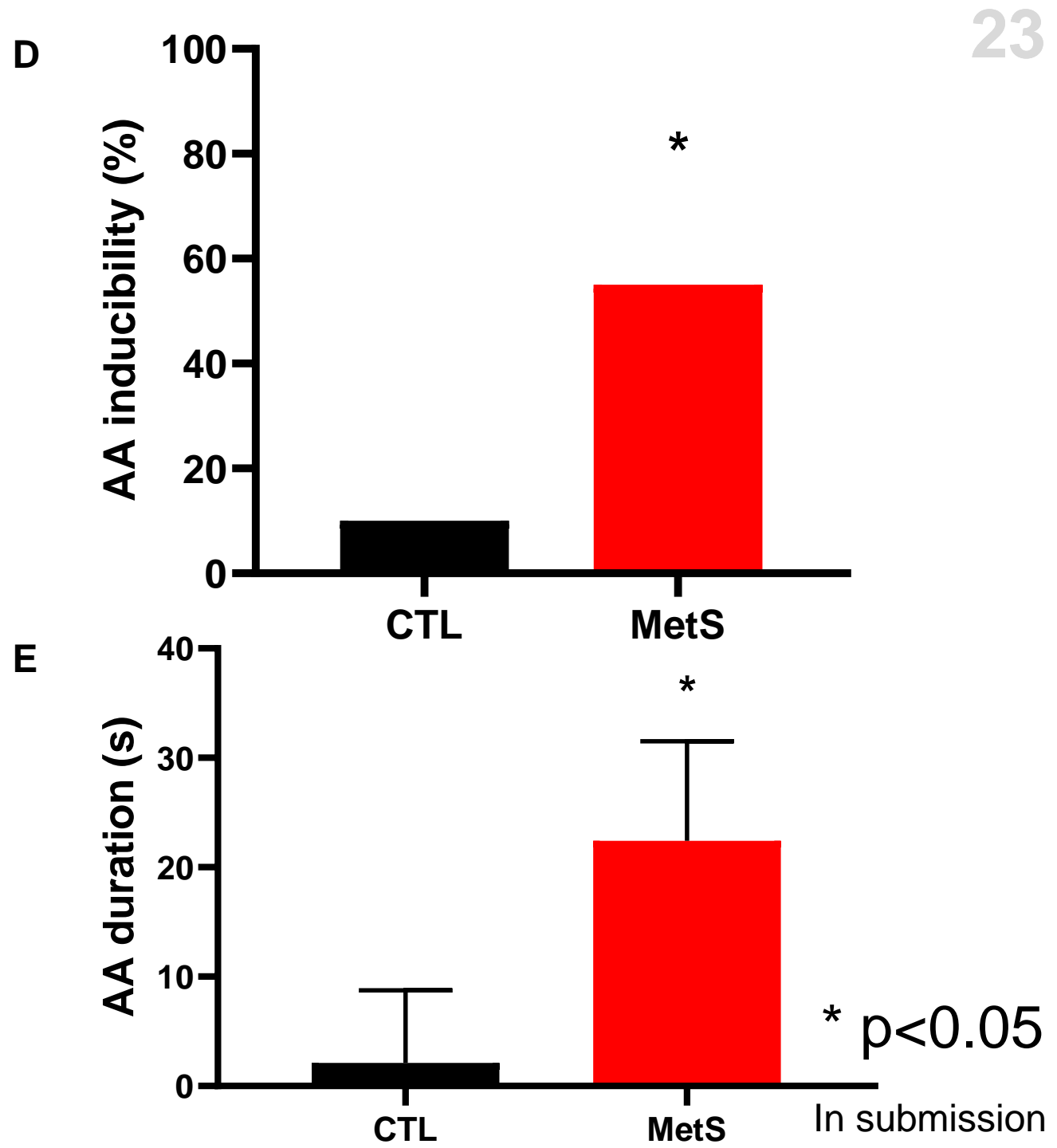
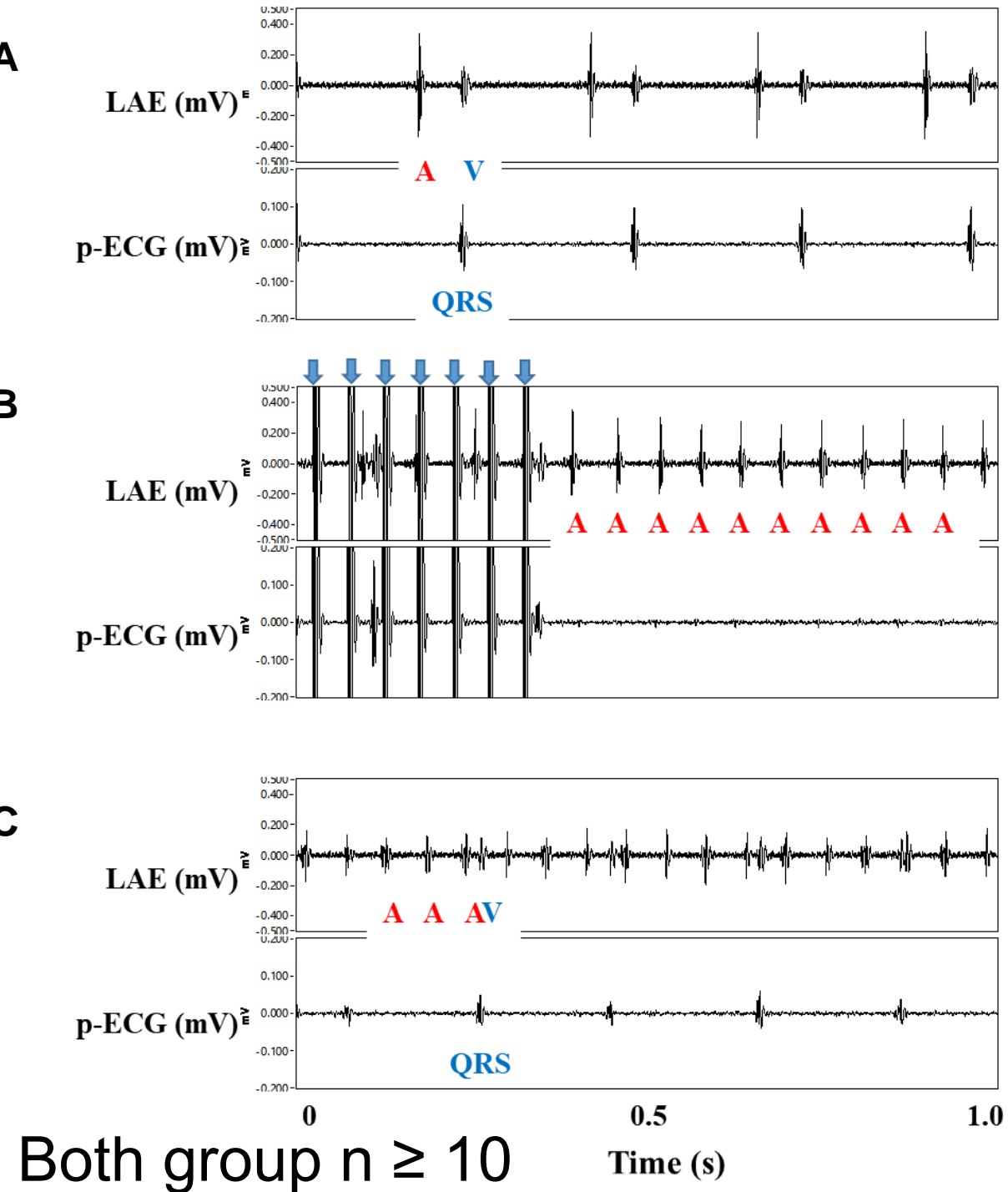
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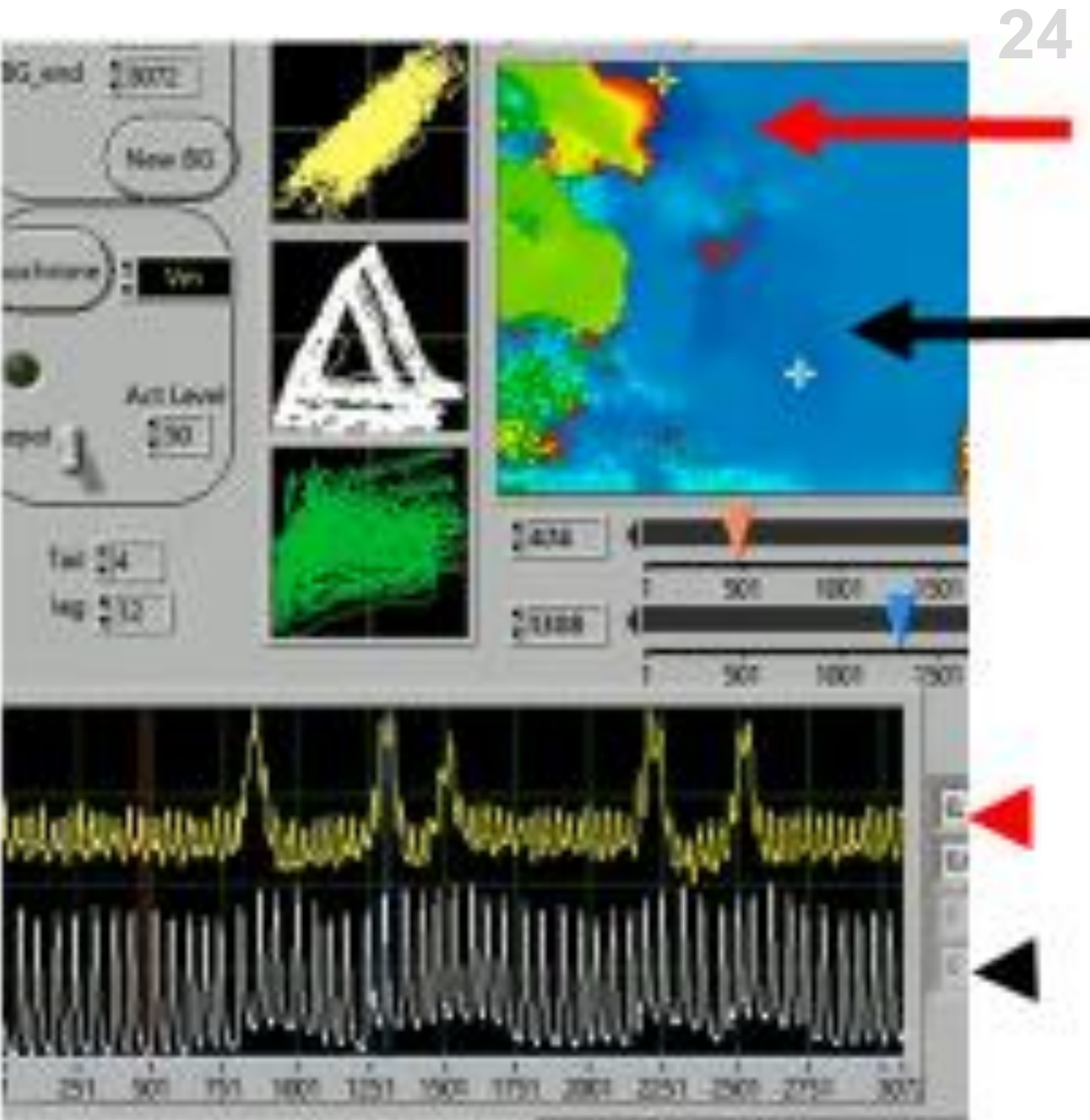
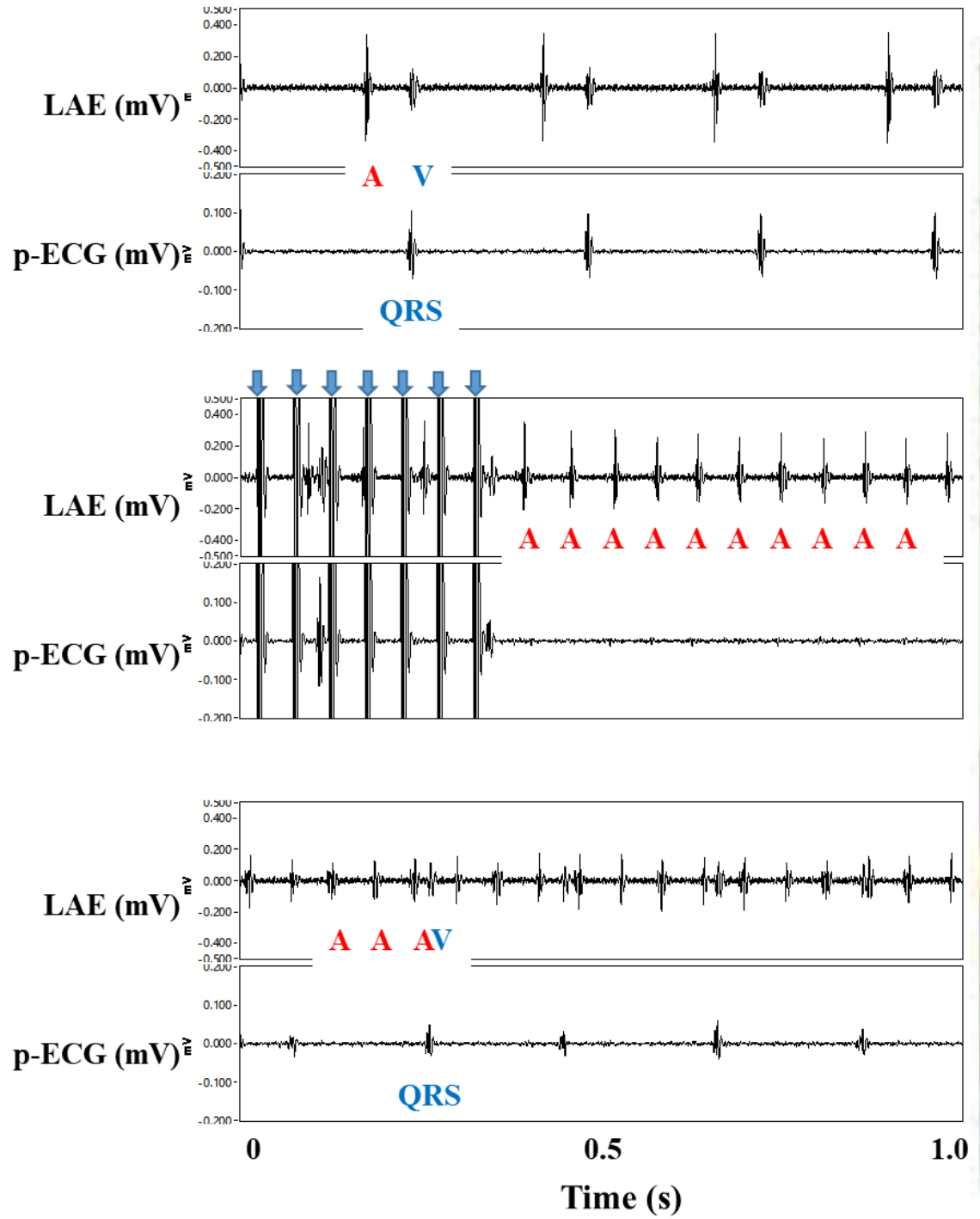
Optical mapping



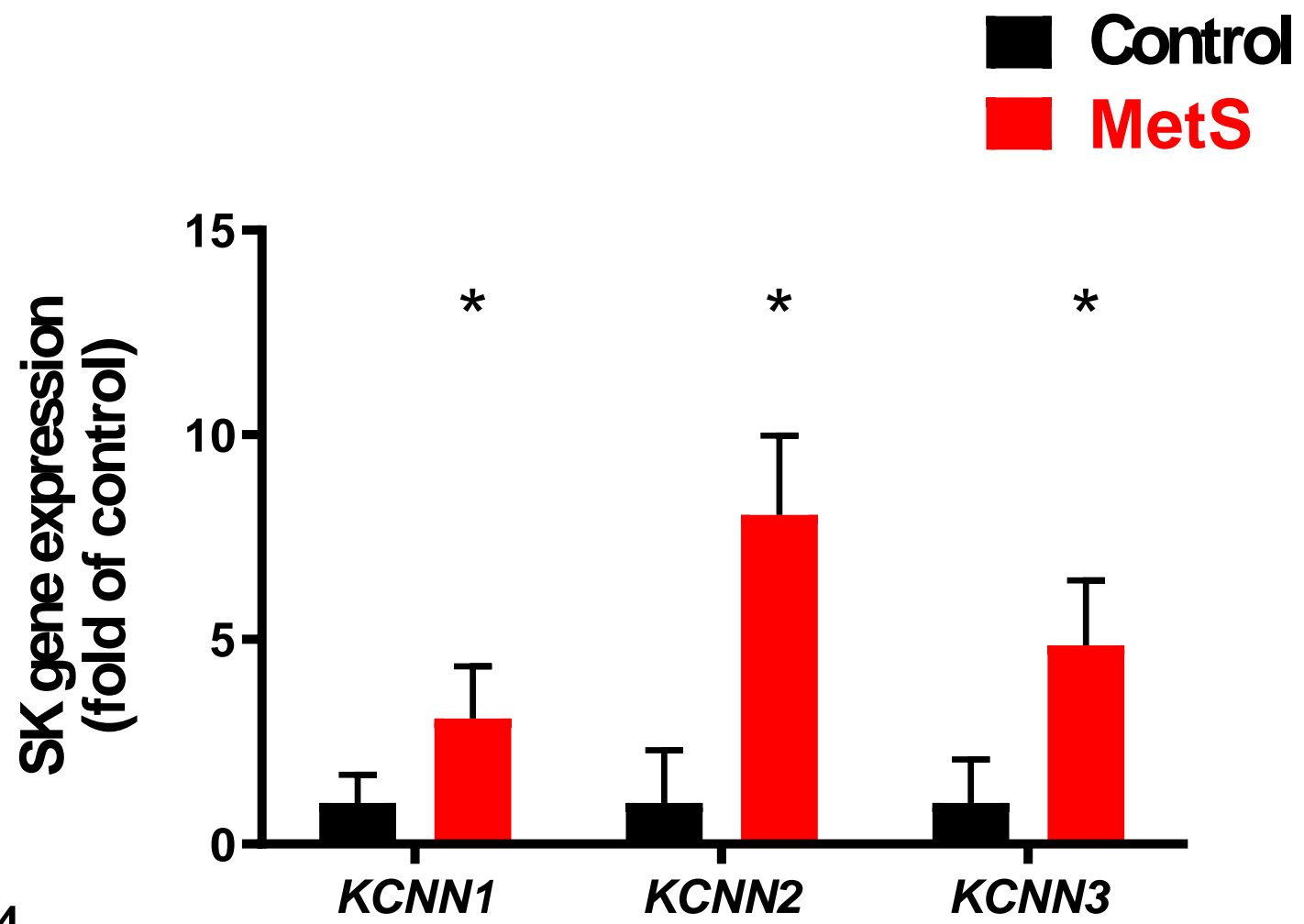








mRNA expression of SK in mice

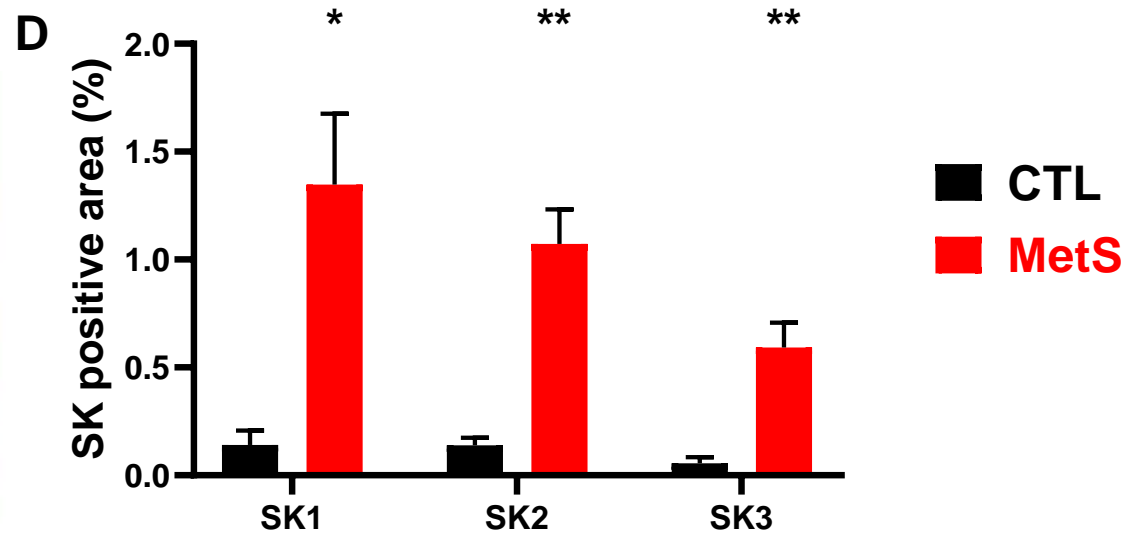
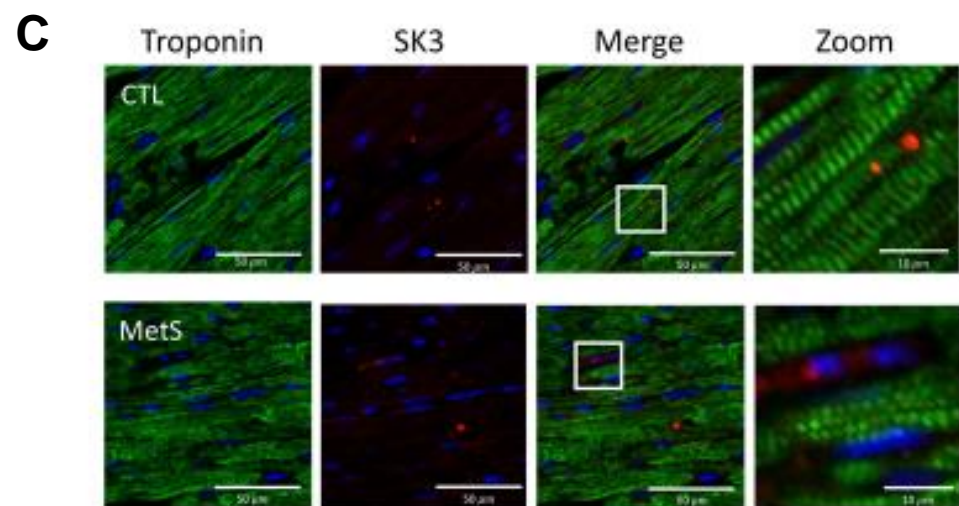
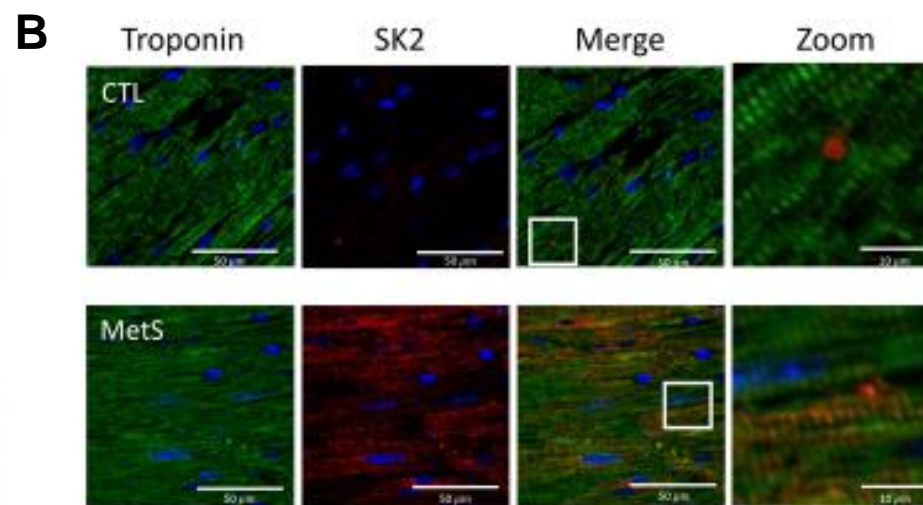
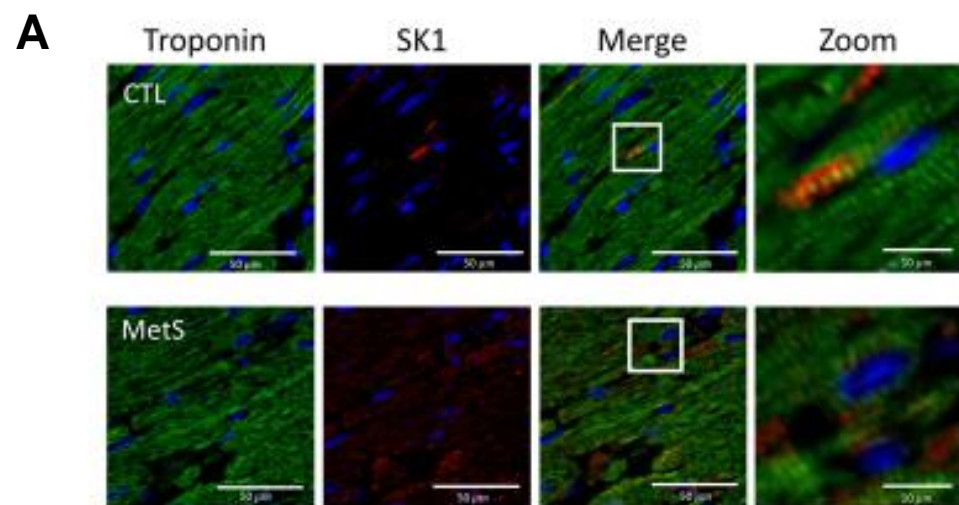


Both group n = 4

* p < .05

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Histology



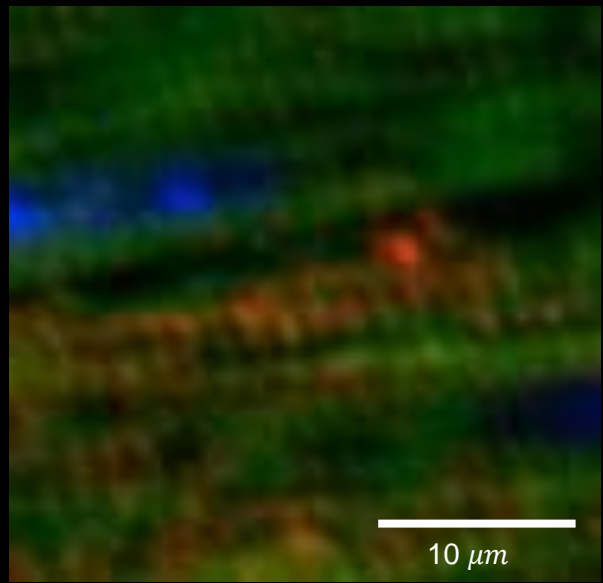
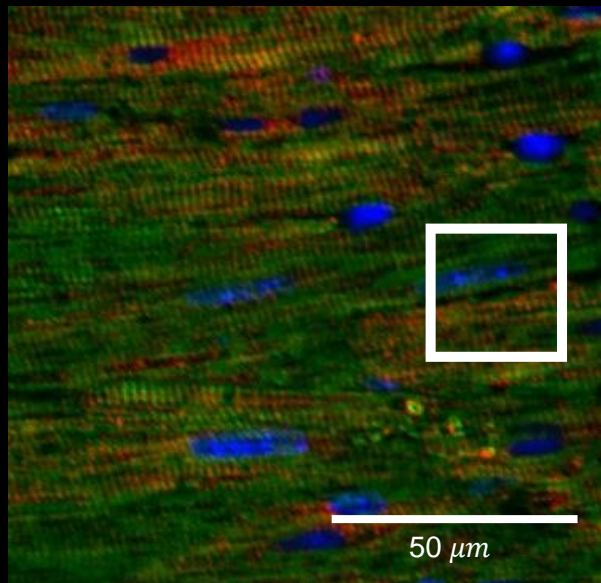
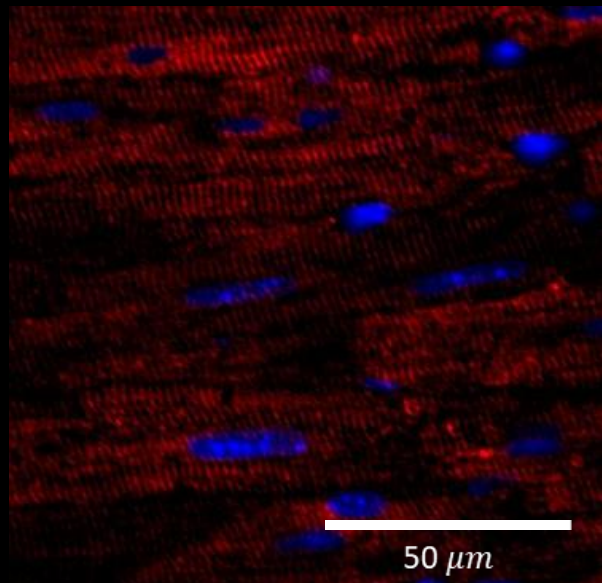
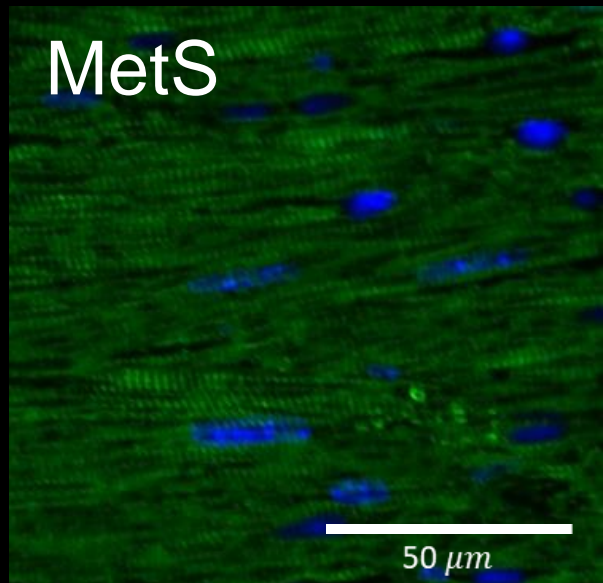
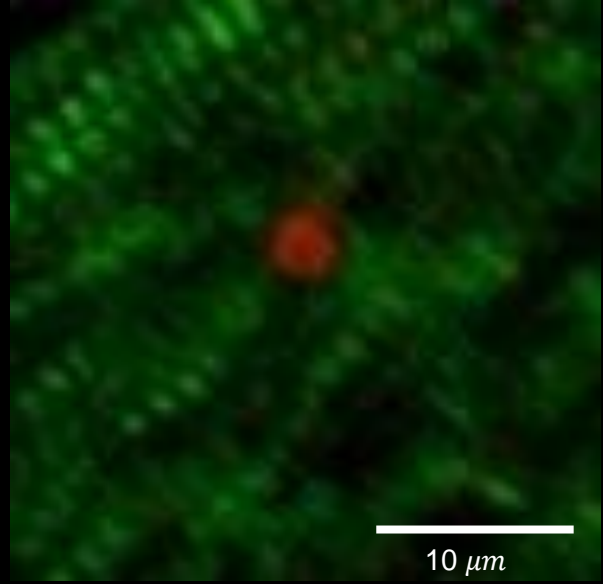
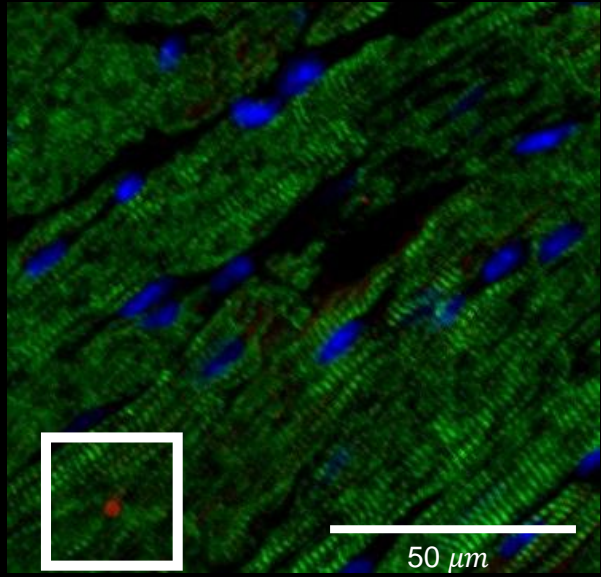
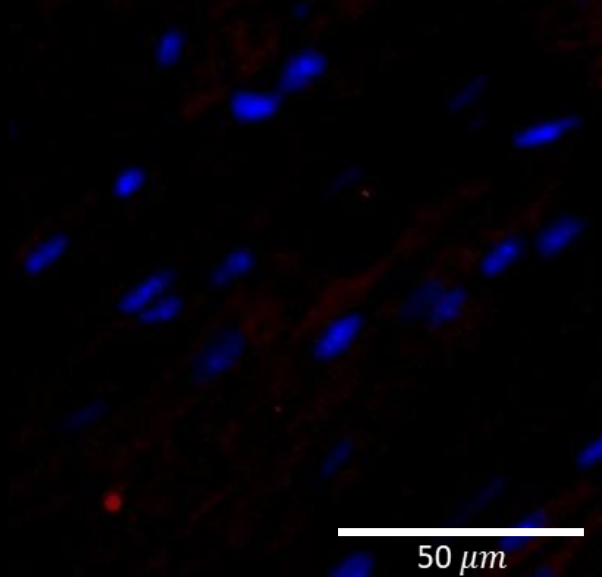
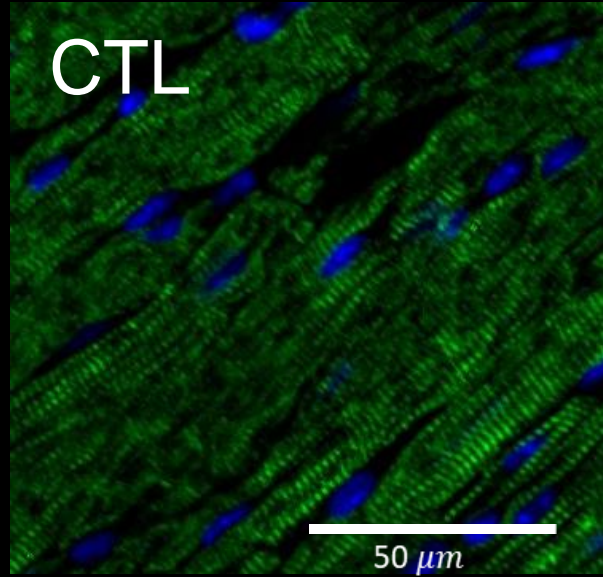
Troponin

SK2

Merge

Zoom

27



Conclusions

- SK channel is playing an important role of atrial myopathy in the metabolic syndrome.
 - The MetS atria have **shorter APD** than controls and the APD shortening could be reversed by **apamin**.
 - The MetS atria and HL-1 cell have **increasing expression of mRNA of the SK channels**.
 - The MetS atria are more **vulnerable to atrial burst** pacing and have **higher AF inducibility** and **longer AF duration** than controls.

Acknowledgement



• KMUH

- 許勝雄 • 賴文德
- 李智雄 • 李坤泰
- 李香君 • 林宗憲
- 卓士傑 • 許柏超



國立交通大學
National Chiao Tung University



- Shien-Fong Lin,
- Chun Liu



- Krannert Institute of Cardiology
- Peng-Sheng Chen,



Thank you for your attention!



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