Autonomic modulation

in Acute Myocardial Infarction

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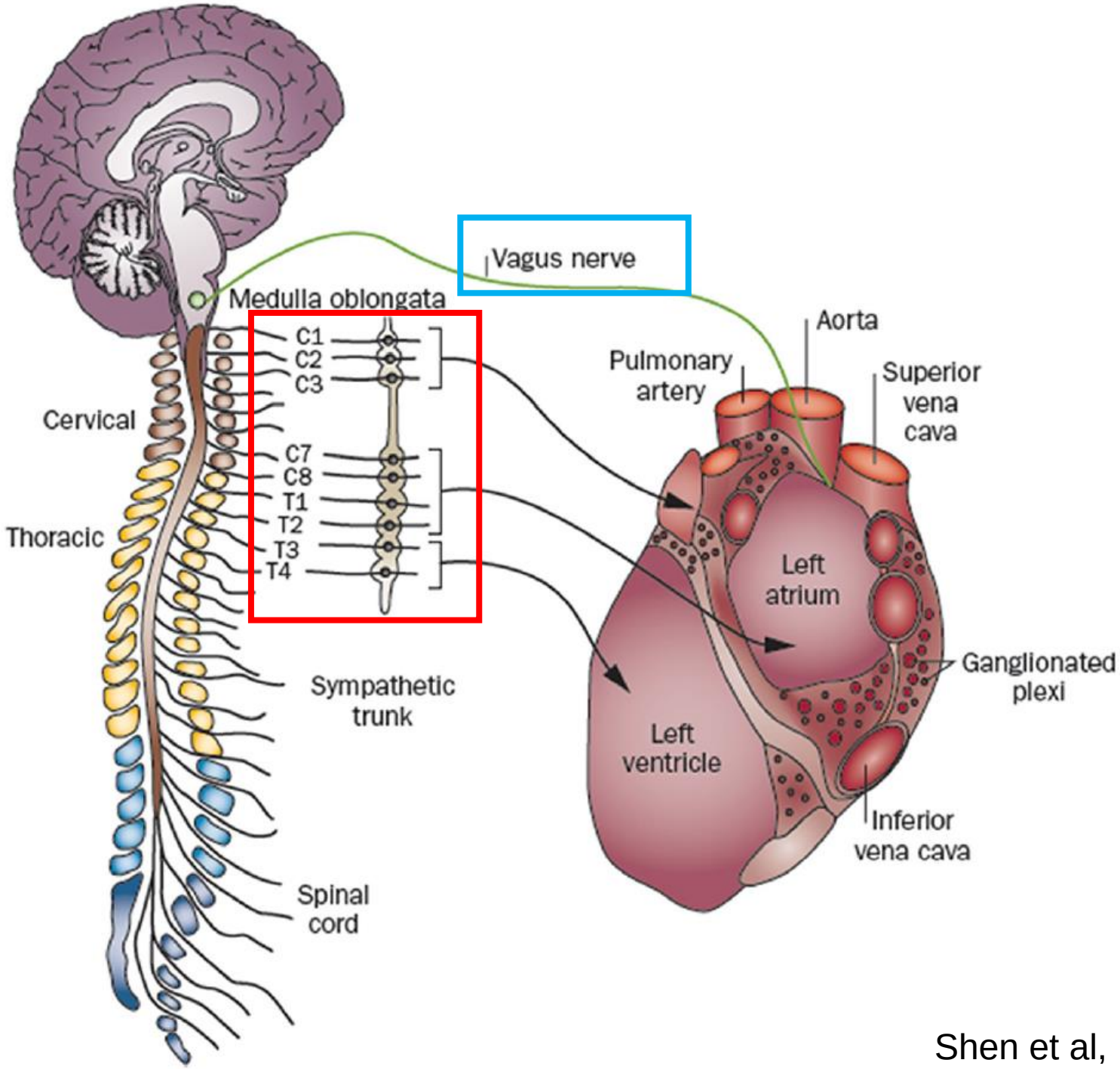
Disclosures

- **WC. Tsai:** None



Shen et al, Nat Rev Cardiol 2012

Role of the Autonomic Nervous System in Modulating Cardiac Arrhythmias

- **Sympathetic** actions:
  - Chronotropic effect,
  - Intracellular calcium handling,
  - Cardiac electrophysiology.
- In normal heart:
  - shortens action potential duration
  - reduces transmural dispersion of repolarization.
- In pathological states (HF, LQTS)
  - enhancing the dispersion of repolarization
  - generation of afterdepolarizations

Shen et al, Circ Res 2014

Sympathetic Nerve Sprouting after MI

GAP43

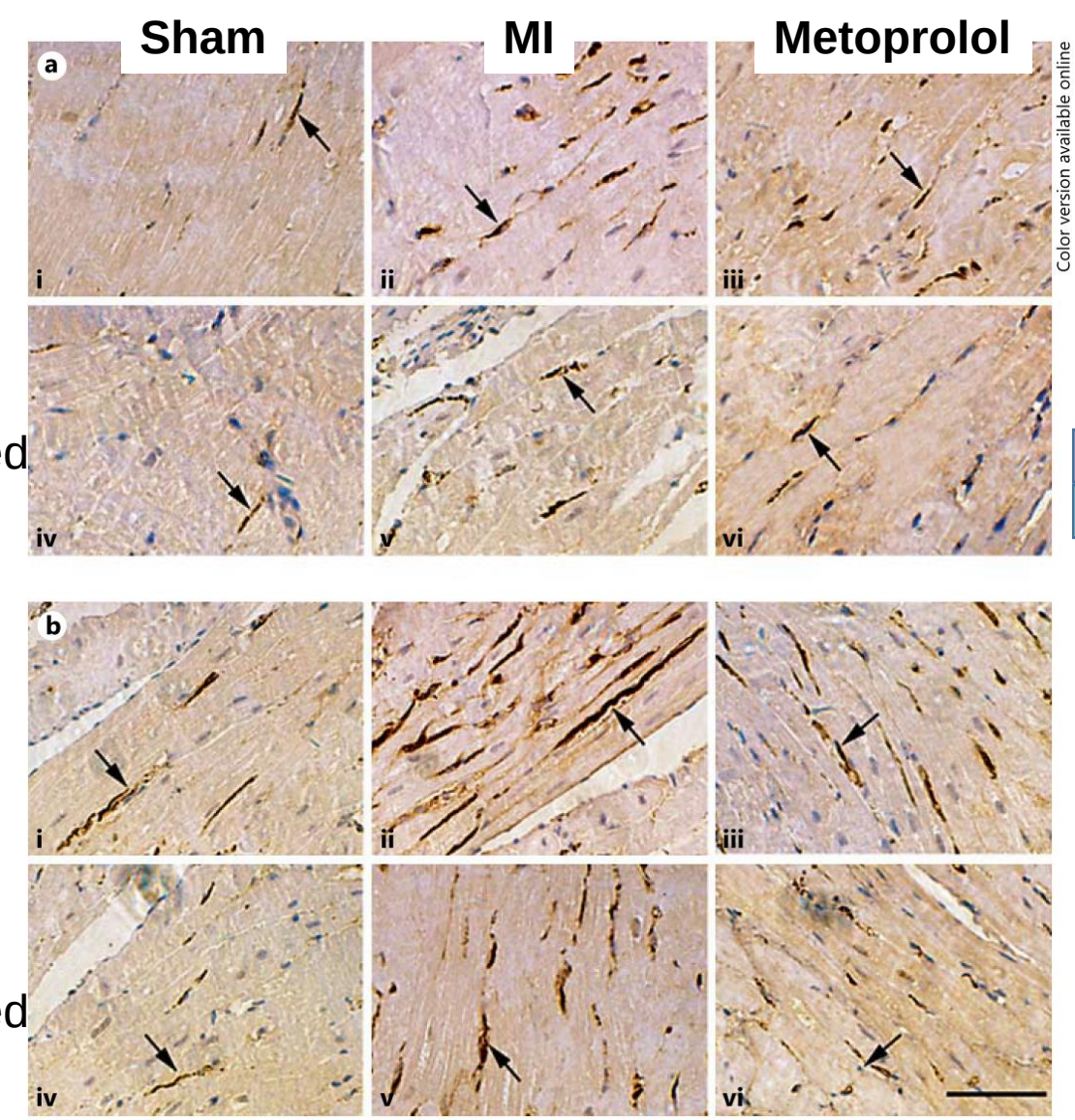
Infarcted border

Non-infarcted LVFW

TH

Infarcted border

Non-infarcted LVFW



Color version available online

Table 2. Nerve fiber density among rabbit groups

	GAP43 (μm²/mm²)		TH (μm²/mm²)	
	infarcted border	noninfarcted LVFW	infarcted border	noninfarcted LVFW
Sham	238±33	233±36	2,401±238	2,378±254
MI	602±47*, †	468±59*, †	3,492±230*, †	3,175±210*, †
Metoprolol	471±44*	288±44#	2,818±213*	2,620±217#

Data are mean ± SD. * $p < 0.01$, # $p < 0.05$ versus sham; † $p < 0.01$ versus metoprolol.

GAP43, growth associated protein 43
TH, tyrosine hydroxylase

Wang et al. Cardiology 2013

Left stellectomy → prevention of VA in AMI

AMI

AMI + LSG block

AMI

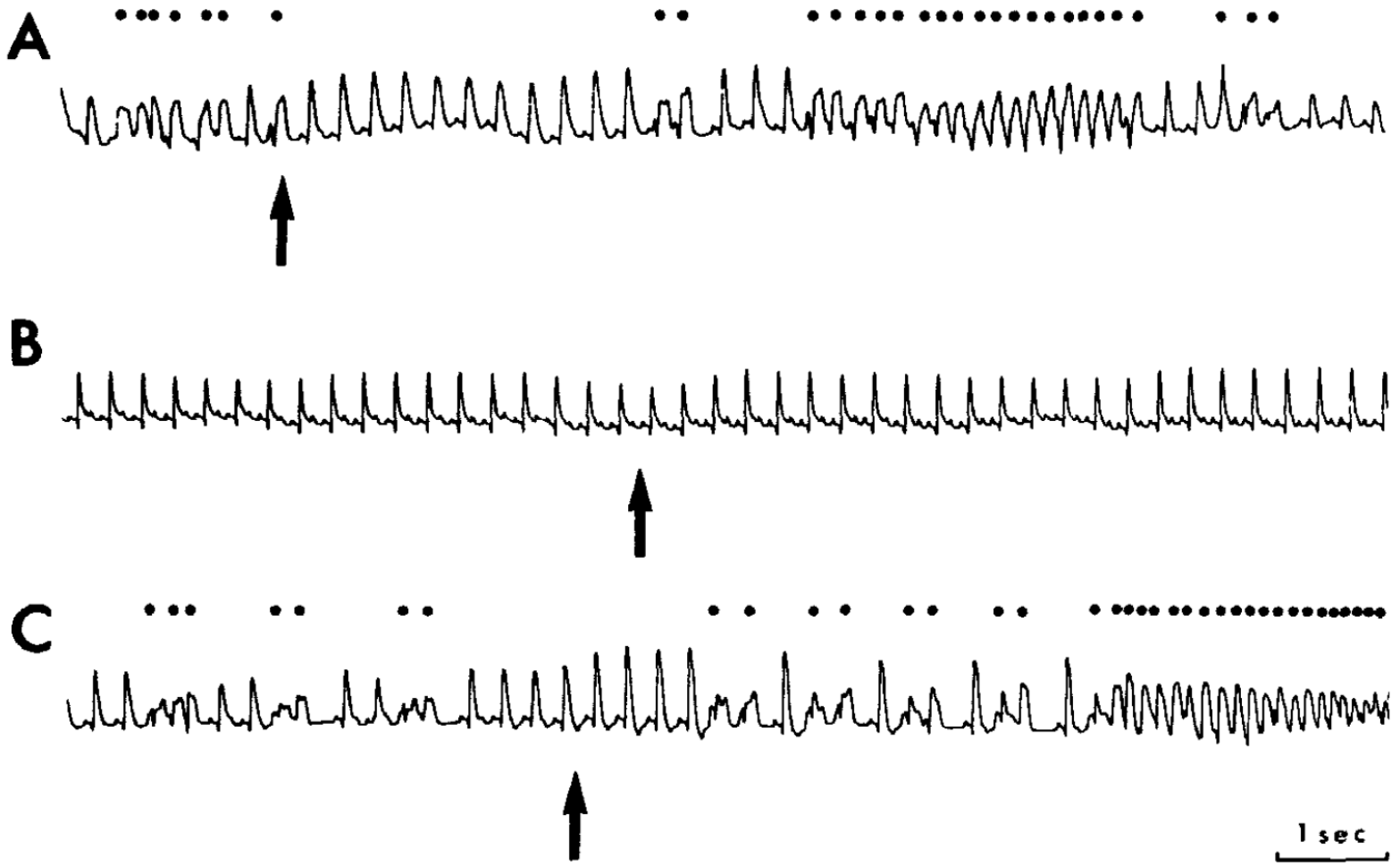
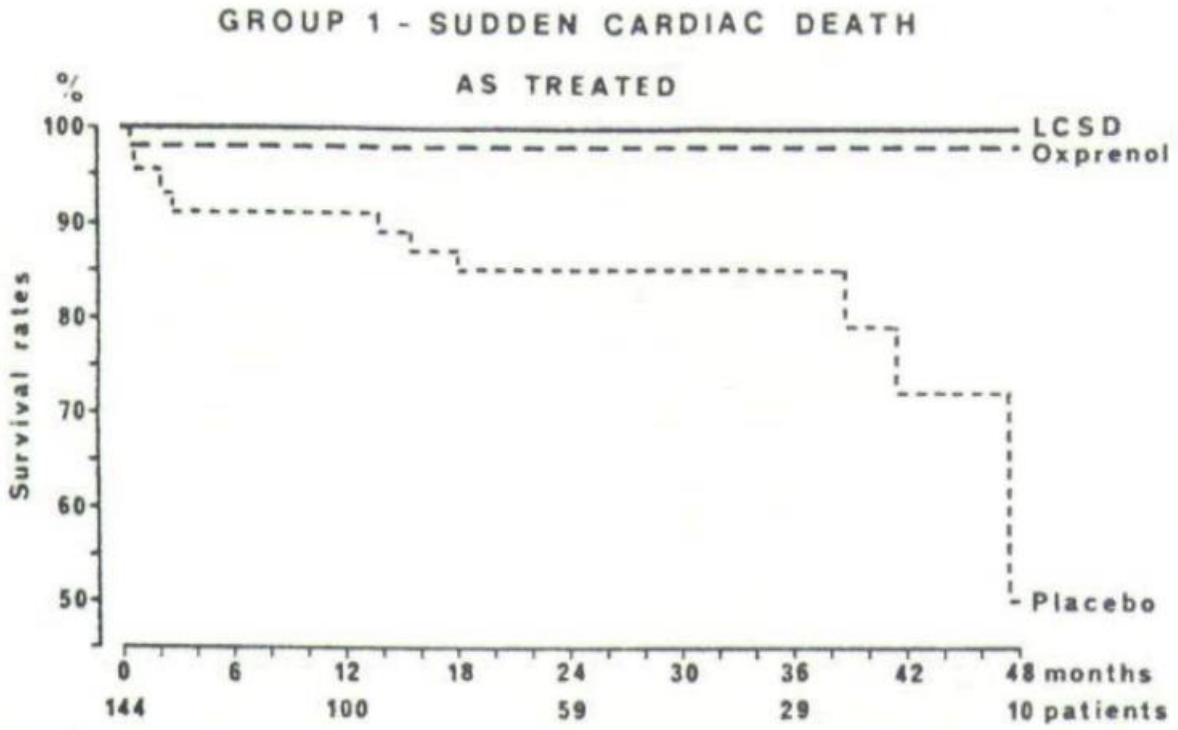


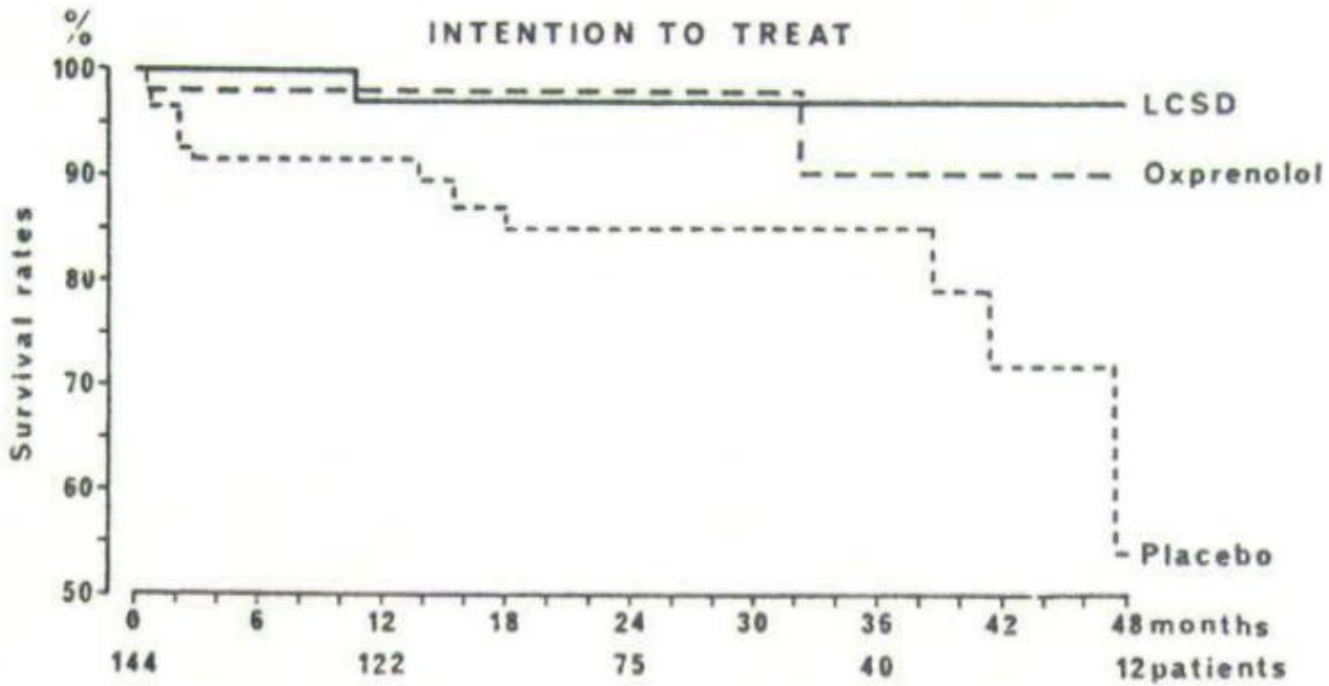
FIGURE 5. See text.

LSG, left stellate ganglion

Schwartz et al, Ann N Y Acad Sci 1984

Prevention of SCD after MI by BB or LCSD

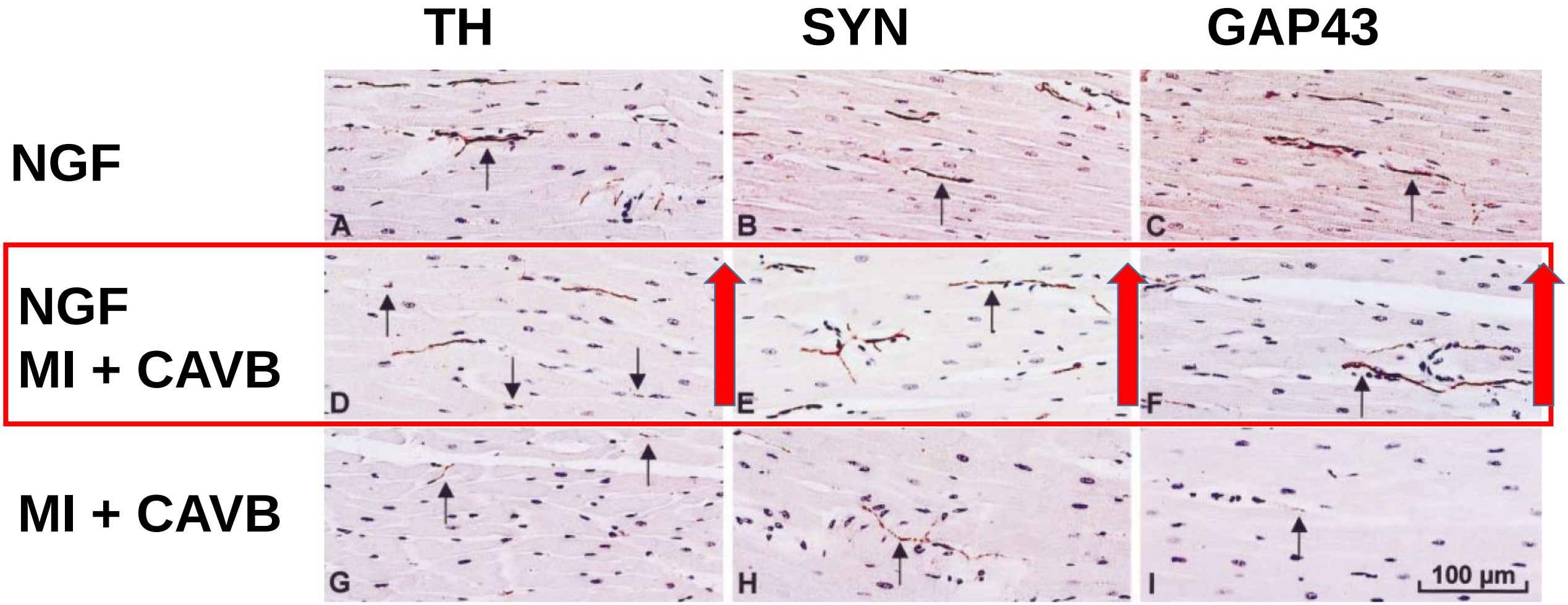




LCSD, left cardiac sympathetic denervation

Schwartz et al, JCE 1992

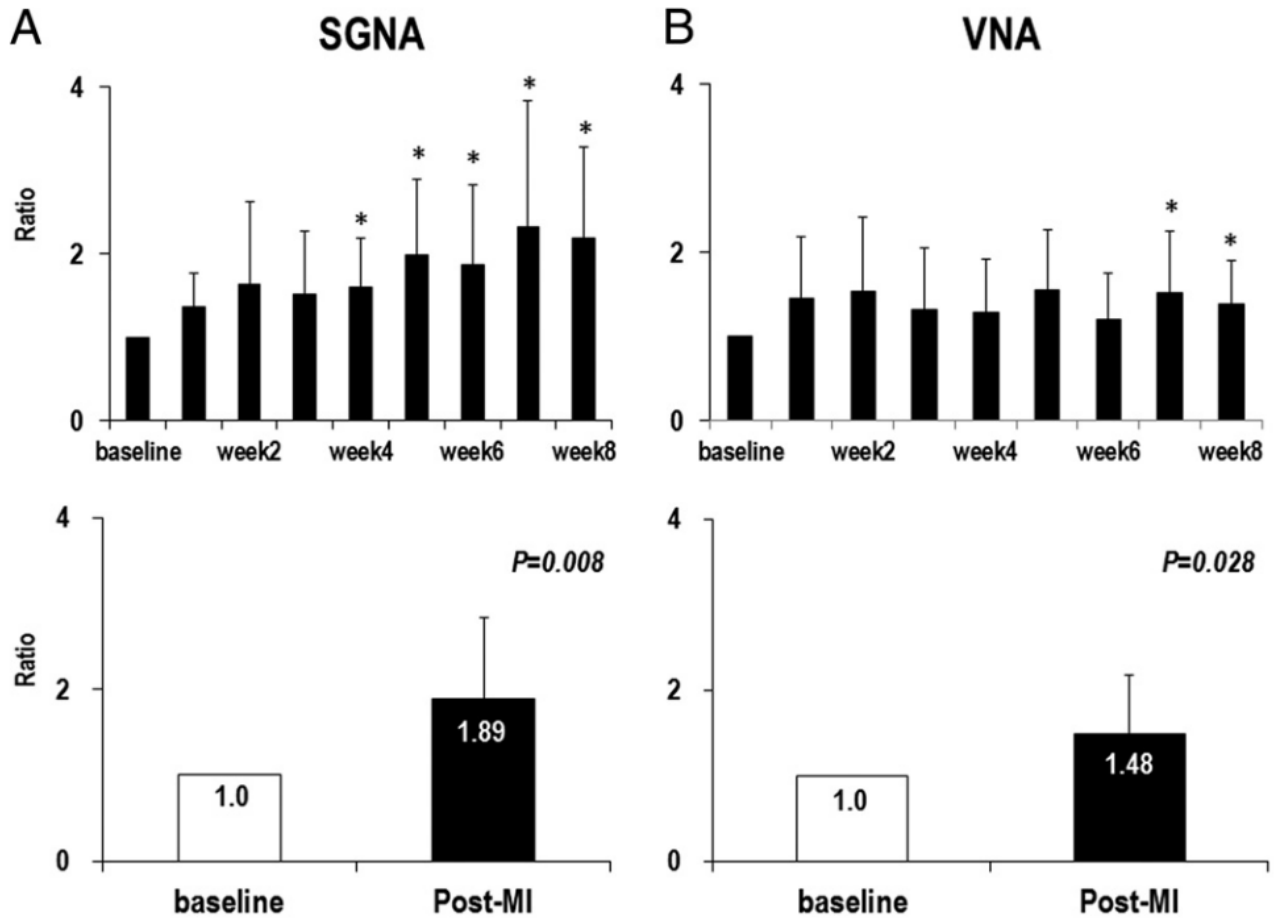
Nerve sprouting and SCD

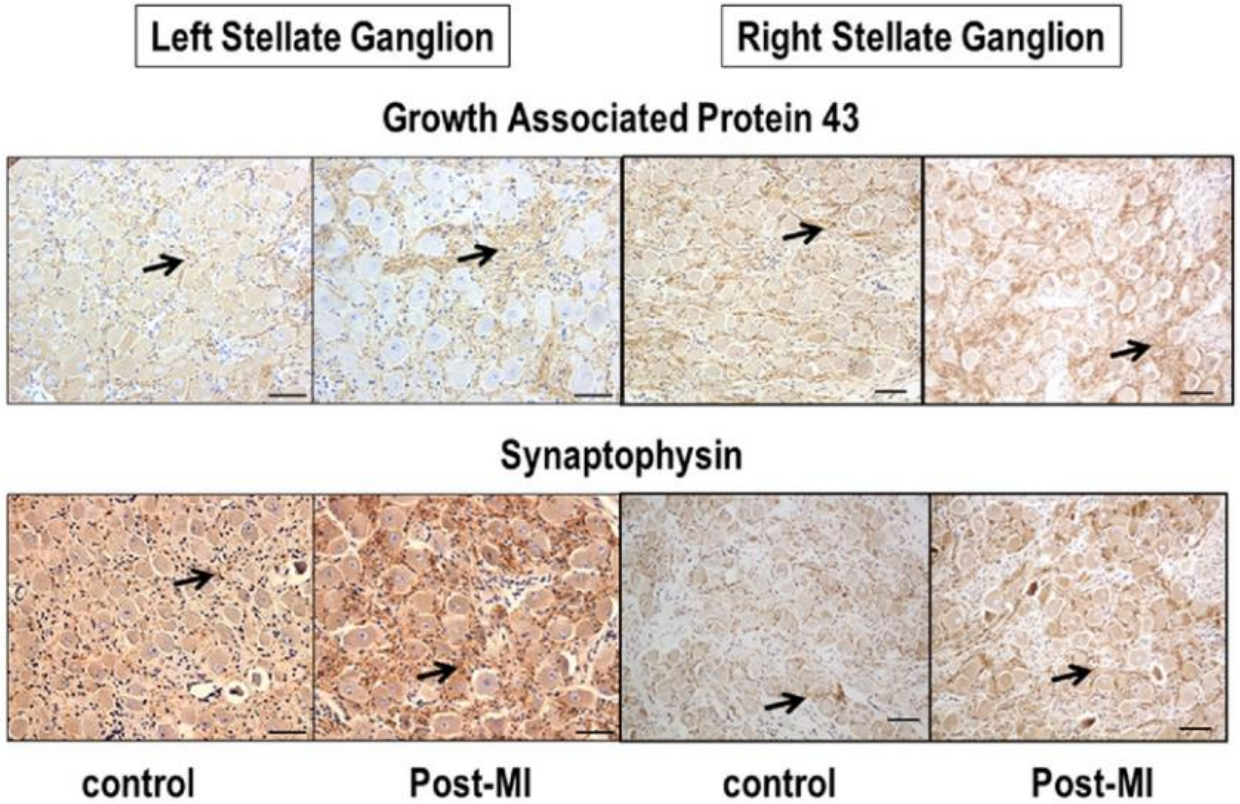


SYN, synaptophysin

Cao et al, Circ Res 2000

Remodeling of the extracardiac autonomic nerve activity and structures after MI

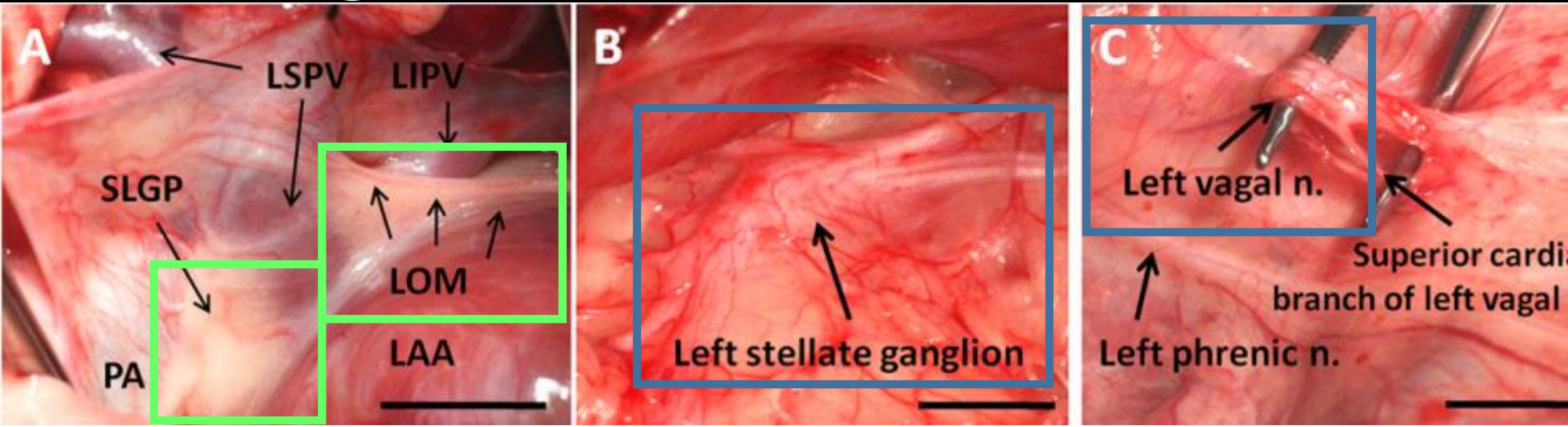




SGNA, stellate ganglion nerve activity
VNA, vagus nerve activity

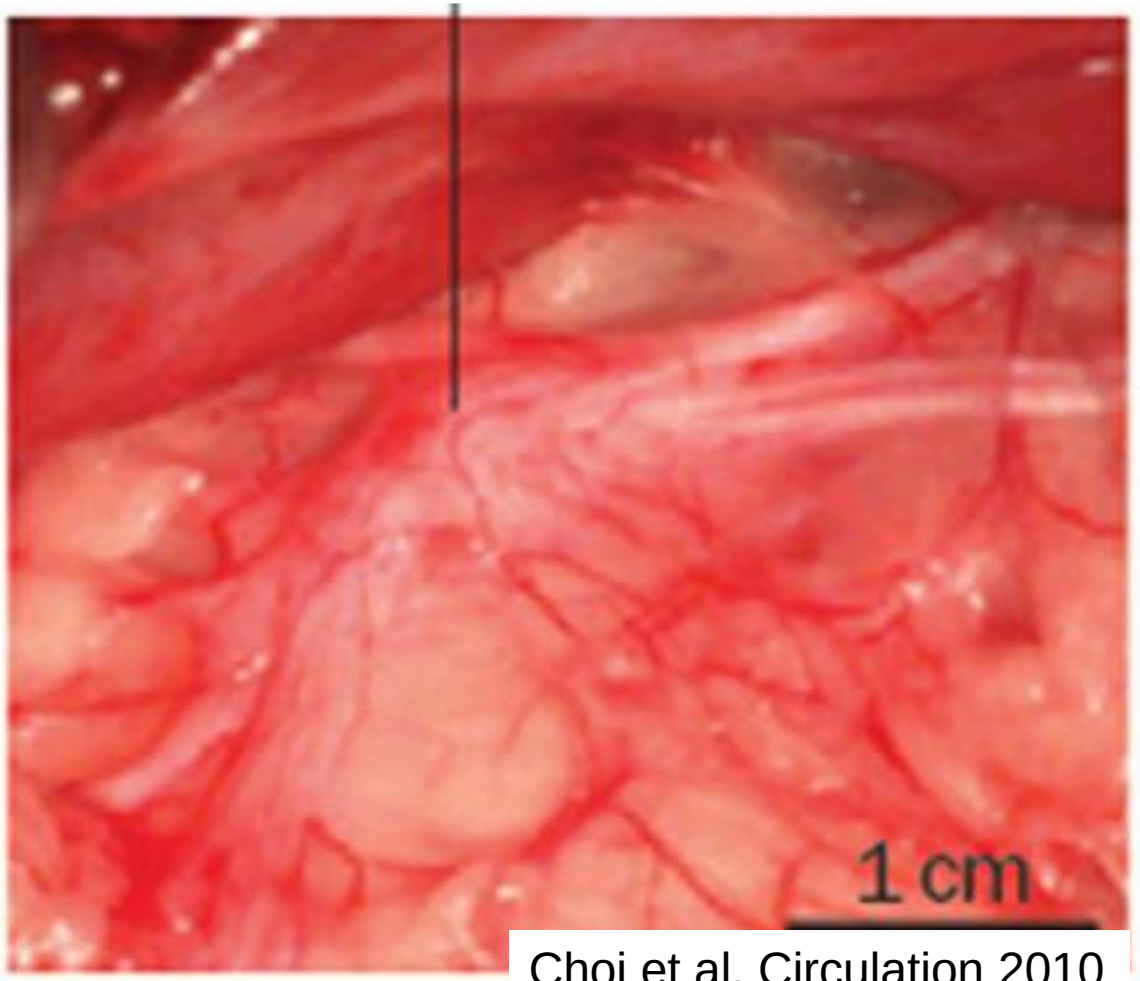
Han S, Chen PS JACC 2012

The important ANS structures affecting the heart



- Extrinsic cardiac nerve
  - stellate ganglion,
  - vagal nerve
- Intrinsic cardiac nerve
  - superior left ganglionated plexi
  - ligament of Marshall nerve

Choi et al, Circulation 2010



Choi et al, Circulation 2010

Cardiac ANS, **Stellate ganglion** does matter!

Current tests for cardiac ANS

Test	Physiological Information	Clinical Usefulness
Heart rate	Net autonomic effect on the sinus node	++
Heart rate variability	Autonomic modulation of sinus node	–
Heart rate recovery	Parasympathetic reactivation after cessation of exercise	–
Baroreflex sensitivity	Sinus node response to baroreceptor activation	–
Heart rate turbulence	Sinus node response to hemodynamic perturbation by a PVC	–
Autonomic reflex testing (Ewing's maneuvers)	Sinus node response to breathing maneuvers, Valsalva, tilt, handgrip	–
Sympathetic nerve recordings	Quantify regional sympathetic output	–
Plasma/urinary catecholamines/ turnover rates	Total body spillover to blood/urine	+++ (pheochromocytoma)
Cardiac sympathetic imaging	Sympathetic nerve distribution and function	–

PVC = premature ventricular complex

JACC 2019;73(10):1189-1206.

DSI recorder for SGNA, VNA, BP recordings

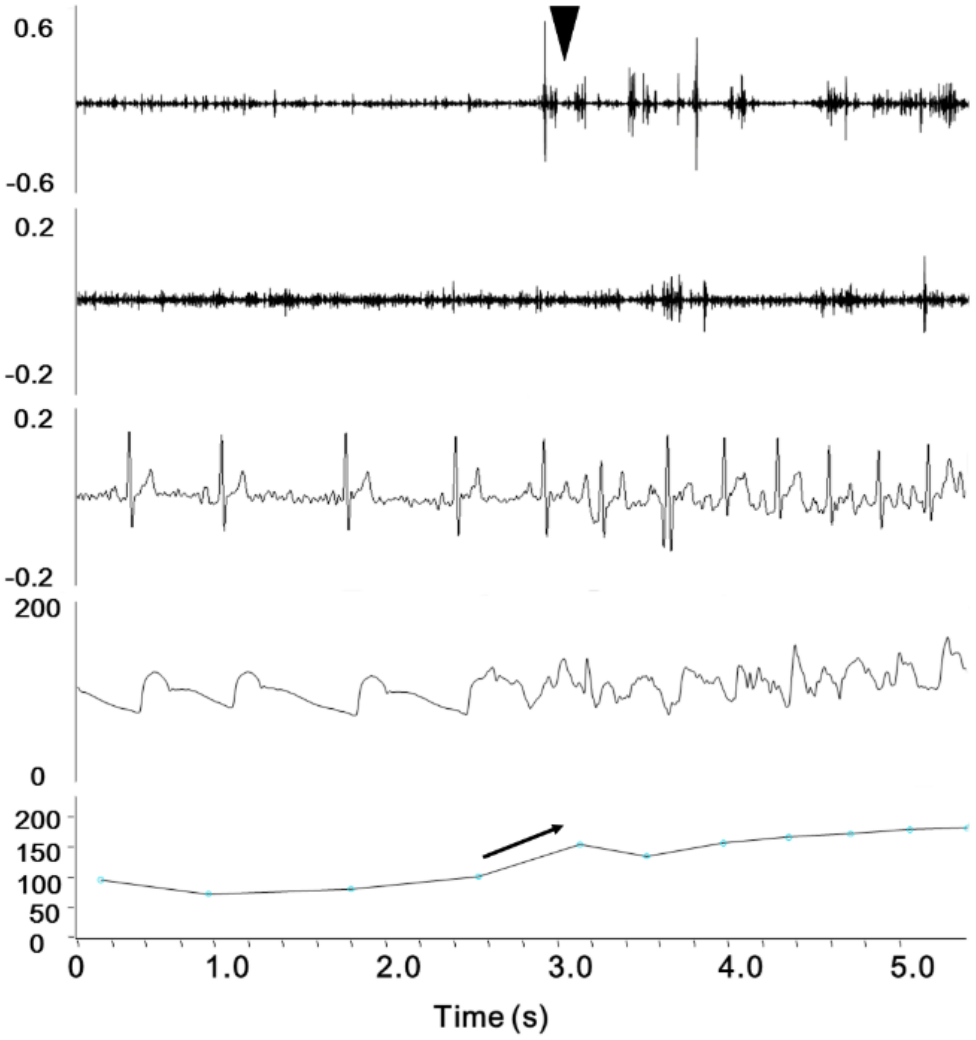
SGNA (mV)

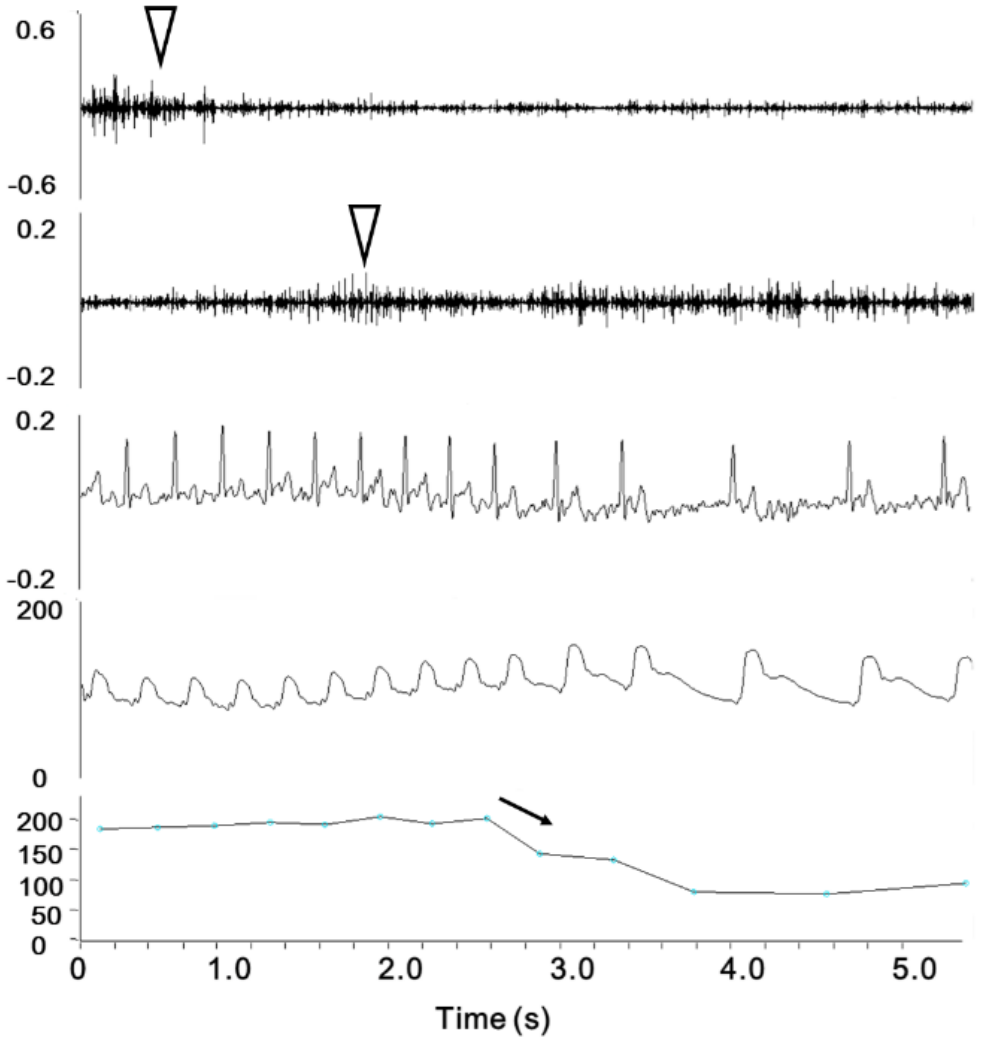
VNA (mV)

ECG (mV)

BP (mmHg)

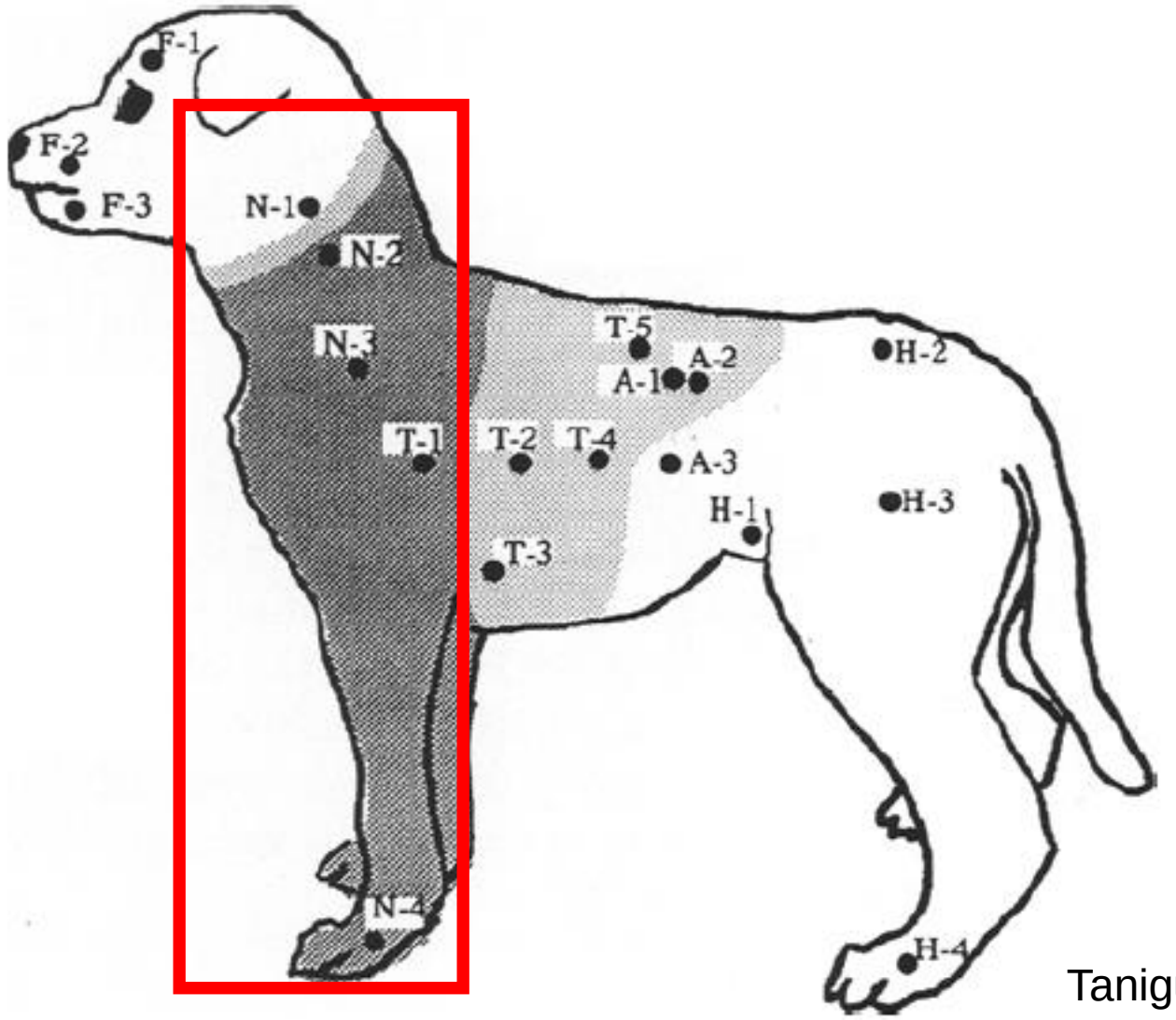
HR (BPM)





Tsai et al, Heart Rhythm 2017

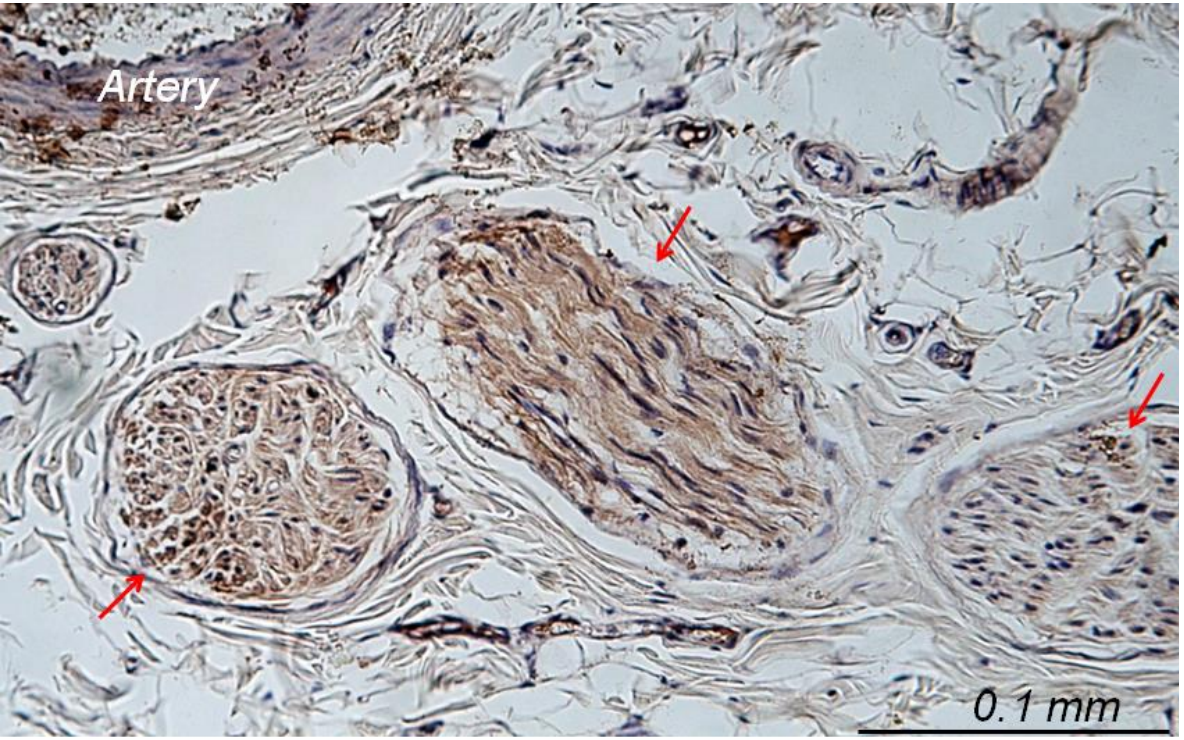
Postganglionic sympathetic fibers from SG

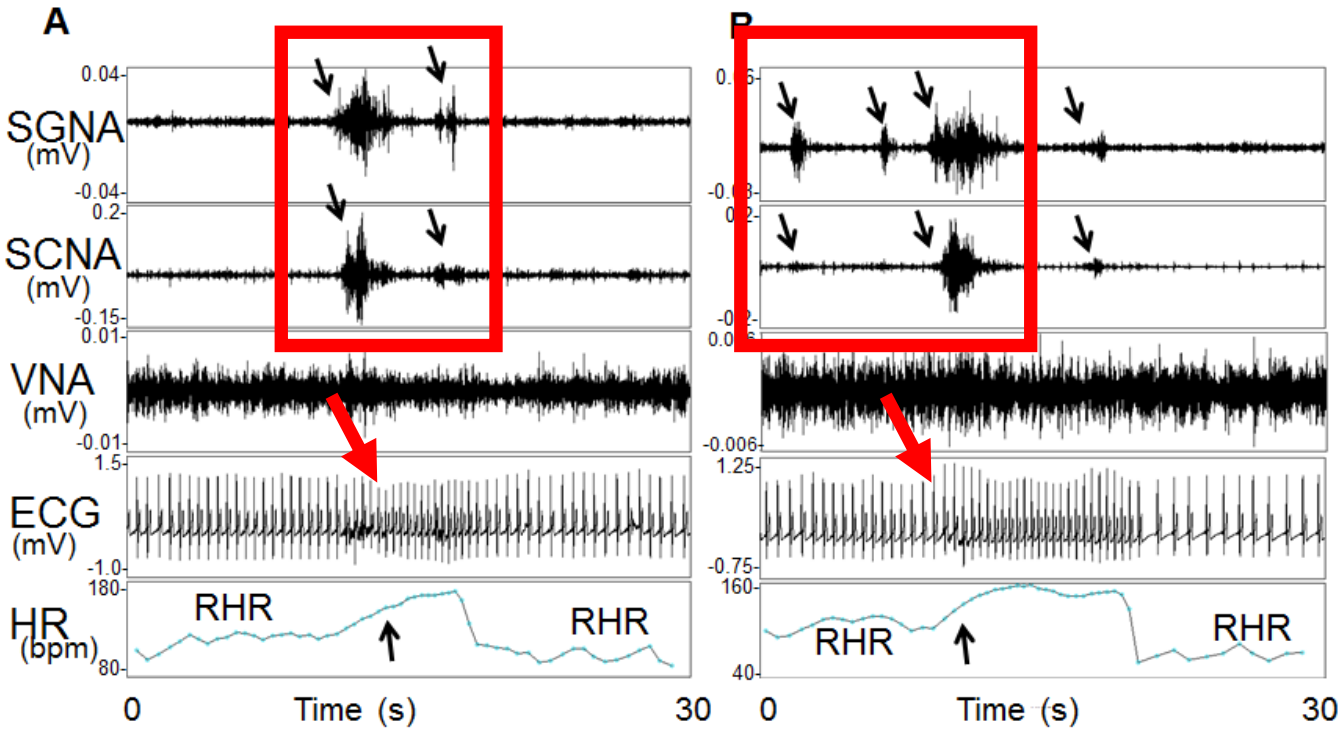


SG, Stellate Ganglion

Taniguchi et al, J. Anesthesia 1994

Subcutaneous Nerve Activity (SCNA)





TH, Tyrosine Hydroxylase ;

Robinson et al, JCE 2014

SCNA is more accurate than the HRV in estimating cardiac sympathetic tone in ambulatory dogs with MI

	Baseline (N = 9)		8 week after MI (N = 9)	
	vs SGNA	vs VNA	vs SGNA	vs VNA
SCNA	0.73 ± 0.17	0.27 ± 0.19	0.82 ± 0.09	0.29 ± 0.14
Time domain				
SDNN	−0.59 ± 0.18	0.02 ± 0.25	−0.56 ± 0.15	0.11 ± 0.22
RMSSD	−0.58 ± 0.21	0.02 ± 0.25	−0.59 ± 0.14	0.06 ± 0.21
pNN_{50}	−0.56 ± 0.25	0.08 ± 0.28	−0.59 ± 0.13	0.01 ± 0.21
Frequency domain				
TP	−0.39 ± 0.19	0.03 ± 0.18	−0.36 ± 0.12	0.13 ± 0.22
VLF	−0.12 ± 0.14	0.02 ± 0.12	−0.09 ± 0.15	0.11 ± 0.16
LF	−0.33 ± 0.17	0.01 ± 0.13	−0.26 ± 0.12	0.13 ± 0.22
HF	−0.43 ± 0.19	0.04 ± 0.21	−0.37 ± 0.17	0.08 ± 0.21
LF_{nu}	0.07 ± 0.26	0.04 ± 0.17	0.17 ± 0.26	0.11 ± 0.11
HF_{nu}	−0.07 ± 0.26	0.04 ± 0.17	−0.17 ± 0.26	−0.11 ± 0.11
LF/HF	0.12 ± 0.20	−0.05 ± 0.14	0.09 ± 0.25	0.08 ± 0.11
Phase-rectified signal average				
Deceleration capacity	−0.63 ± 0.18	0.02 ± 0.25	−0.63 ± 0.15	0.15 ± 0.23
Acceleration capacity	0.61 ± 0.18	−0.03 ± 0.25	0.61 ± 0.13	−0.09 ± 0.24

SCNA , Subcutaneous nerve activity

Chan et al, Heart Rhythm 2015

Using **skin sympathetic nerve activity (SKNA)** to estimate SGNA in dogs

Table 1 Correlations among nerve activities measured at different sites and heart rate

Protocol 1

Dog no.	iRSGNA vs iSKNA-I	iRSGNA vs iSKNA-II	iRSGNA vs iSKNA-R	iRSGNA vs iSKNA-L	HR vs iRSGNA	HR vs iSKNA-I	HR vs iSKNA-II	HR vs iSKNA-R	HR vs iSKNA-L
A	r = 0.948	0.933	NA	NA	0.834	0.886	0.859	NA	NA
	P < .001	< .001			.005	.001	.003		
B	r = 0.749	0.729	0.864	0.715	0.875	0.823	0.907	0.725	0.586
	P = .020	.026	.003	.031	.002	.006	.001	.027	.097
C	r = 0.985	0.881	0.951	0.885	0.867	0.783	0.933	0.600	0.583
	P < .001	.002	< .001	.002	.002	.013	< .001	.088	.099
D	r = 0.950	0.773	0.748	0.564	0.926	0.929	0.715	0.551	0.539
	P < .001	.014	.020	.114	< .001	< .001	.030	.125	.135
E	r = 0.751	0.603	0.802	0.772	0.881	0.766	0.548	0.453	0.507
	P = .020	.086	.009	.015	.002	.016	.126	.221	.163
Mean	0.877	0.784	0.841	0.734	0.877	0.837	0.792	0.582	0.554
95% Confidence interval	(0.732, 1.000)	(0.622, 0.945)	(0.703, 0.980)	(0.521, 0.947)	(0.836, 0.918)	(0.752, 0.923)	(0.593, 0.992)	(0.402, 0.762)	(0.494, 0.614)

Protocol 2

Dog no.	iLSGNA vs iSKNA-I	iLSGNA vs iSKNA-II	iLSGNA vs iSKNA-R	iLSGNA vs iSKNA-L	HR vs iLSGNA	HR vs iSKNA-I	HR vs iSKNA-II	HR vs iSKNA-R	HR vs iSKNA-L
F	r = 0.820	0.607	0.728	0.788	0.647	0.801	0.537	0.809	0.769
	P < .001	.002	< .001	< .001	.001	< .001	.008	< .001	< .001
G	r = 0.803	0.604	0.510	0.463	0.591	0.499	0.482	0.510	0.463
	P < .001	.013	.018	.035	.016	.049	.059	.018	.035
H	r = 0.540	0.546	0.339	0.506	0.421	0.759	0.789	0.644	0.352
	P = .025	.023	.123	.016	.093	< .001	< .001	.001	.108
I	r = 0.819	0.772	0.760	0.912	0.574	0.763	0.776	0.749	0.627
	P < .001	< .001	< .001	< .001	.001	< .001	< .001	< .001	< .001
Mean	0.746	0.632	0.584	0.667	0.558	0.706	0.646	0.678	0.553
95% Confidence interval	(0.527, 0.964)	(0.477, 0.787)	(0.270, 0.899)	(0.321, 1.000)	(0.404, 0.712)	(0.484, 0.927)	(0.393, 0.899)	(0.469, 0.887)	(0.261, 0.844)

HR = heart rate; NA = not available; SGNA = stellate ganglion nerve activity; SKNA = skin nerve activity.

Jiang et al, Heart Rhythm 2015

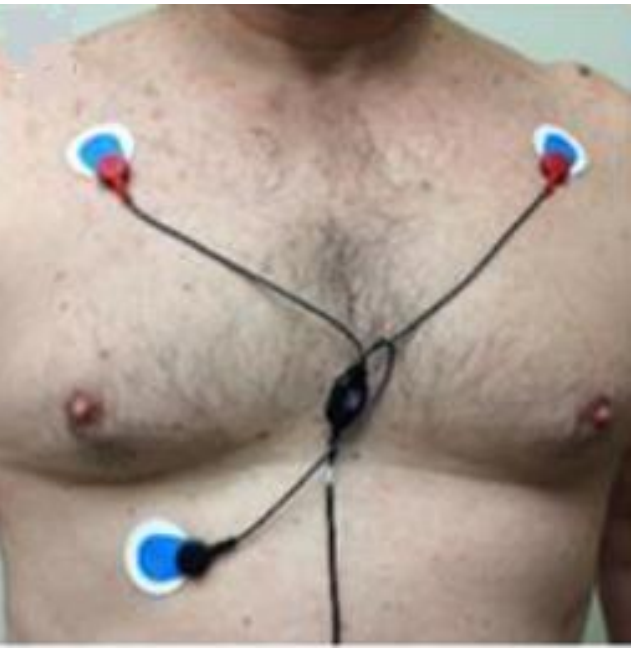
ANS study in Taiwan

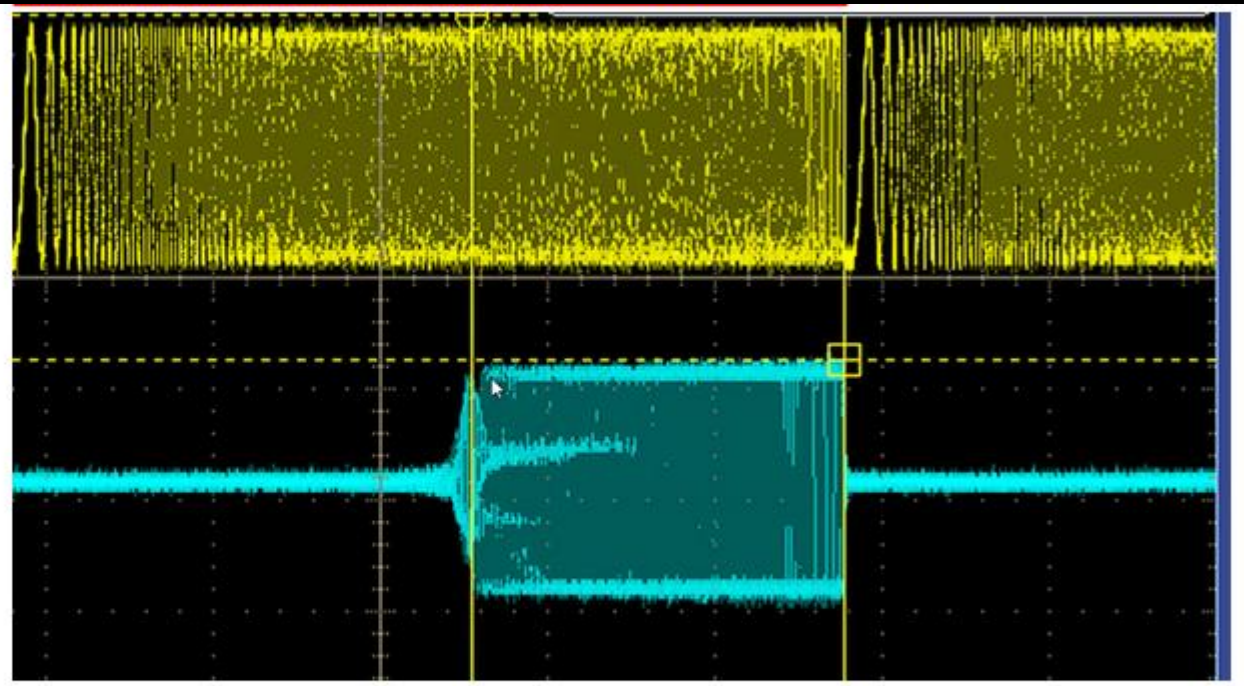
Stellate Ganglion Nerve Activity Recording

➔ **Subcutaneous Sympathetic Nerve Activity Recording**

➔ **Skin Sympathetic Nerve Activity (SKNA) Recording**

Filtering the electrical signal on the skin





ECG, 0.5-150 Hz

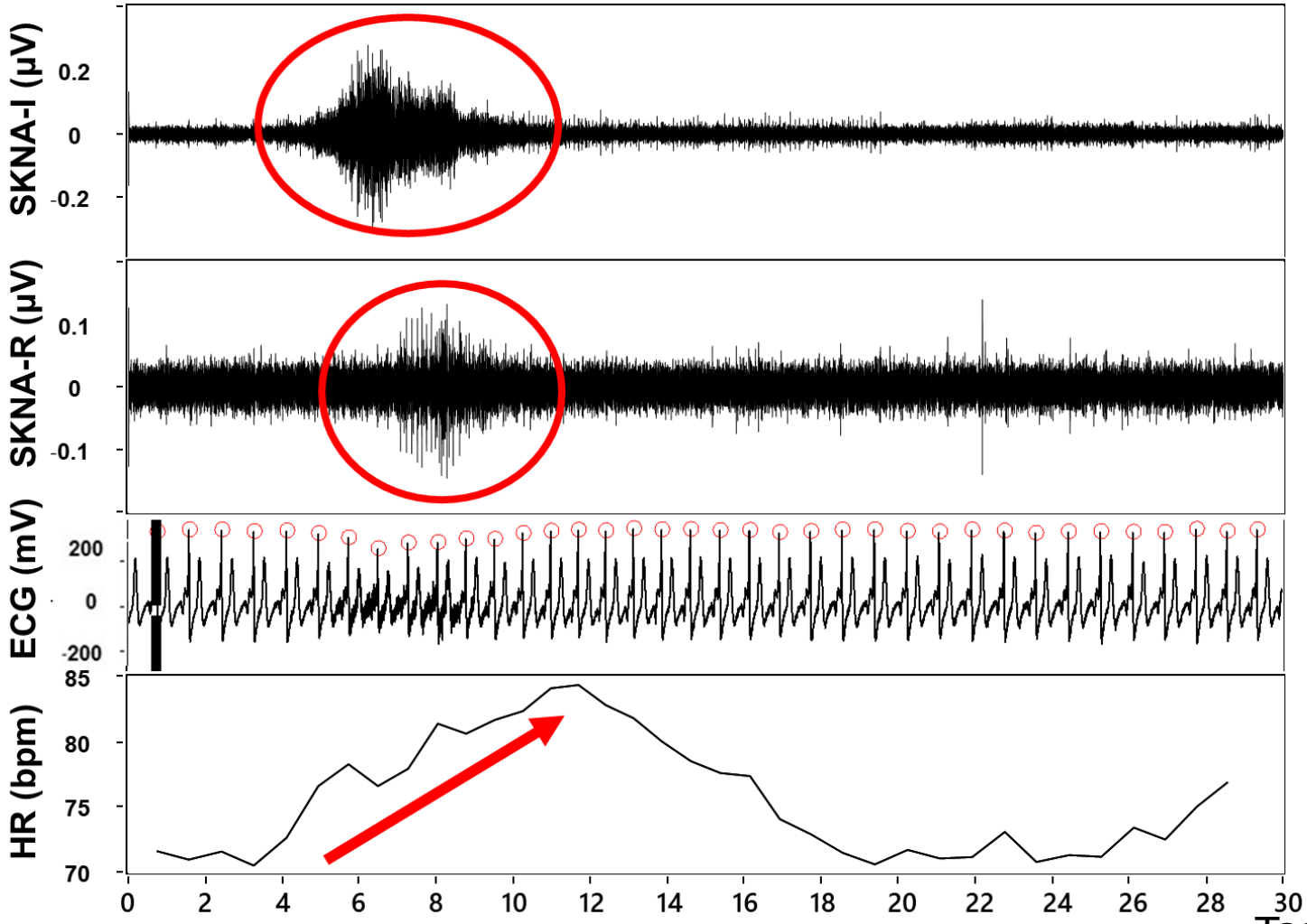
Muscle, up to 400 Hz

nerve, 0-1000 Hz

Microneurography typically high pass at 700 Hz

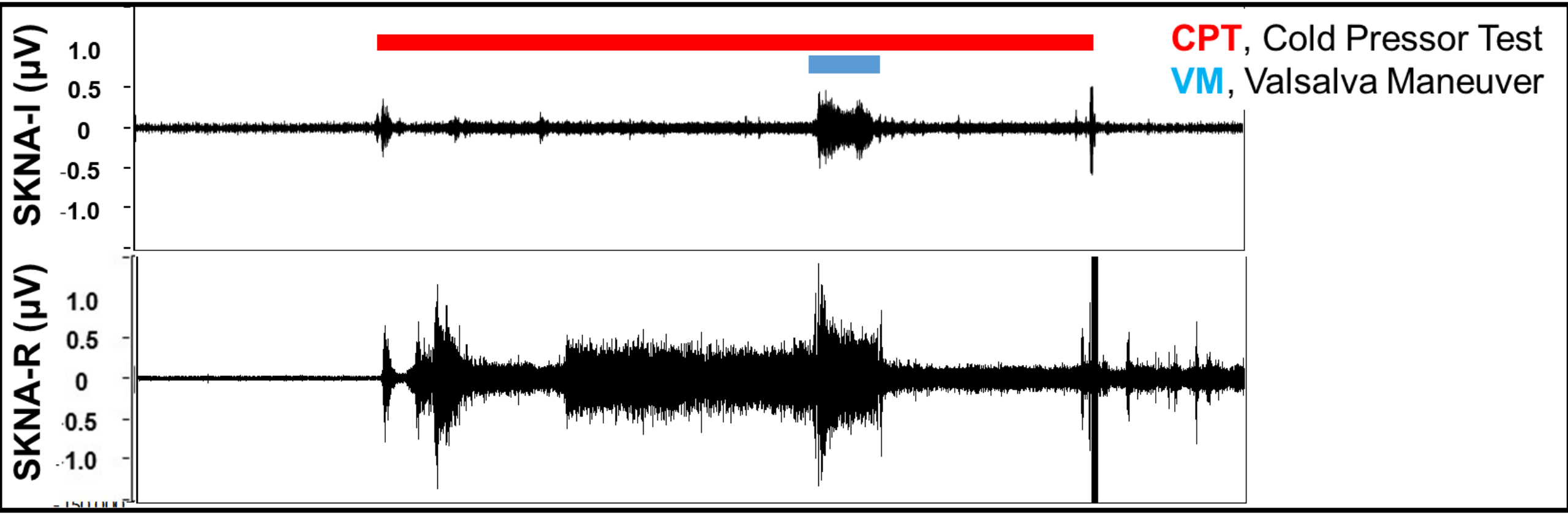
Everett et al. Trends Cardiovasc Med, 2017
Kusayama et al, Nature Protocols, 2020

Sympathetic activity correlated with heart rate increasing



Tsai et al. Unpublished data

SKNA recording from myself!



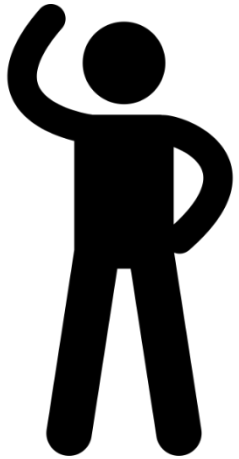
Tsai et al. Unpublished data

Using

Skin Sympathetic Nerve Activity

to estimate Sympathetic Tone in AMI patients

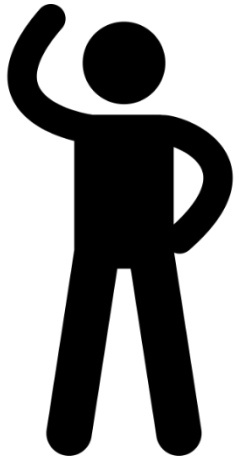
128 AMI	154 controls



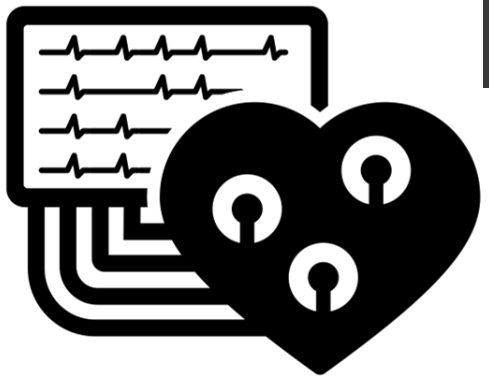
Tsai et al. submitted

128 AMI

154 controls



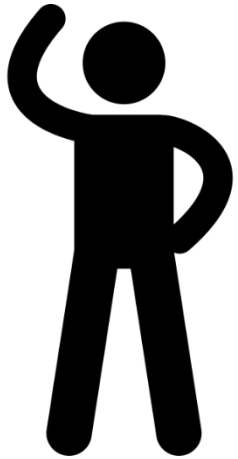
neuECG



Tsai et al. submitted

128 AMI

154 controls



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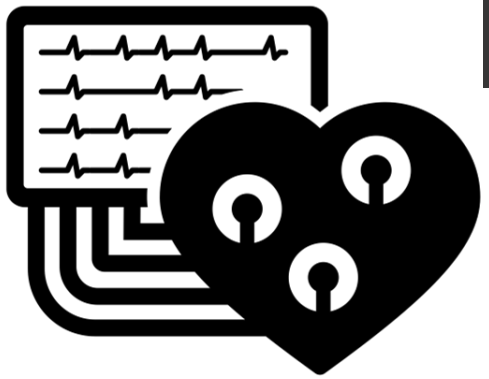


ECG - HRV

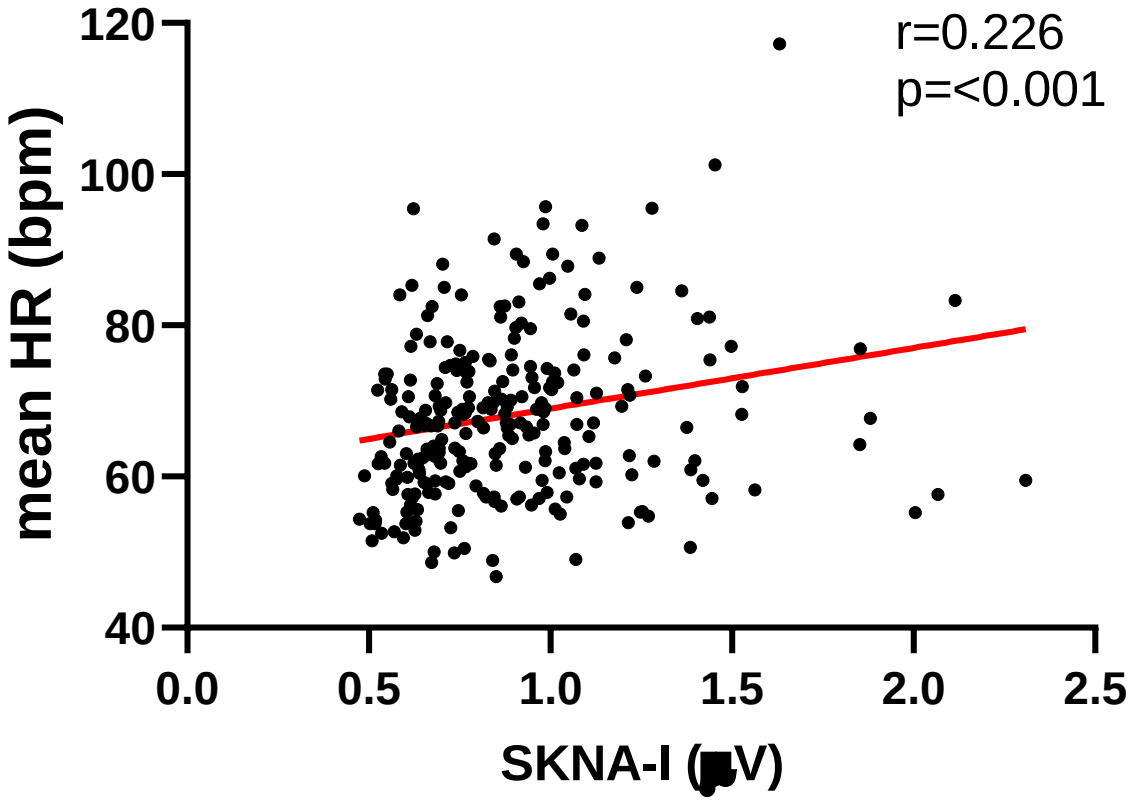
SKNA

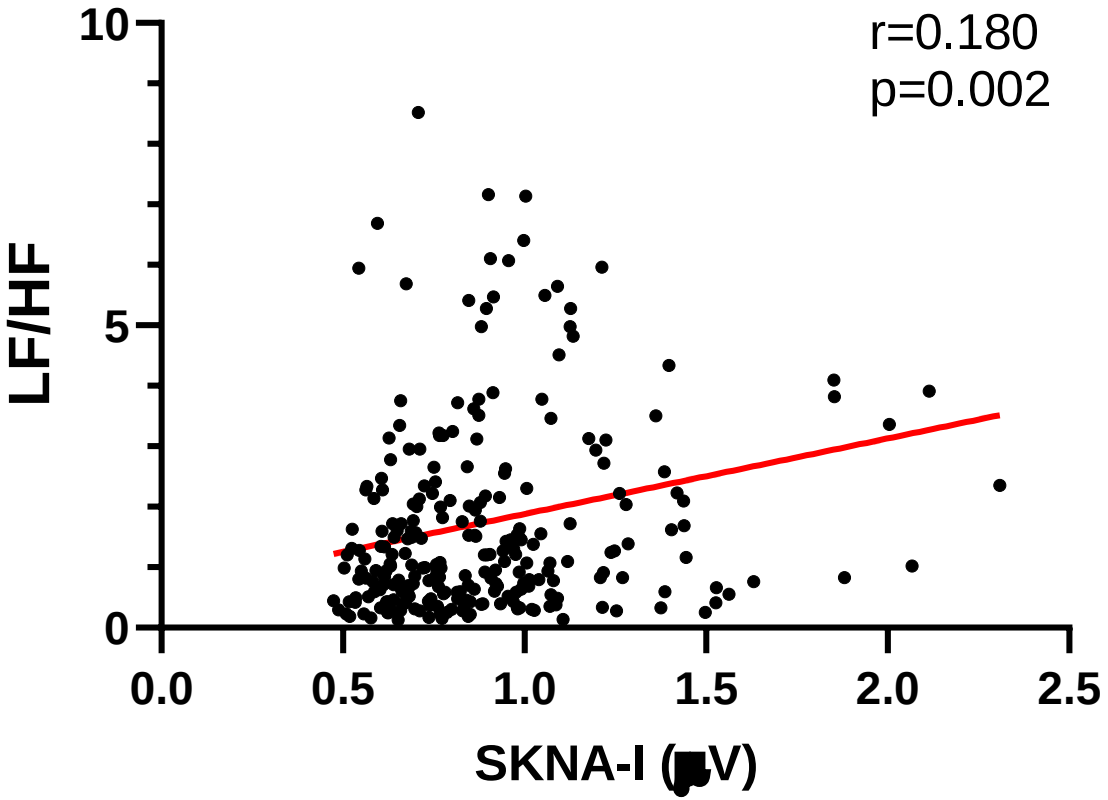
Data processing

eSKNA

Tsai et al. submitted

SKNA is correlated with HR and HRV





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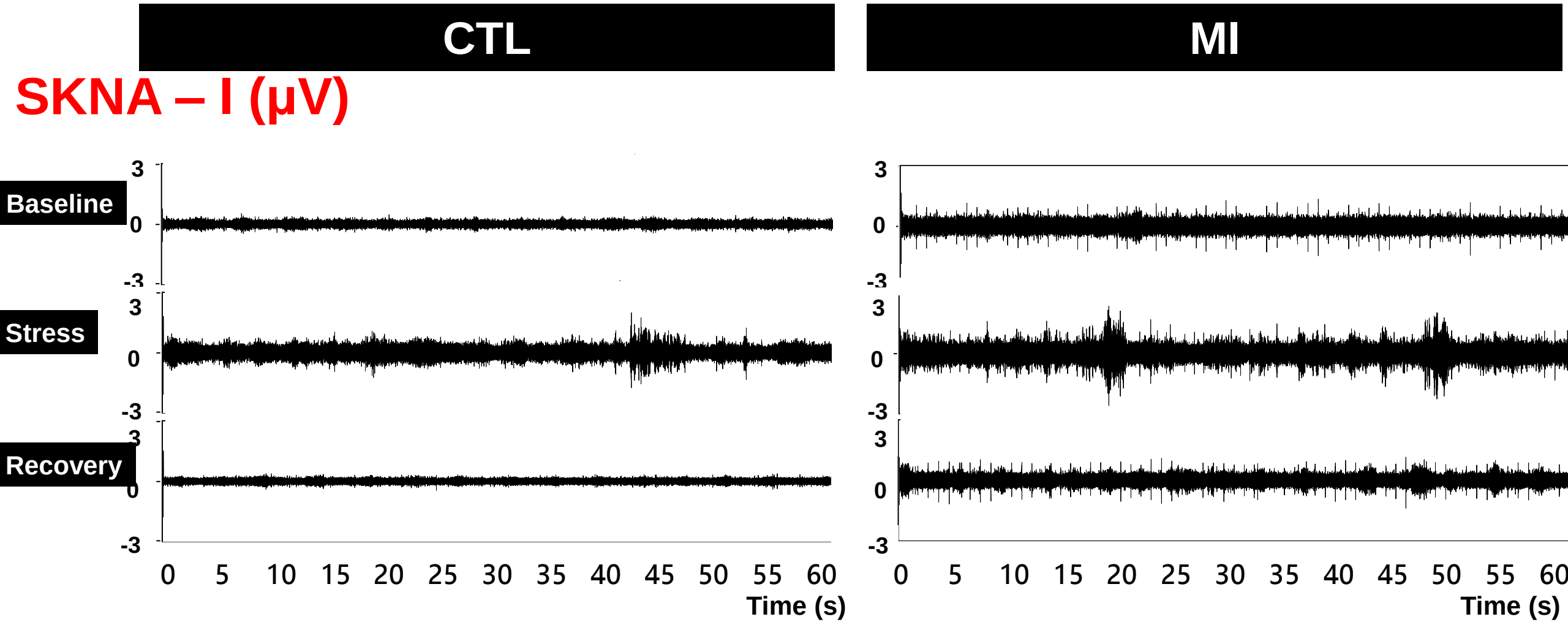
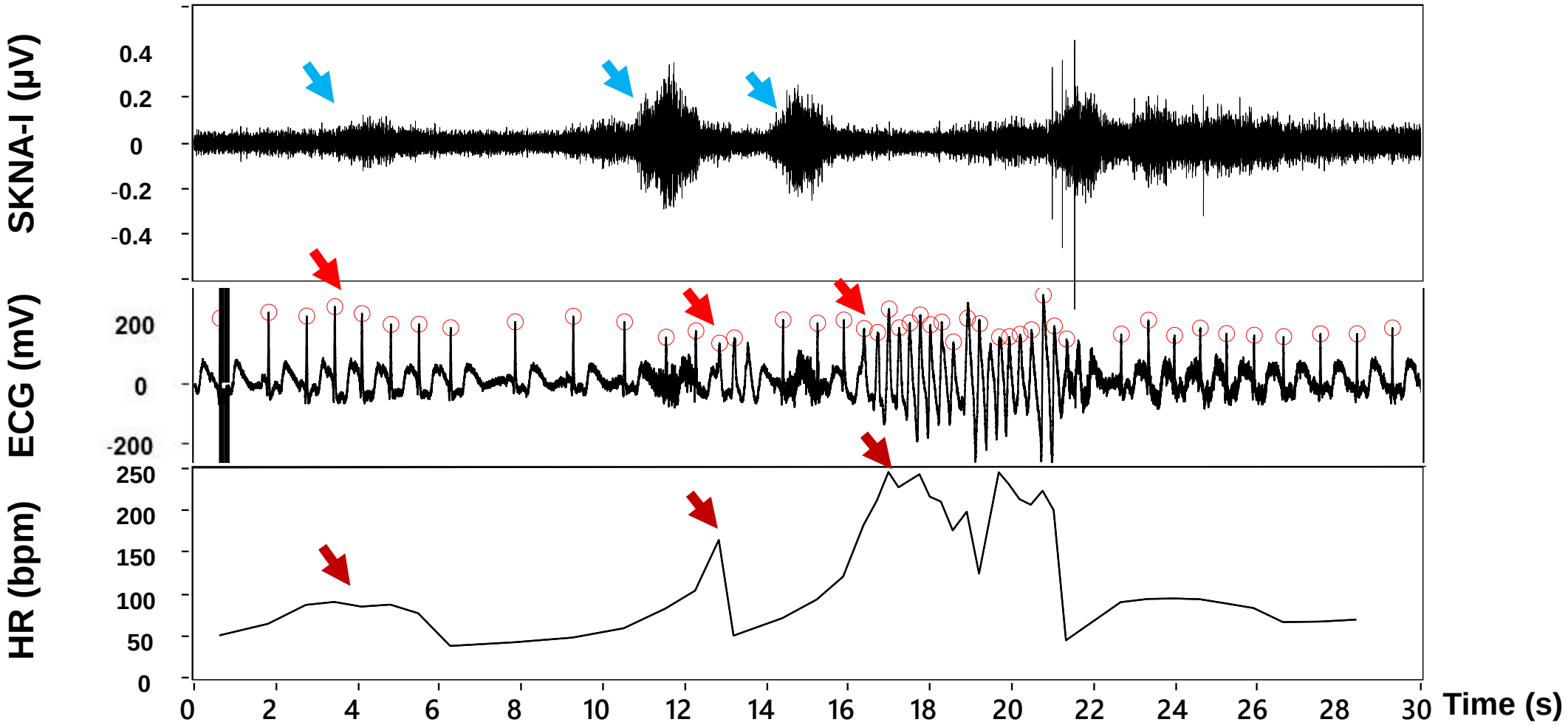
SKNA is higher in MI than CTL



Tsai et al. submitted

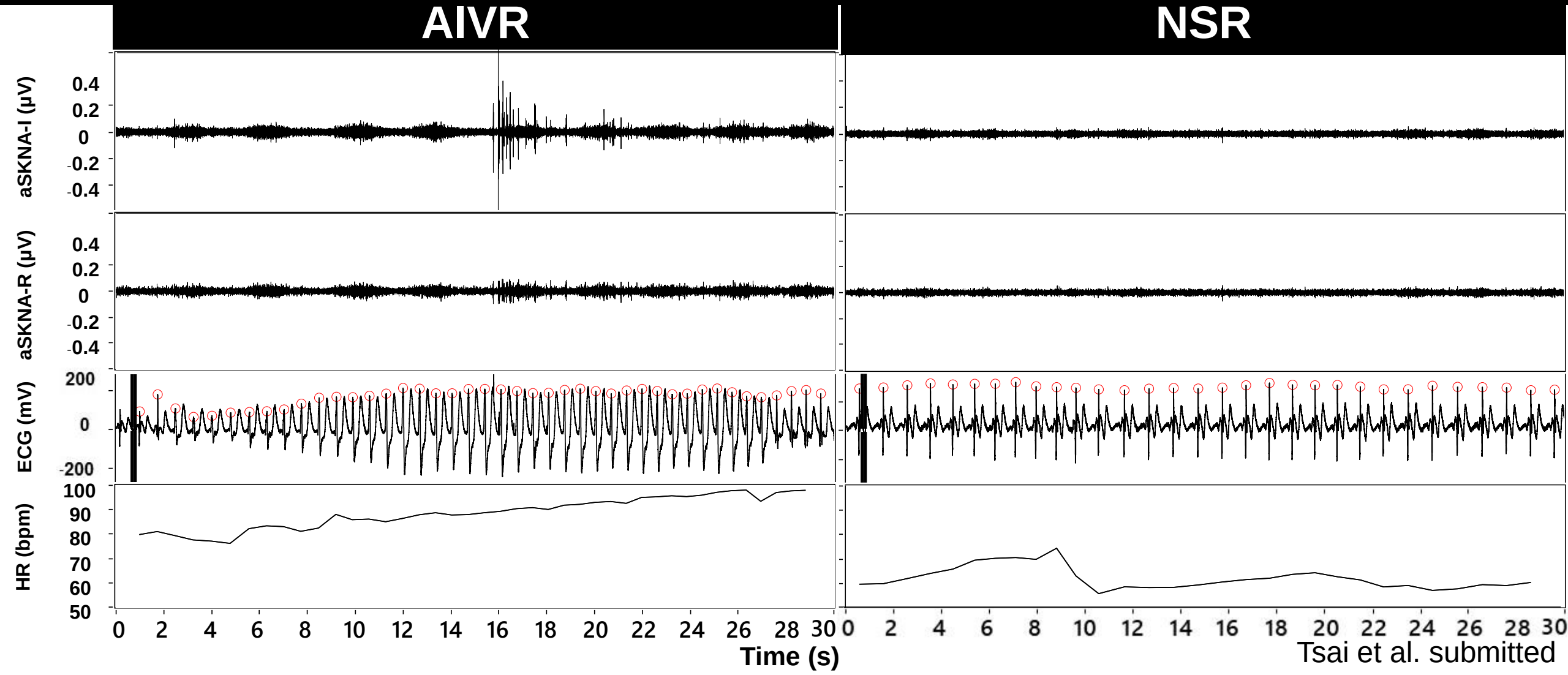
SKNA right before VT in a STEMI patient



SKNA, skin sympathetic nerve activity

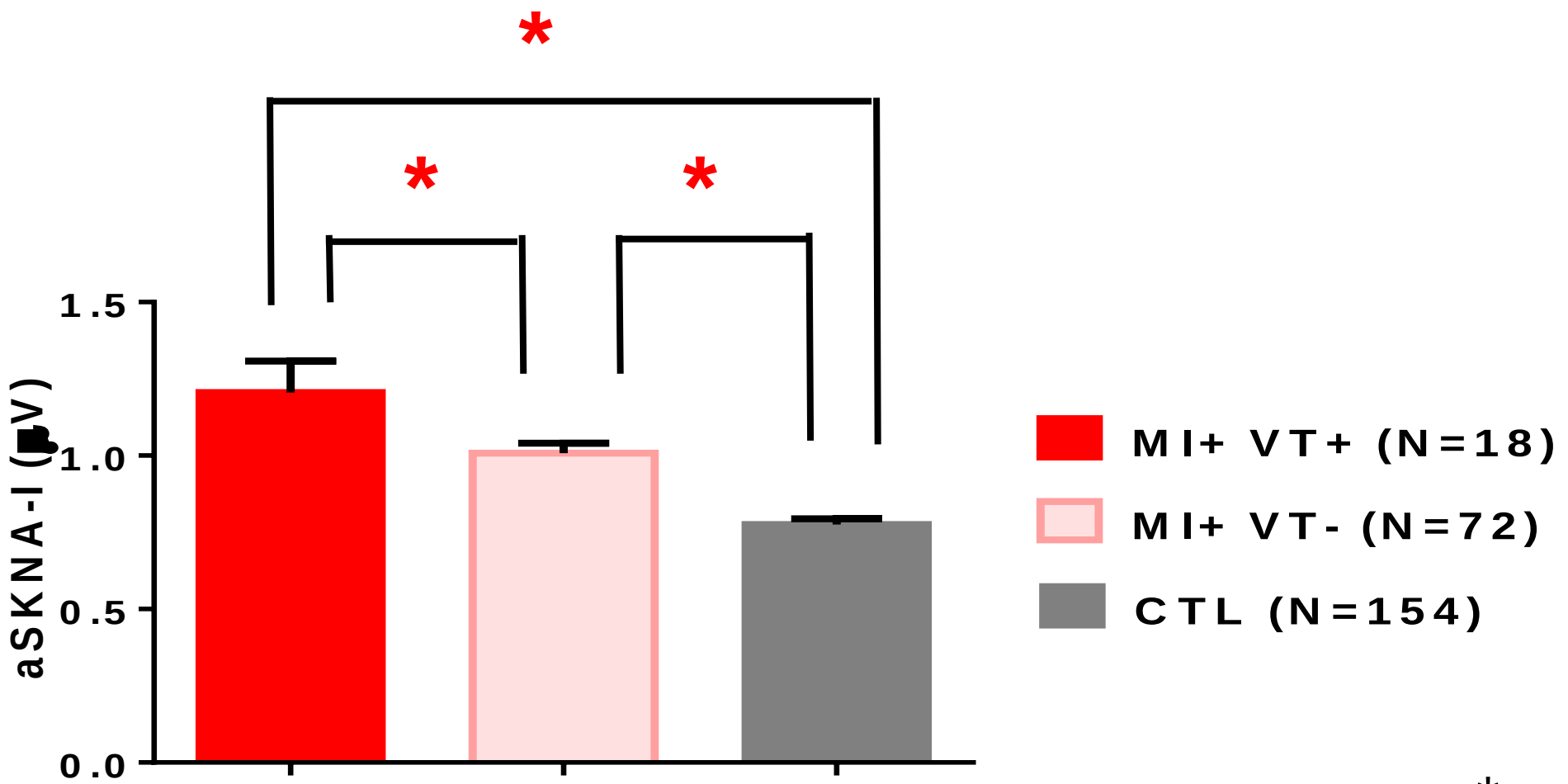
Tsai et al. submitted

AIVR is associated with high SKNA



Tsai et al. submitted

SKNA is higher in MI+VT+ than MI+VT- and MI-



* p<.05

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The adjusted risks for MI according to SKNA

SKNA-I	Unadjusted OR(95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 HR(95% CI)
Myocardial infarction				
Continuous (per 0.1 μV increasing)	1.50(1.32-1.70)	1.52(1.32-1.75)	1.5 (1.27-1.78)	1.53 (1.26-1.87)
Quartile 1	1(Reference)	1(Reference)	1(Reference)	1(Reference)
Quartile 2	4.48 (1.86-10.80)	5.04 (1.94-13.04)	4.12 (1.33-12.72)	5.37 (1.66-17.41)
Quartile 3	11.22 (4.68-26.93)	12.20 (4.65-32.01)	8.59 (2.76-26.76)	7.54 (2.29-24.84)
Quartile 4	22.39 (9.01-55.66)	24.44 (8.63-69.19)	24.46 (7.10-84.25)	32.39 (8.12-129.23)
P-trend	<0.001	<0.001	<0.001	<0.001

SKNA-I quartiles cut at 0.680, 0.842 and 1.014 μV
Multivariate model 1 is adjusted for age and sex
Multivariate model 2 comprises model 1 as well as smoke, diabetes mellitus, hypertension, dyslipidemia
Multivariate model 3 comprises model 2 as well as body mass index, estimated glomerular filtration rate, alcohol drinking, areca nut using,

Tsai et al. submitted

SKNA is associated with the risk of VA in MI

	Model 1[a]		Model 2[b]		Model 3[c]	
	aOR[a]	(95% CI)	aOR[b]	(95% CI)	aOR[c]	(95% CI)
SKNA-I, 0.1μV	1.23	(1.05-1.44)	1.23	(1.04-1.45)	1.23	(1.03-1.47)
Cigarette smoking, yes vs. no			1.05	(0.39-2.80)	1.09	(0.40-3.01)
Alcohol drinking, yes vs. no			0.70	(0.24-2.02)	0.63	(0.20-1.96)
Betel-quid chewing, yes vs. no			1.0	-	1.0	-
BMI, kg/m^2			1.03	(0.91-1.18)	1.05	(0.91-1.20)
Hypertension, yes vs. no					0.53	(0.15-1.93)
Diabetes, yes vs. no					0.74	(0.21-2.60)
Dyslipidemia, yes vs. no					0.73	(0.19-2.85)

aOR, adjusted odds ratio; BMI, Body mass index; SKNA-I, skin sympathetic nerve activity.

[a] aOR was obtained from logistic regression models adjusted for age, gender

[b] aOR was obtained from Model 1 and additionally adjusted for cigarette smoking, alcohol drinking, betel-quid chewing and body mass index.

[c] aOR was obtained from Model 2 and additionally adjusted for hypertension, diabetes mellitus and dyslipidemia.

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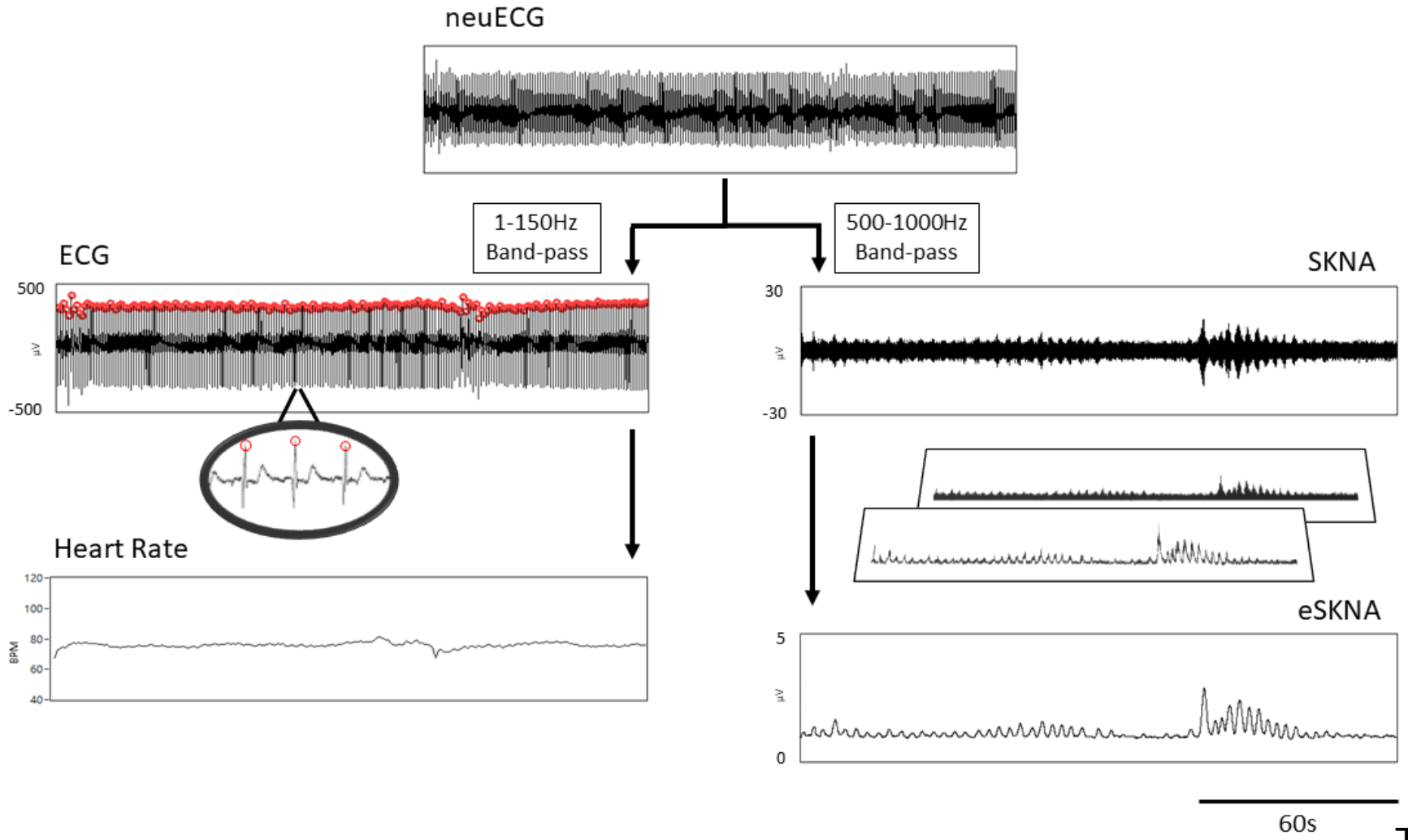
Signal processing



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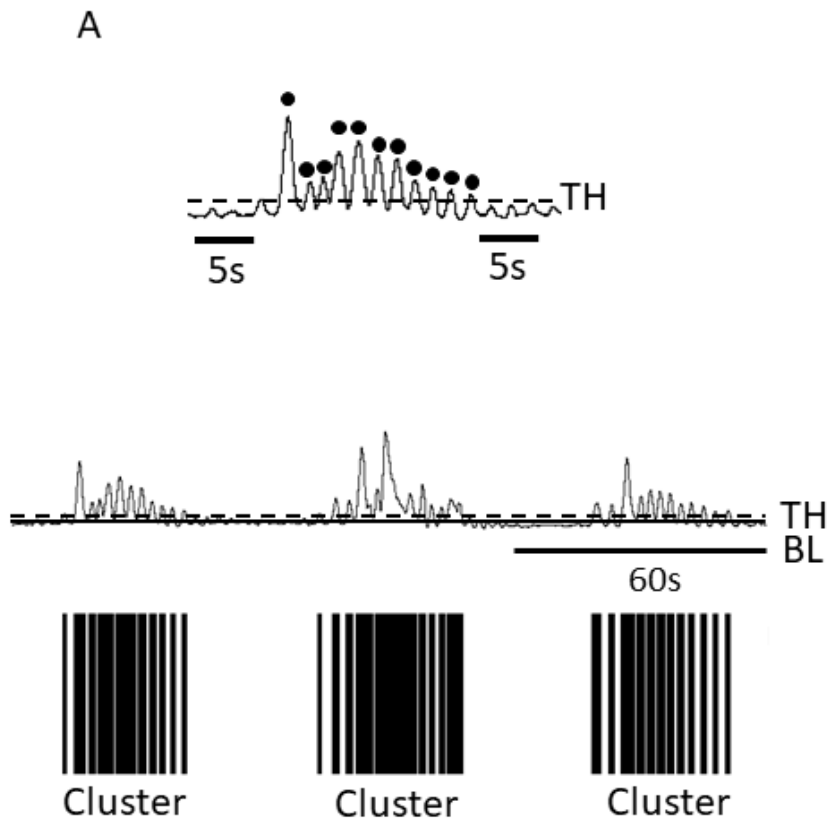
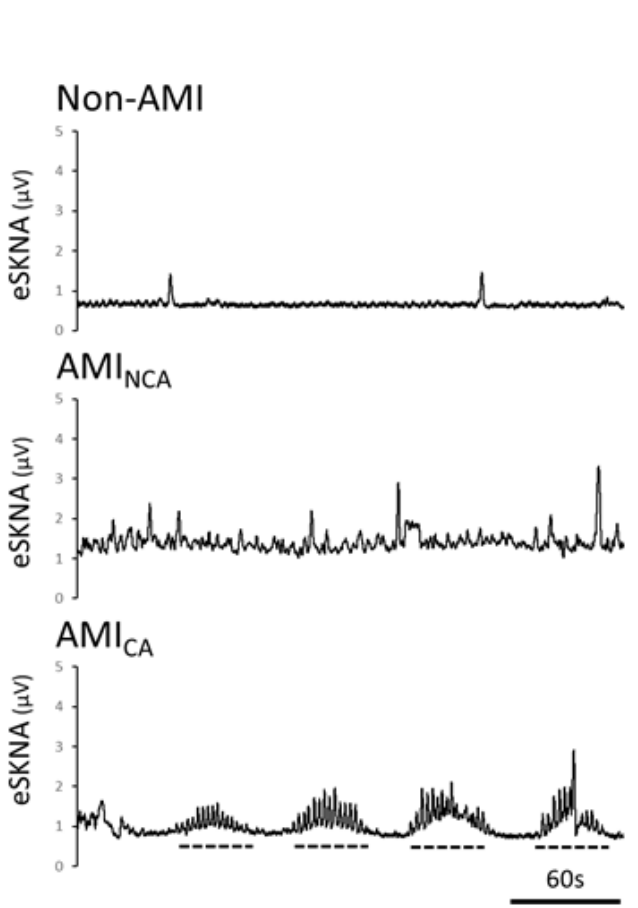
SKNA cluster in AMI

Black dots are the defined bursts which are the peaks above the threshold.

Threshold = (Baseline-Min) × 5 + Min

Baseline is defined as the average of the lower 20 percentile samples in the selected window. Min is the minimum value in the selected window.





TH, Threshold; BL, Baseline, NCA, non-cluster; CA, cluster

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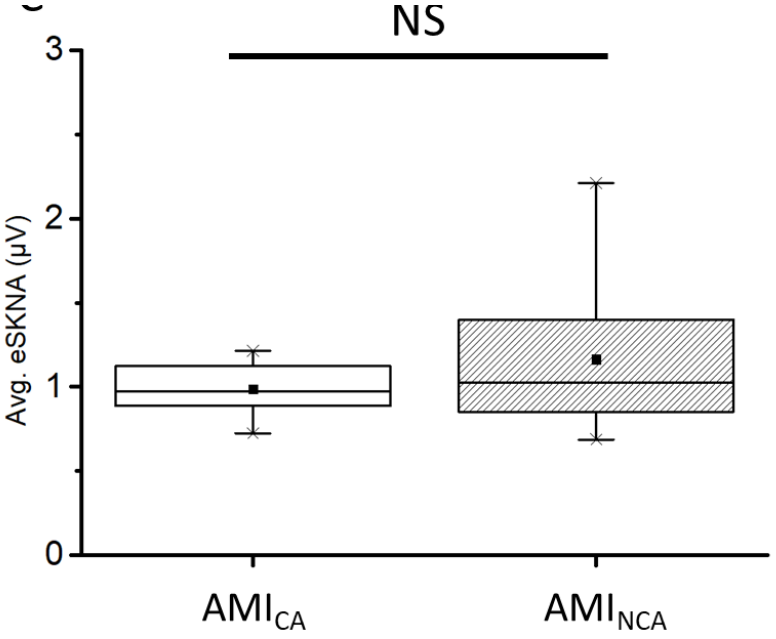
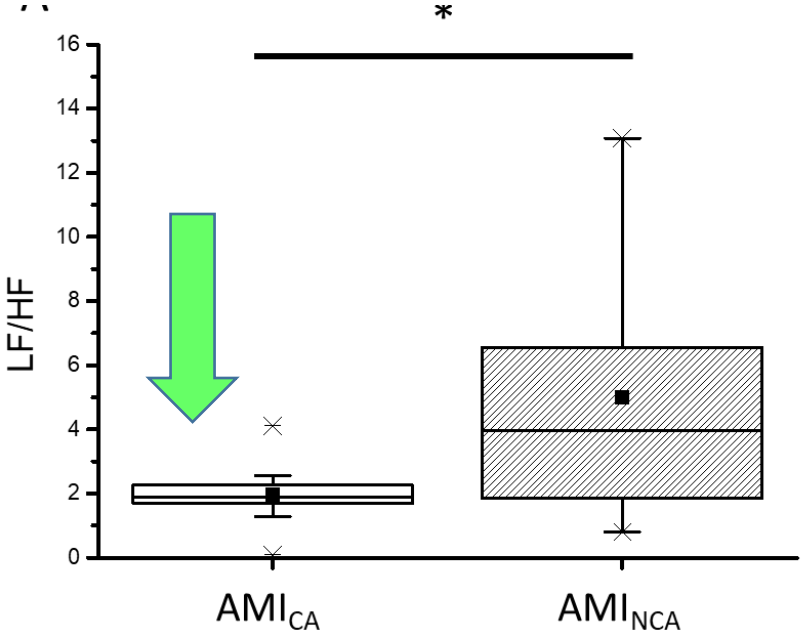
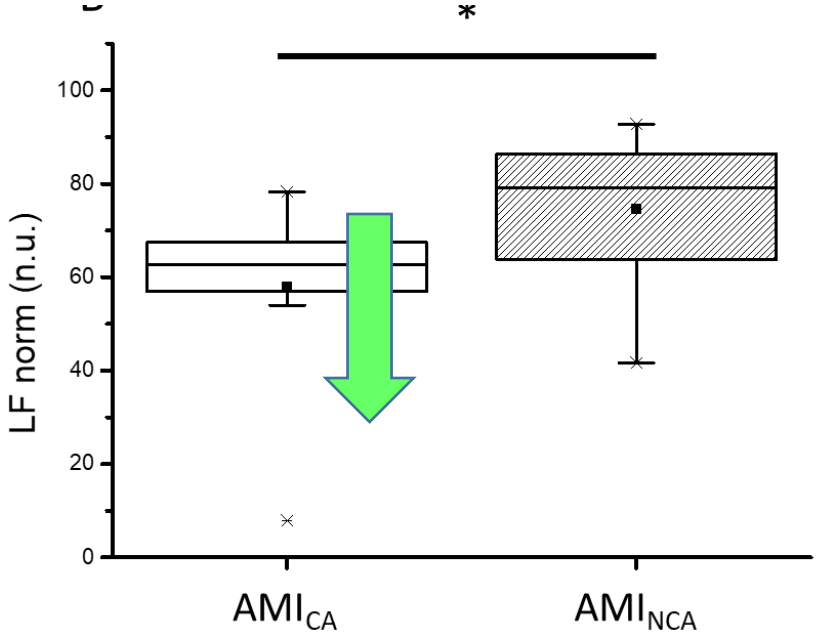
SKNA cluster and HRV







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Conclusions

- Autonomic modulation is playing an important role in AMI.

  ➔ **SKNA**: a potential clinical test for cardiac ANS evaluation.

  ➔**SKNA** might be associated with **MI** and the **VT !**

- We firstly identify the SKNA clustering phenomenon in AMI

  → **SKNA clustering** phenomenon could represent the ANS regulation and homeostasis → A novel biomarker to classify the ANS regulation ability

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Thank you for your attention!

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