

Modulation of Cardiac Afferent Signaling: A New Strategy for Heart Failure Therapy?

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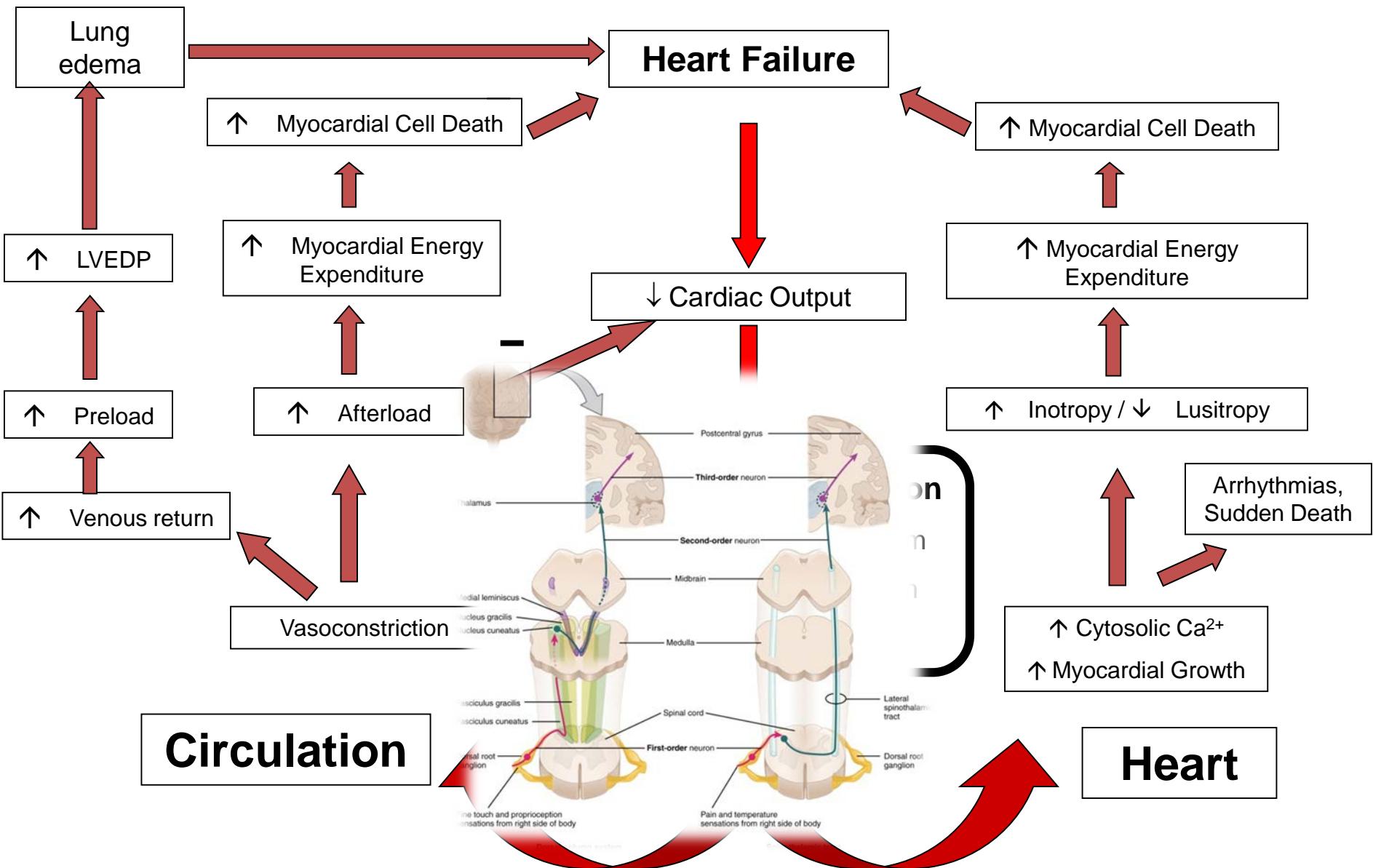




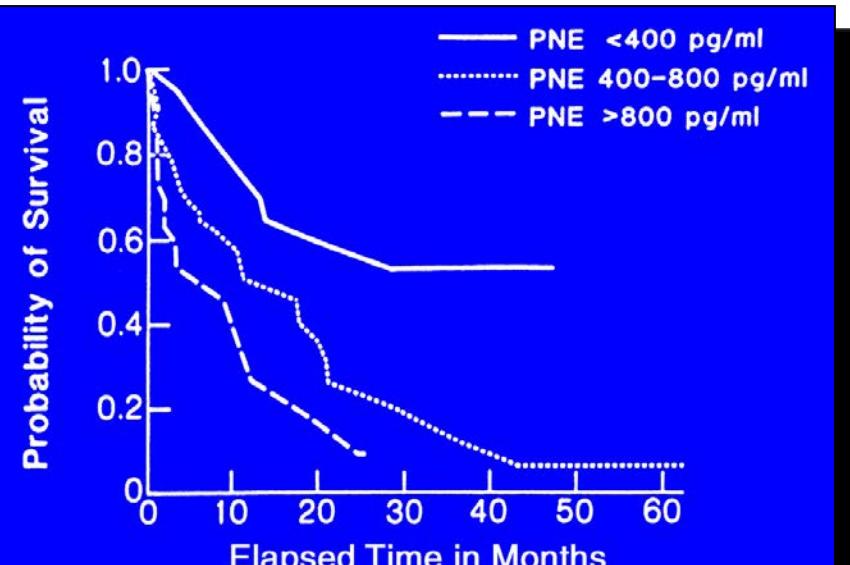
Disclosures

- Sorrento Therapeutics Inc. grant recipient

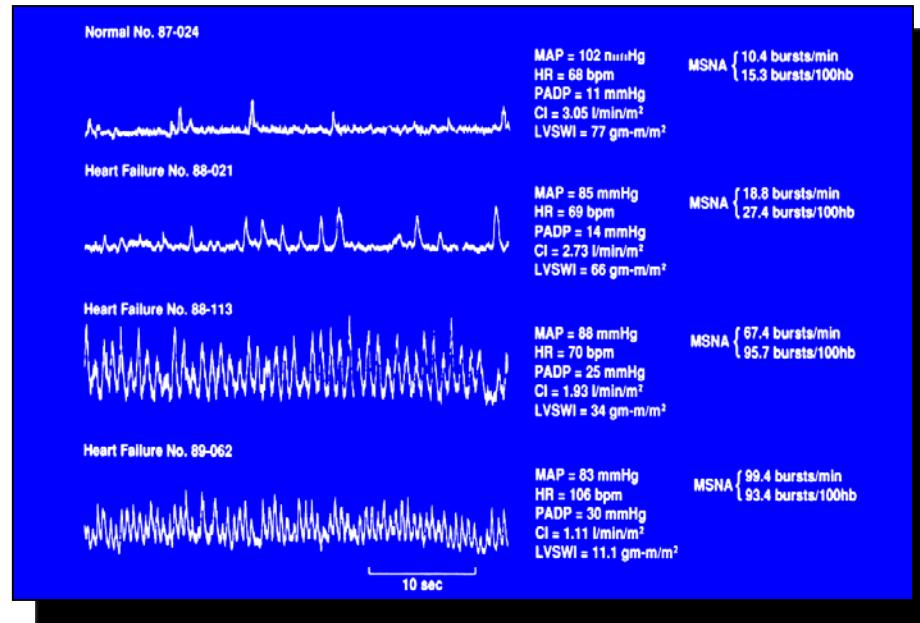
The Vicious Cycle of Heart Failure



Sympathetic Nerve Activity in Heart Failure

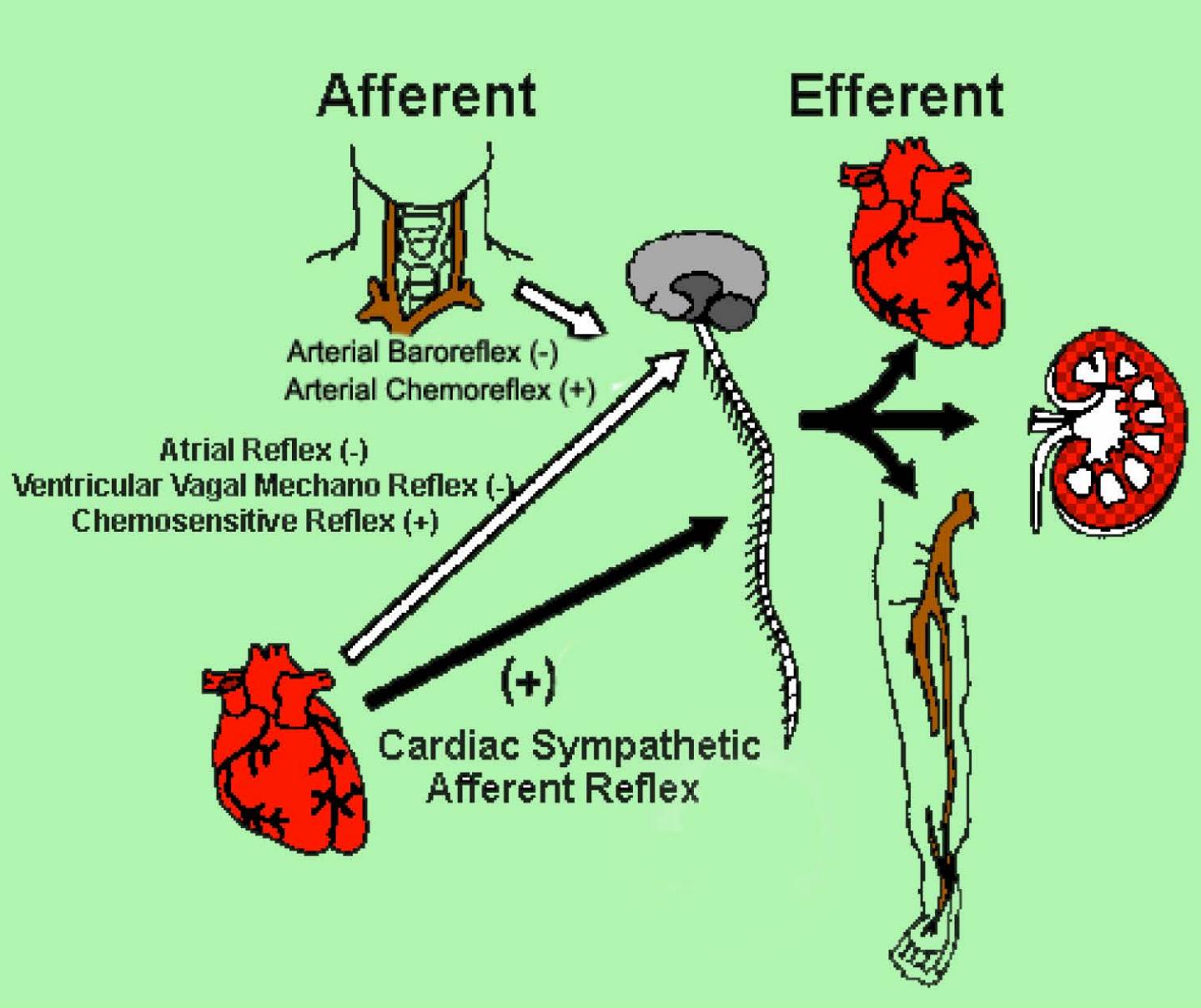


Cohn,J.N. et al: N Engl J Med. 311: 819, 1984

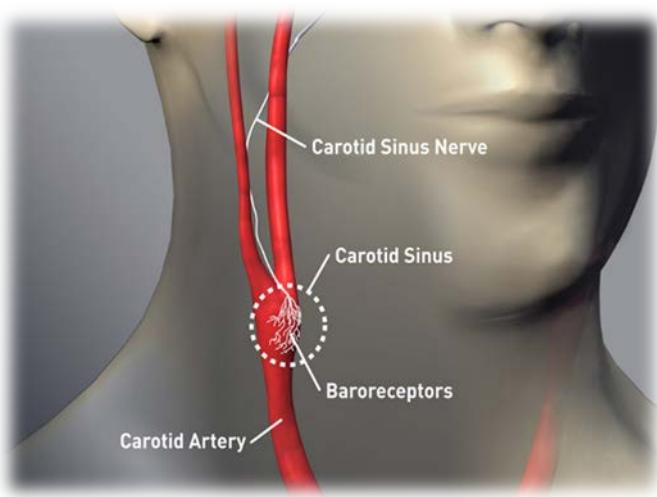


Ferguson, D. W. et al.: J. Am. Coll. Cardiol., 16:1125, 1990

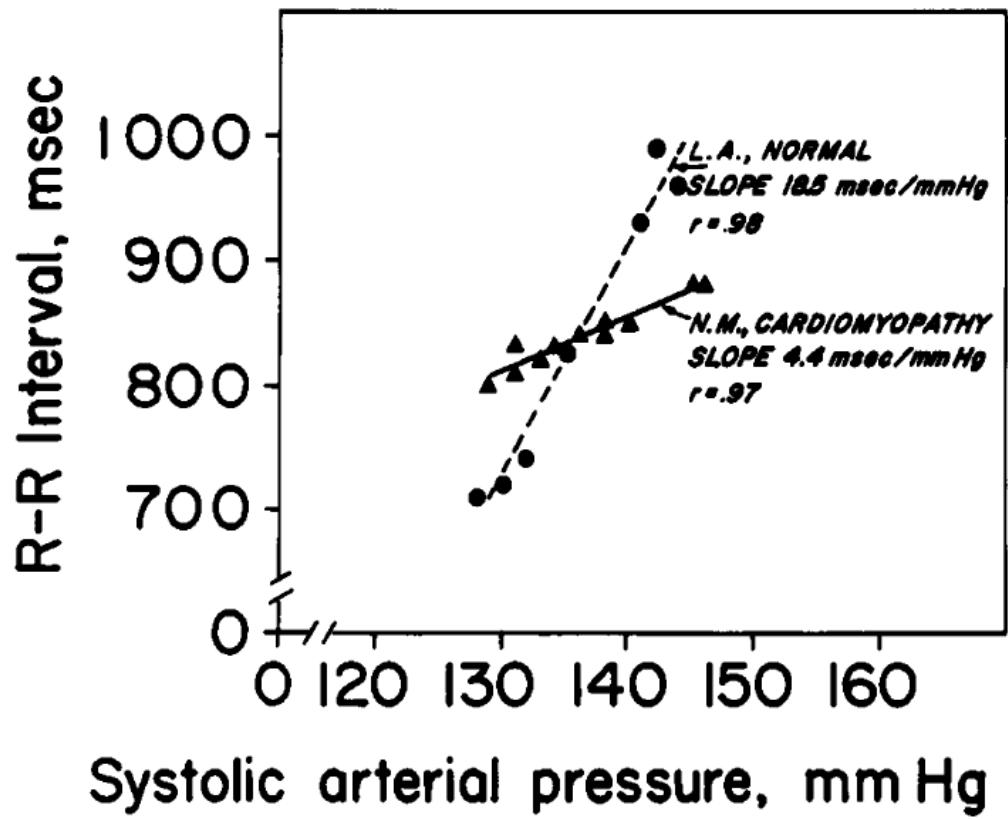
Reflex Control in Heart Failure



The Baroreflex

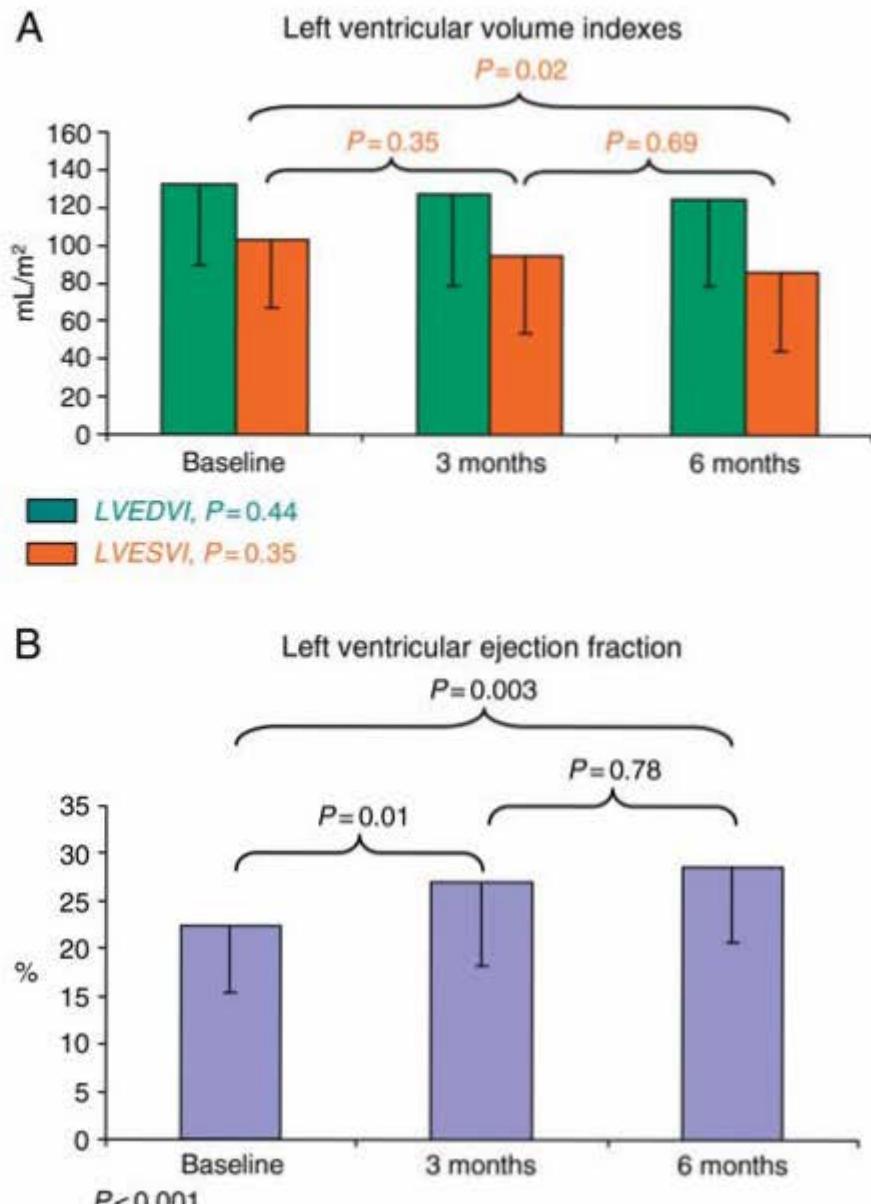
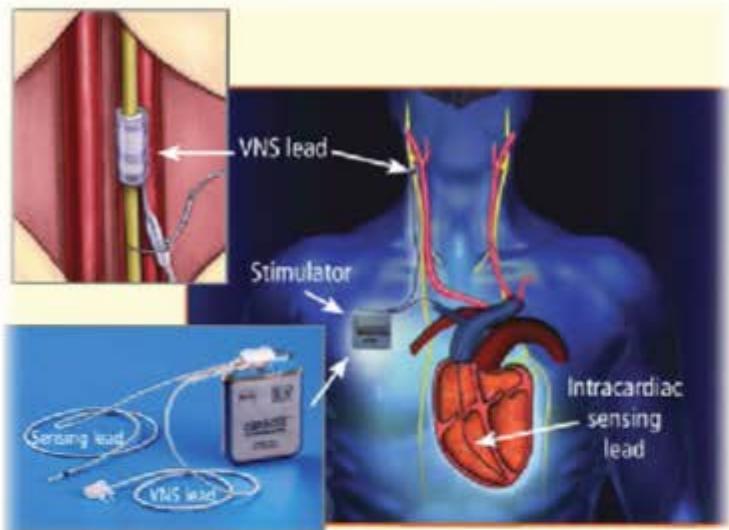


CVRx.com

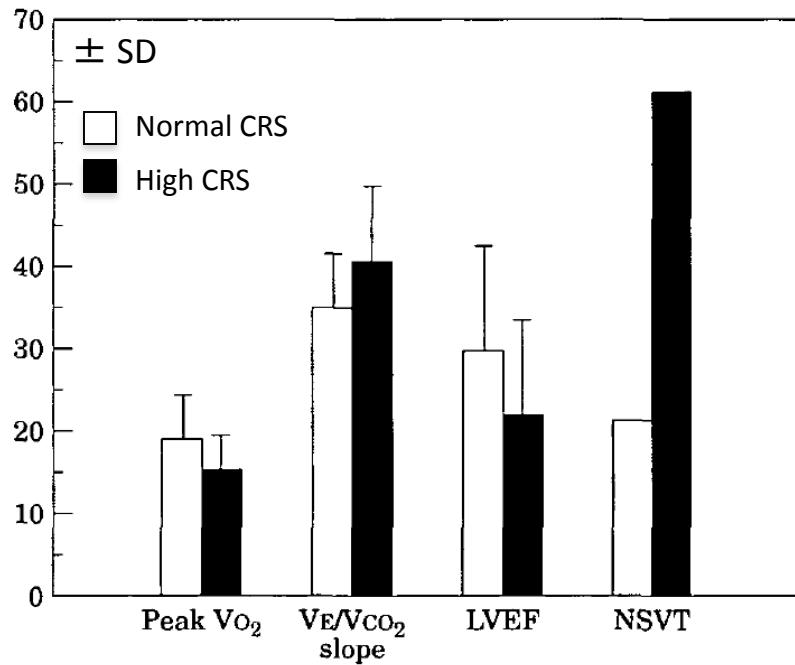
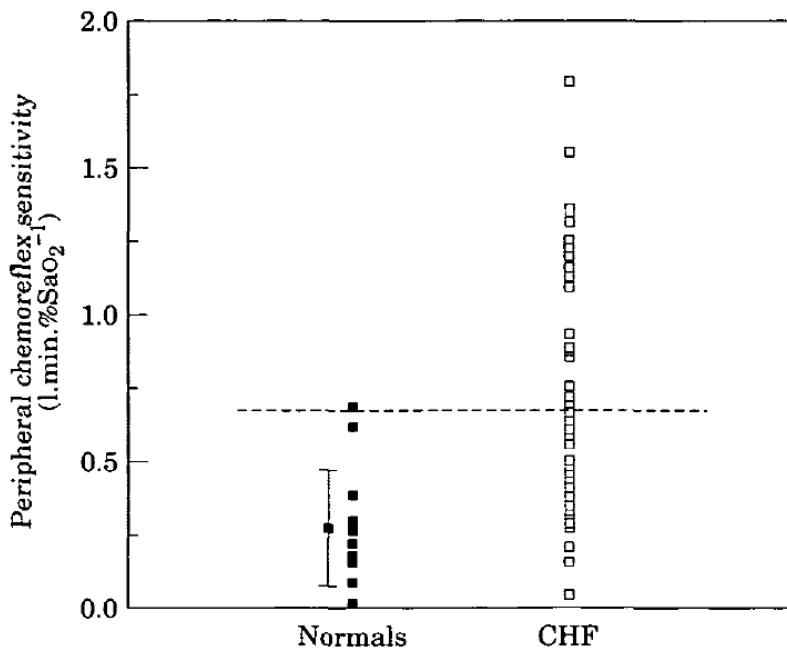
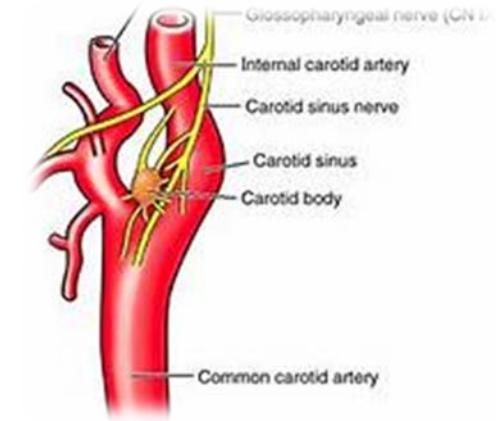


Eckberg, D. et al. N. Engl. J. Med. 1971

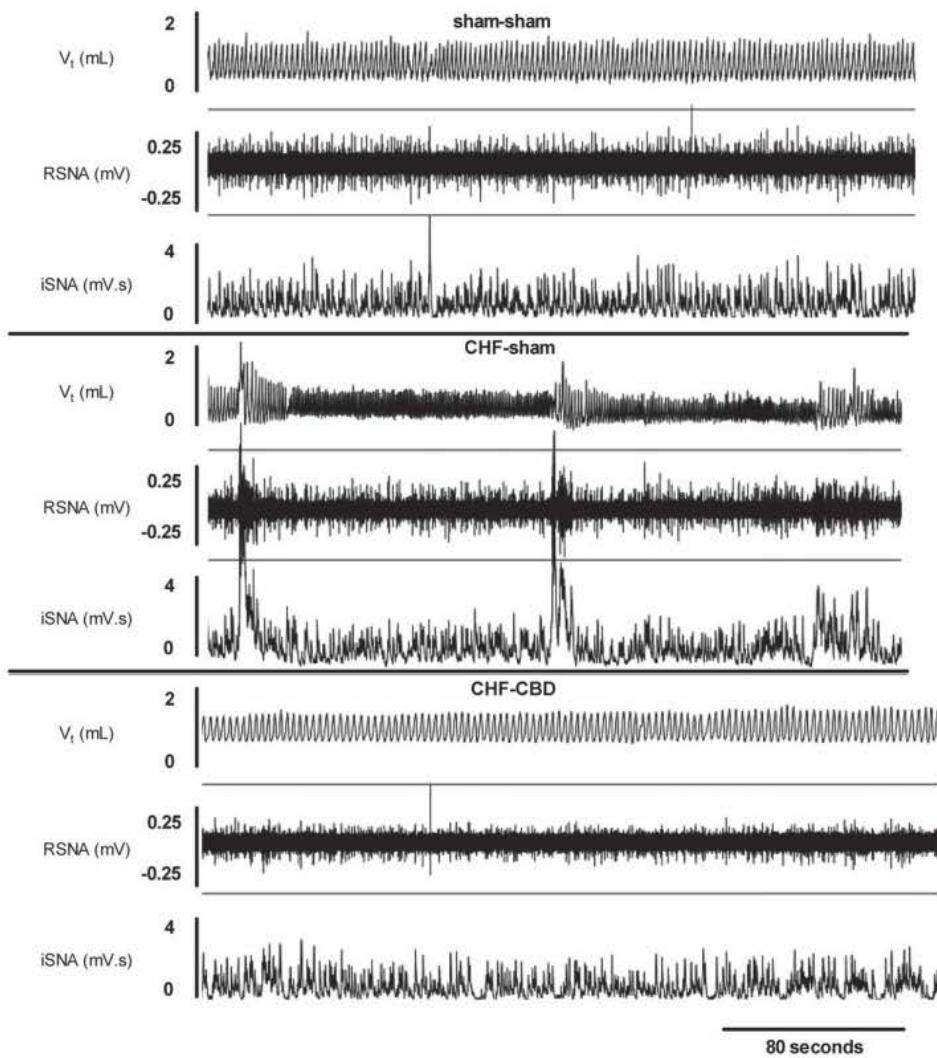
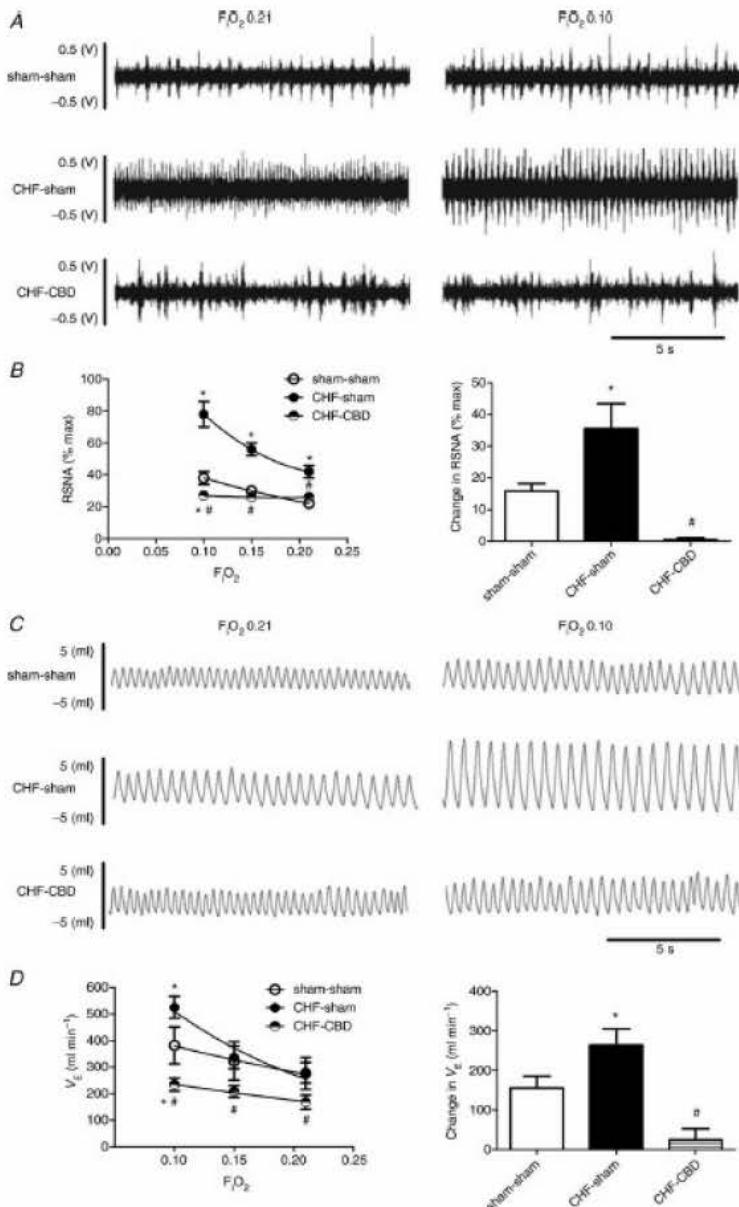
Vagal Nerve Stimulation



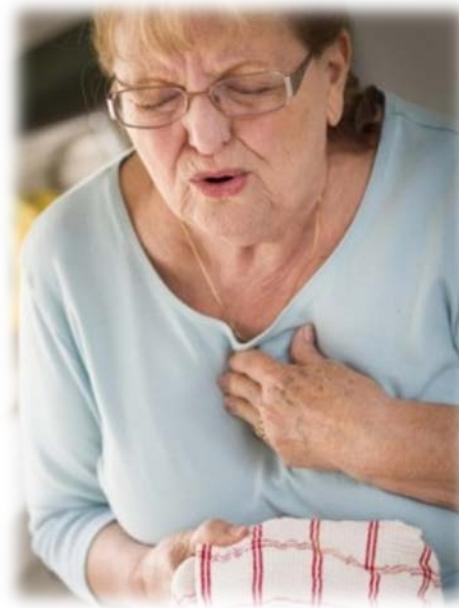
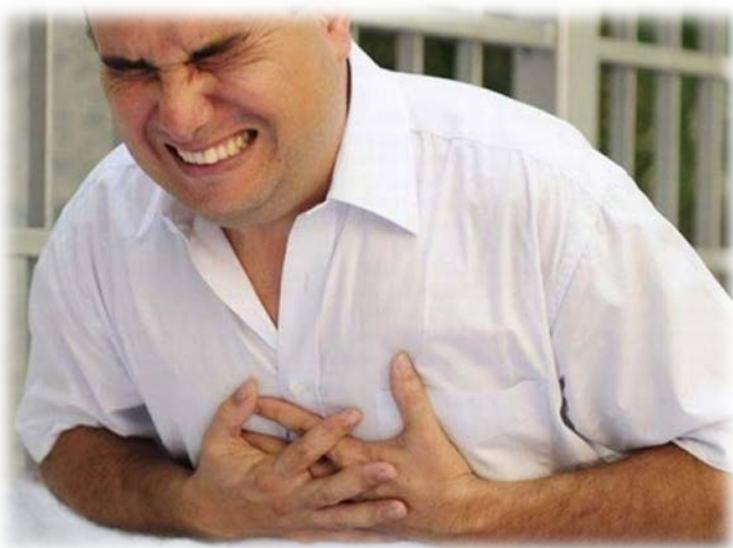
Chemoreflex Sensitivity



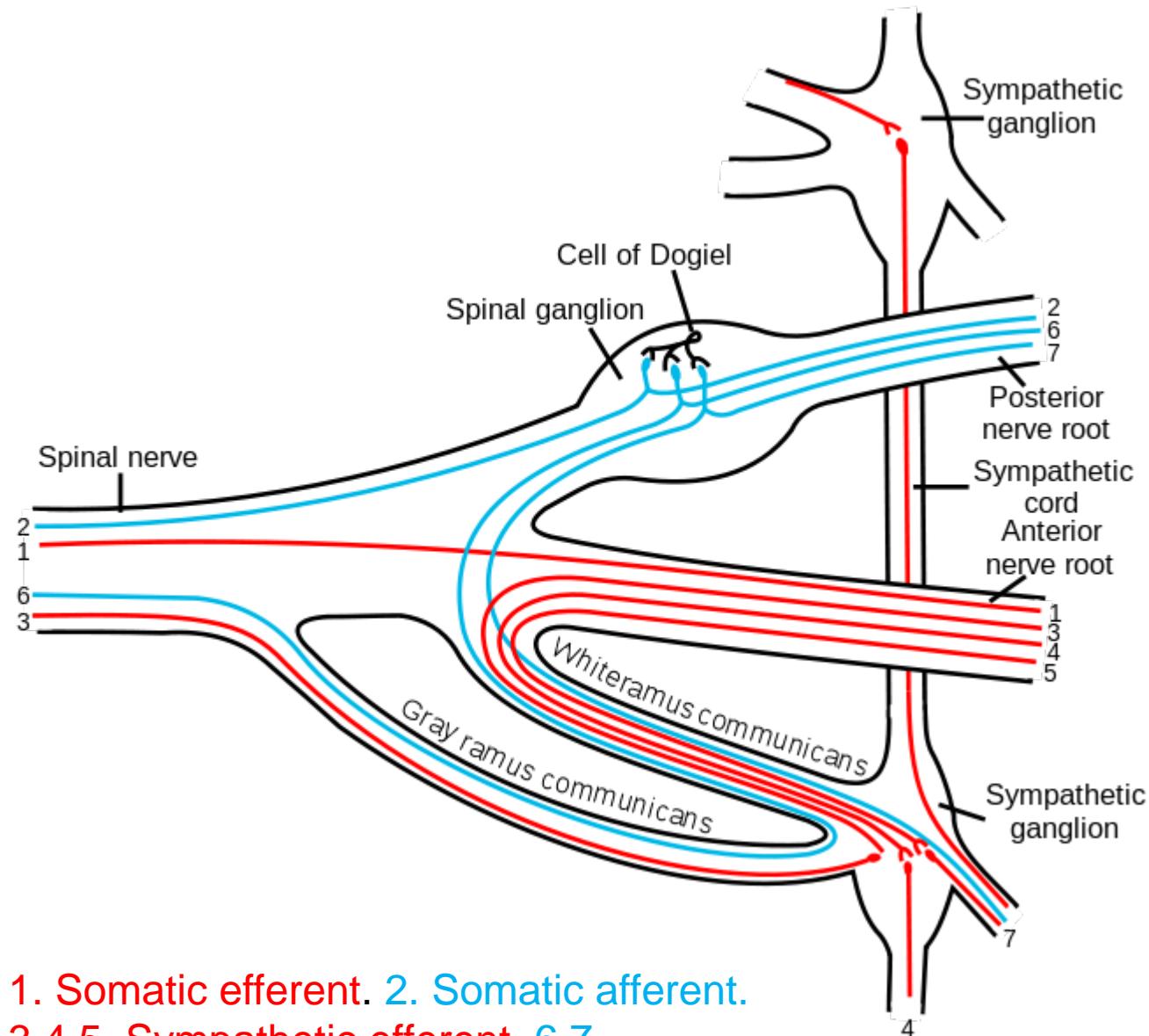
Carotid Body Denervation



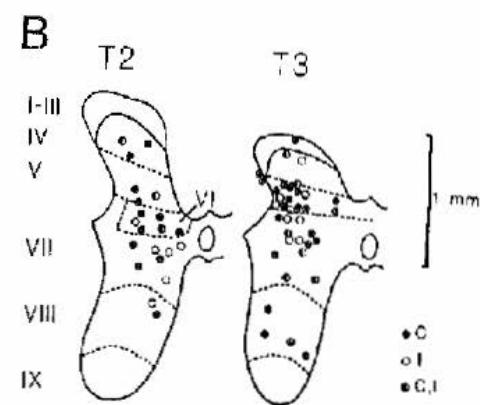
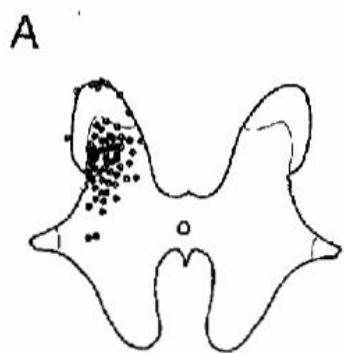
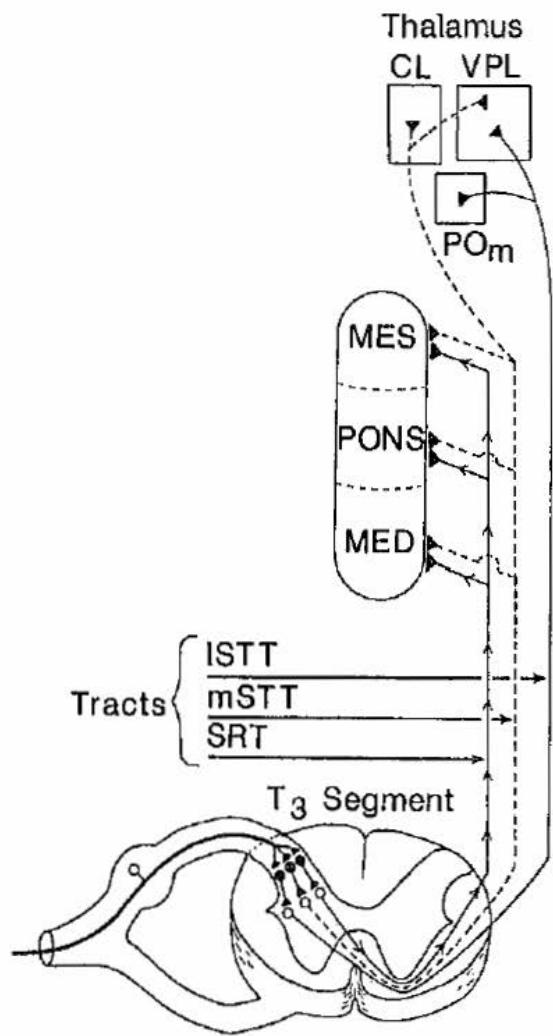
Cardiac Sympathetic Afferents in Heart Failure: It's not just about the pain



Visceral afferent structure



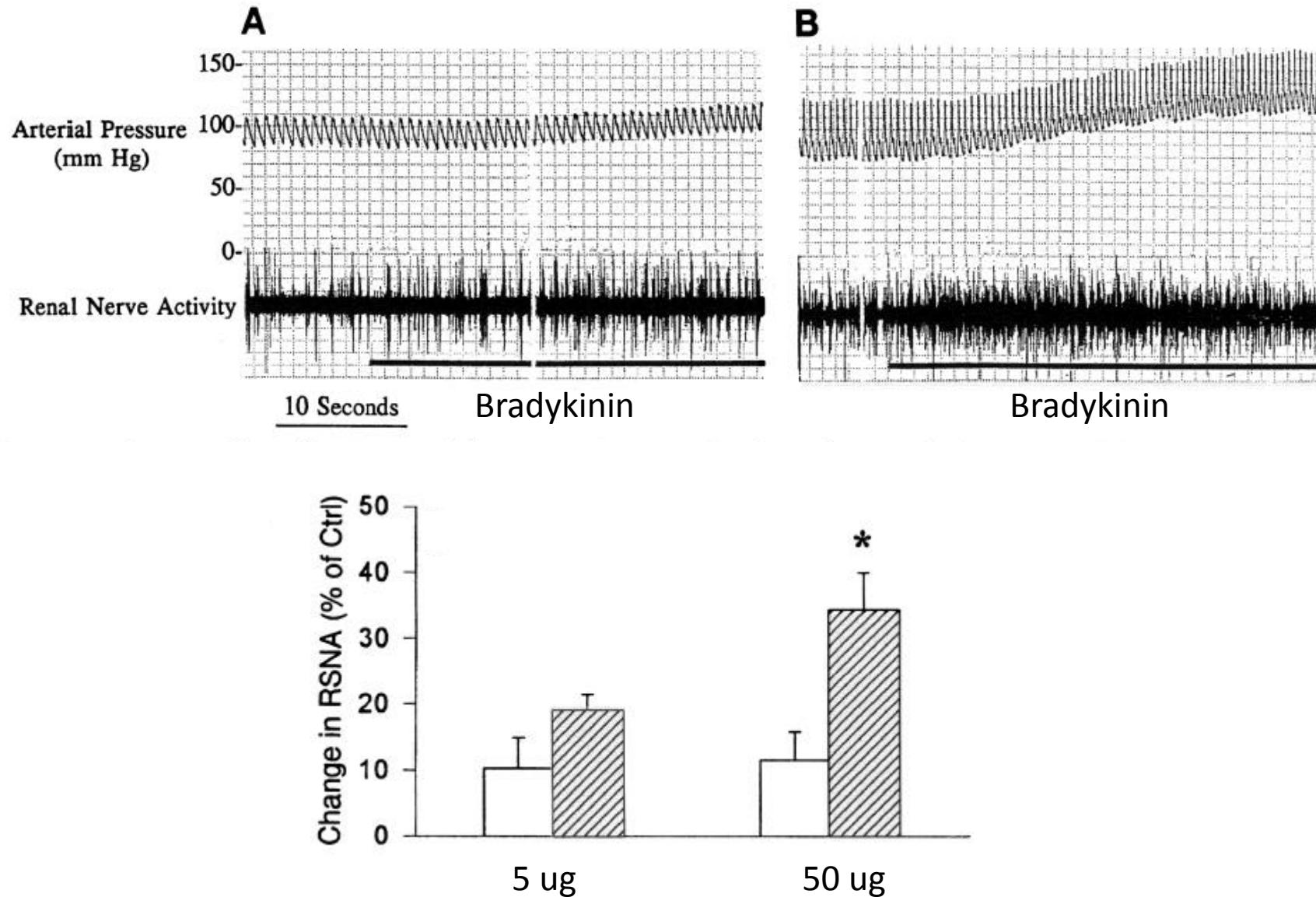
1. Somatic efferent.
2. Somatic afferent.
- 3,4,5. Sympathetic efferent.
- 6,7. Sympathetic afferent.



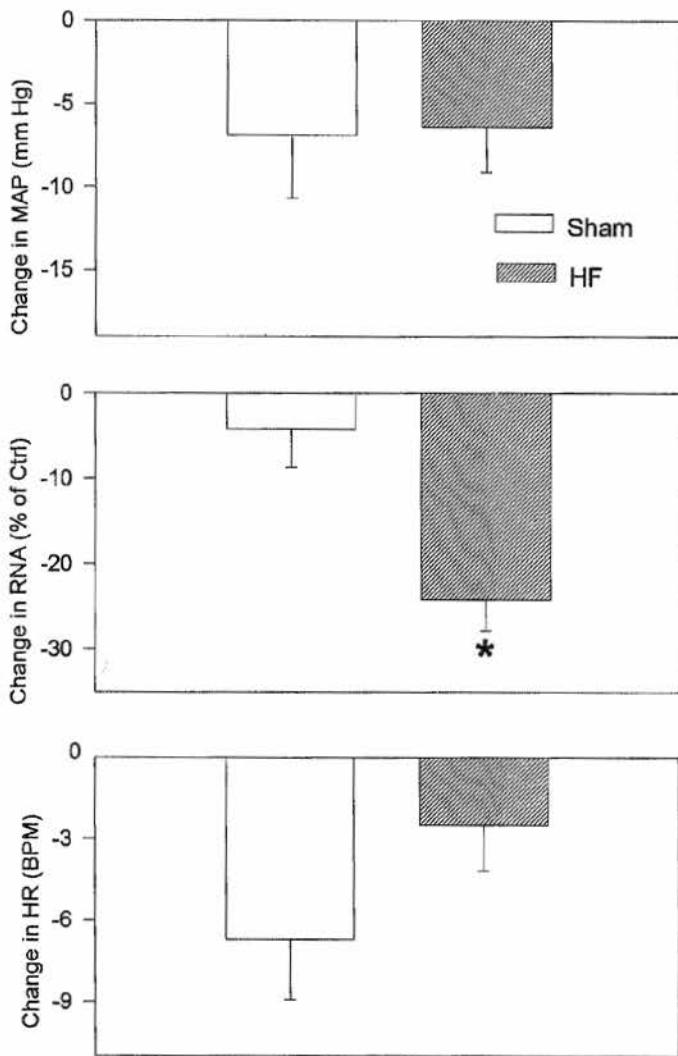
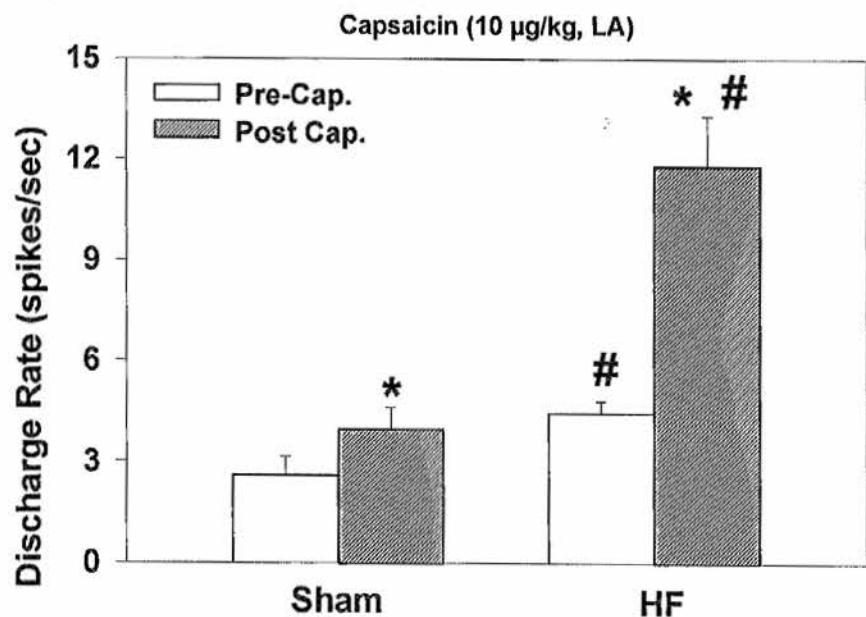
Stimuli for Cardiac Sympathetic Afferents

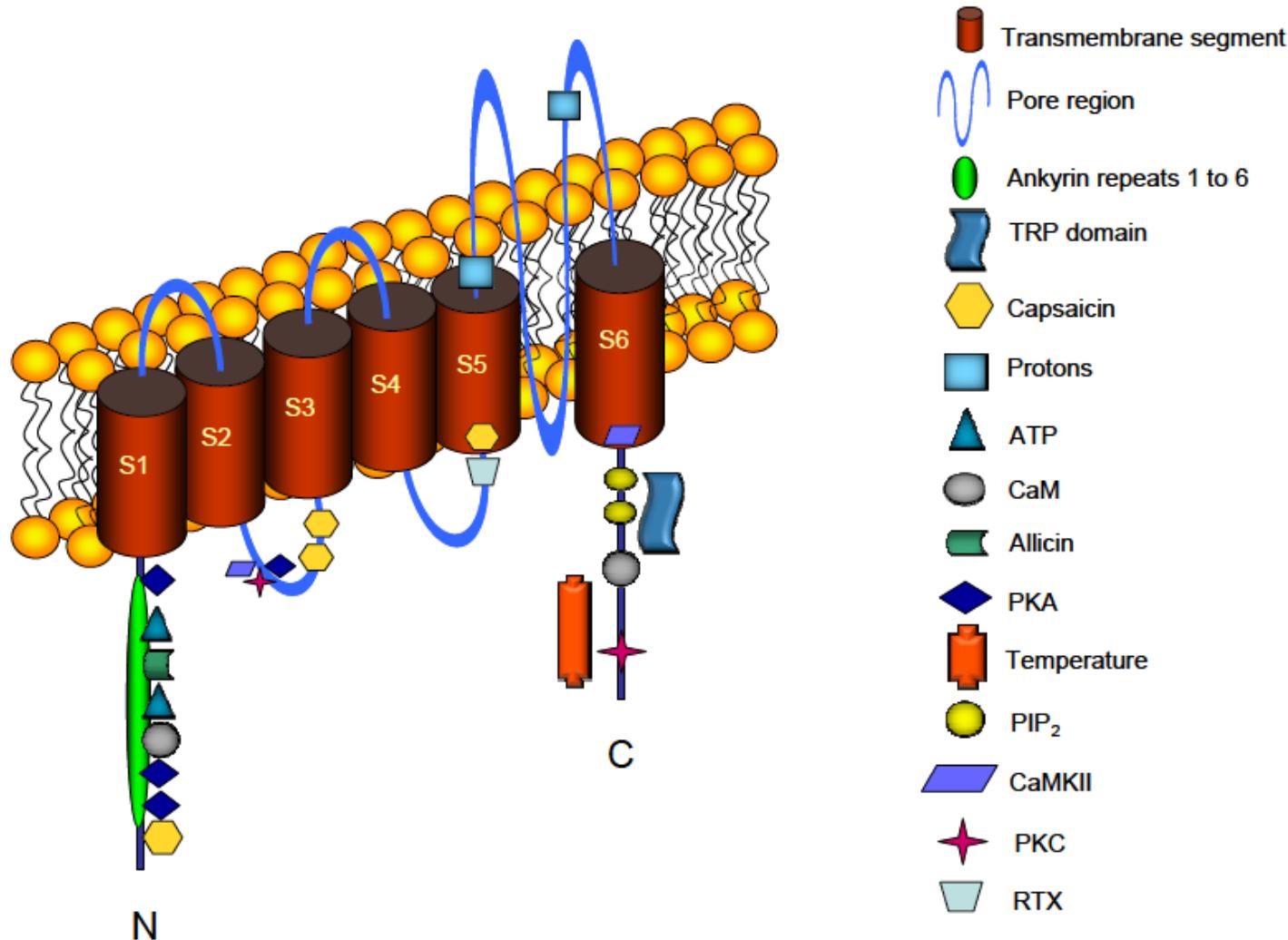
- Hydrogen ion
- Oxygen radicals
- Potassium
- Lactate
- ATP
- Prostaglandins and other AA metabolites
- Bradykinin
- Substance P
- Capsaicin

CARDIAC SYMPATHETIC AFFERENT REFLEX IN HEART FAILURE



Epicardial lidocaine reduces SNA in heart failure

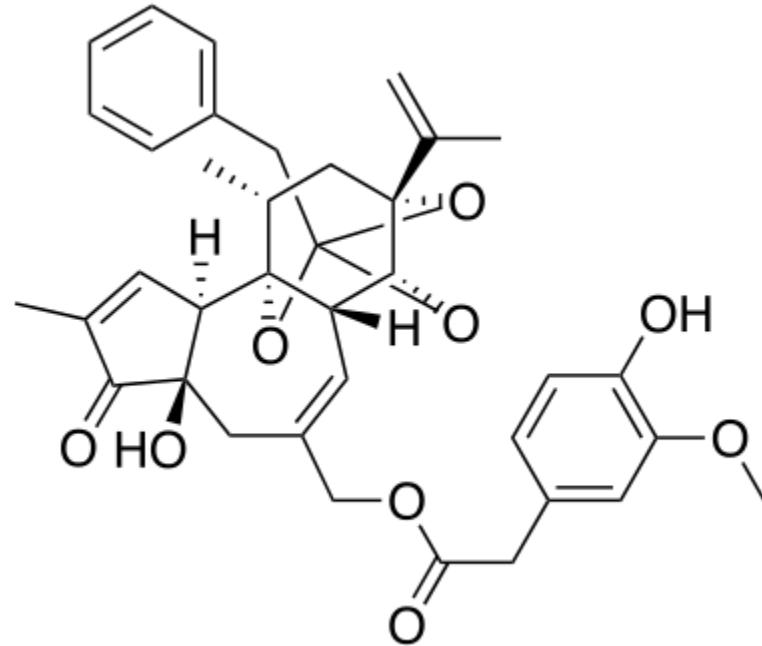




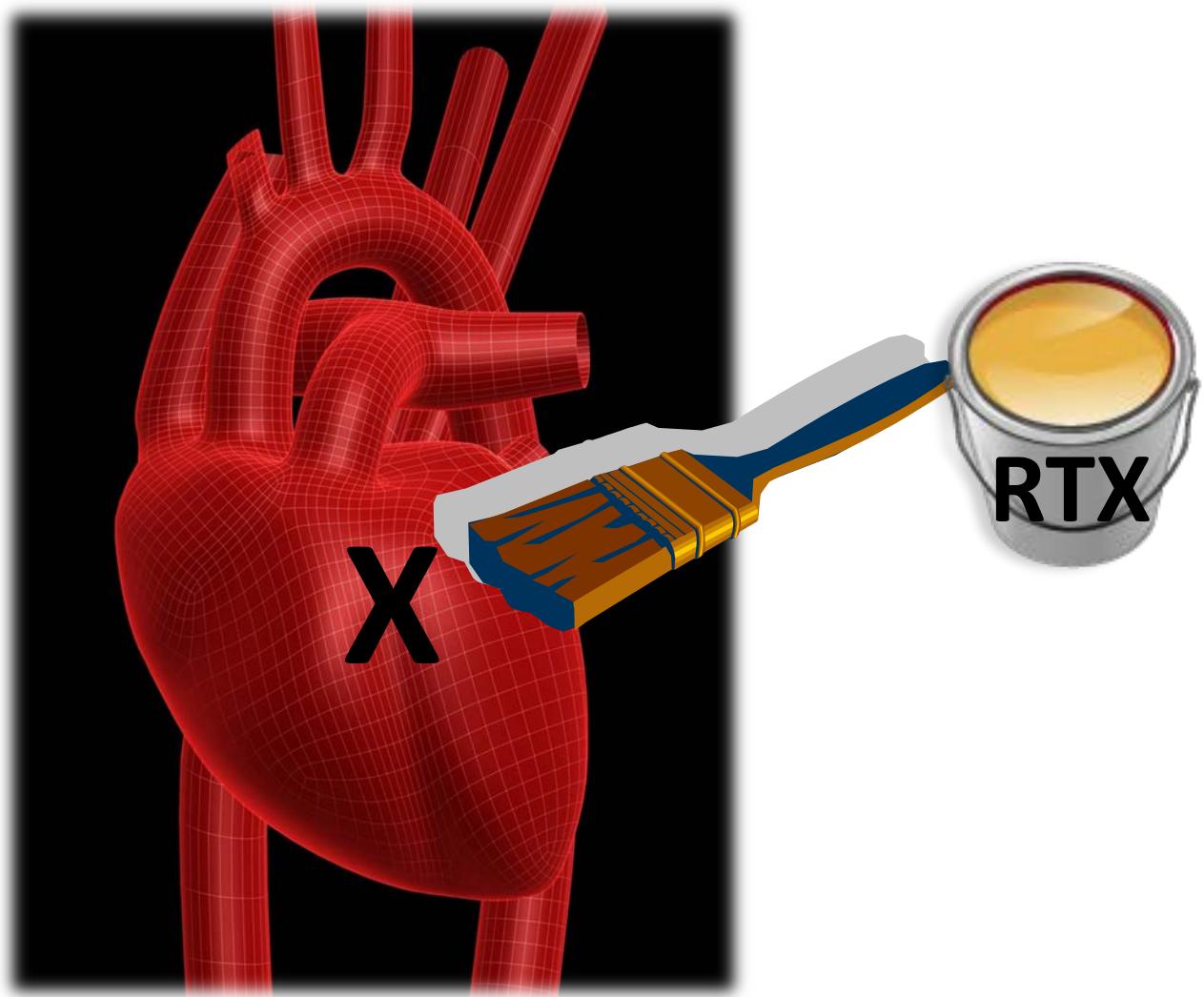
TRPV1



Euphorbia resinifera 16 Billion Scoville Units

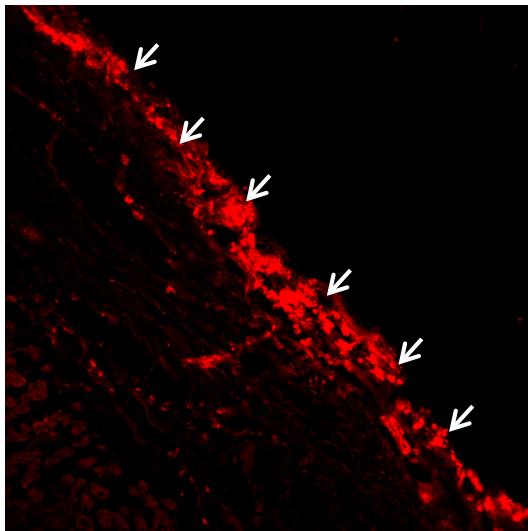


Resineferitoxin (RTX)

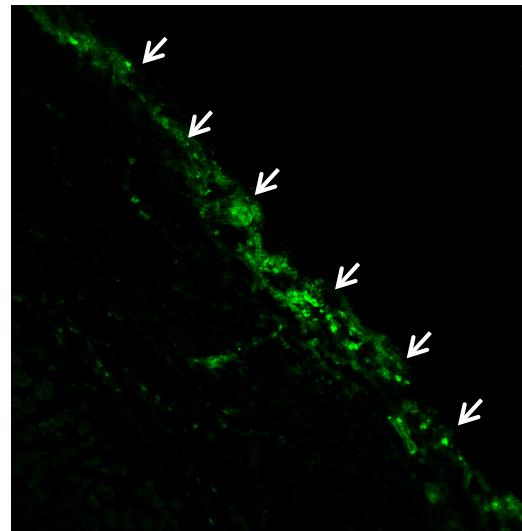


Sham+Vehicle

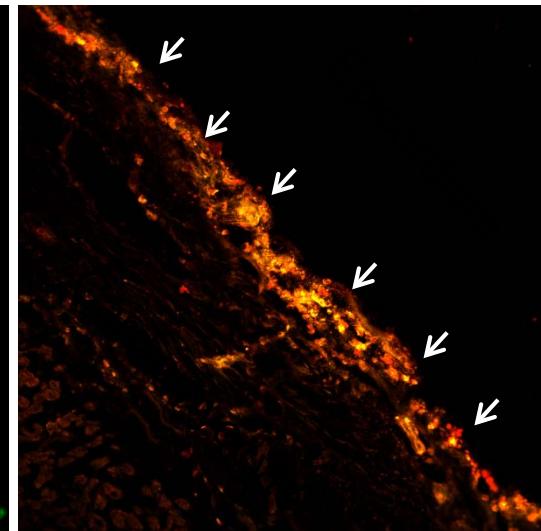
PGP 9.5



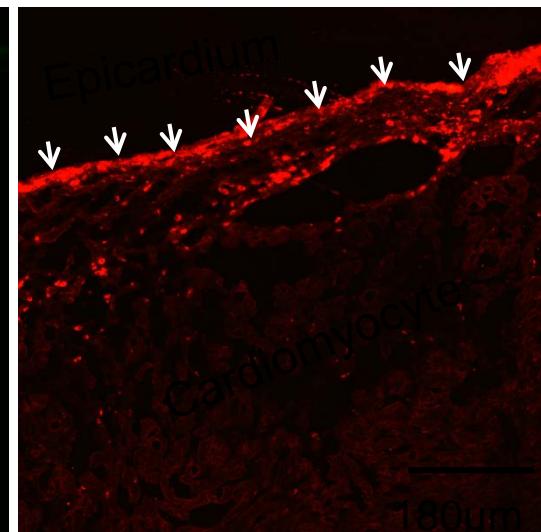
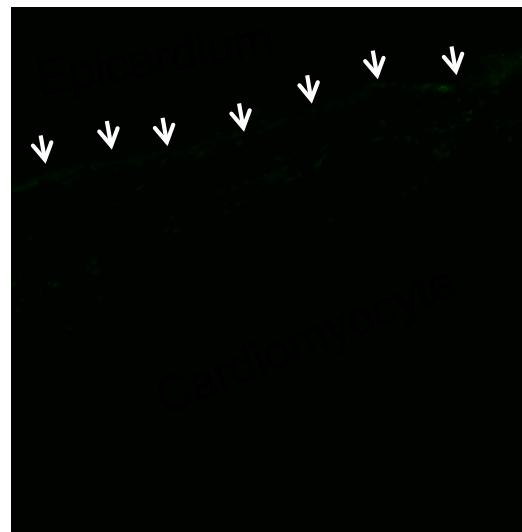
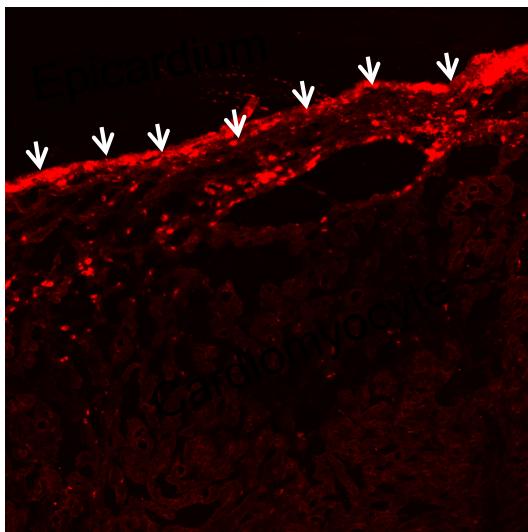
TRPV1

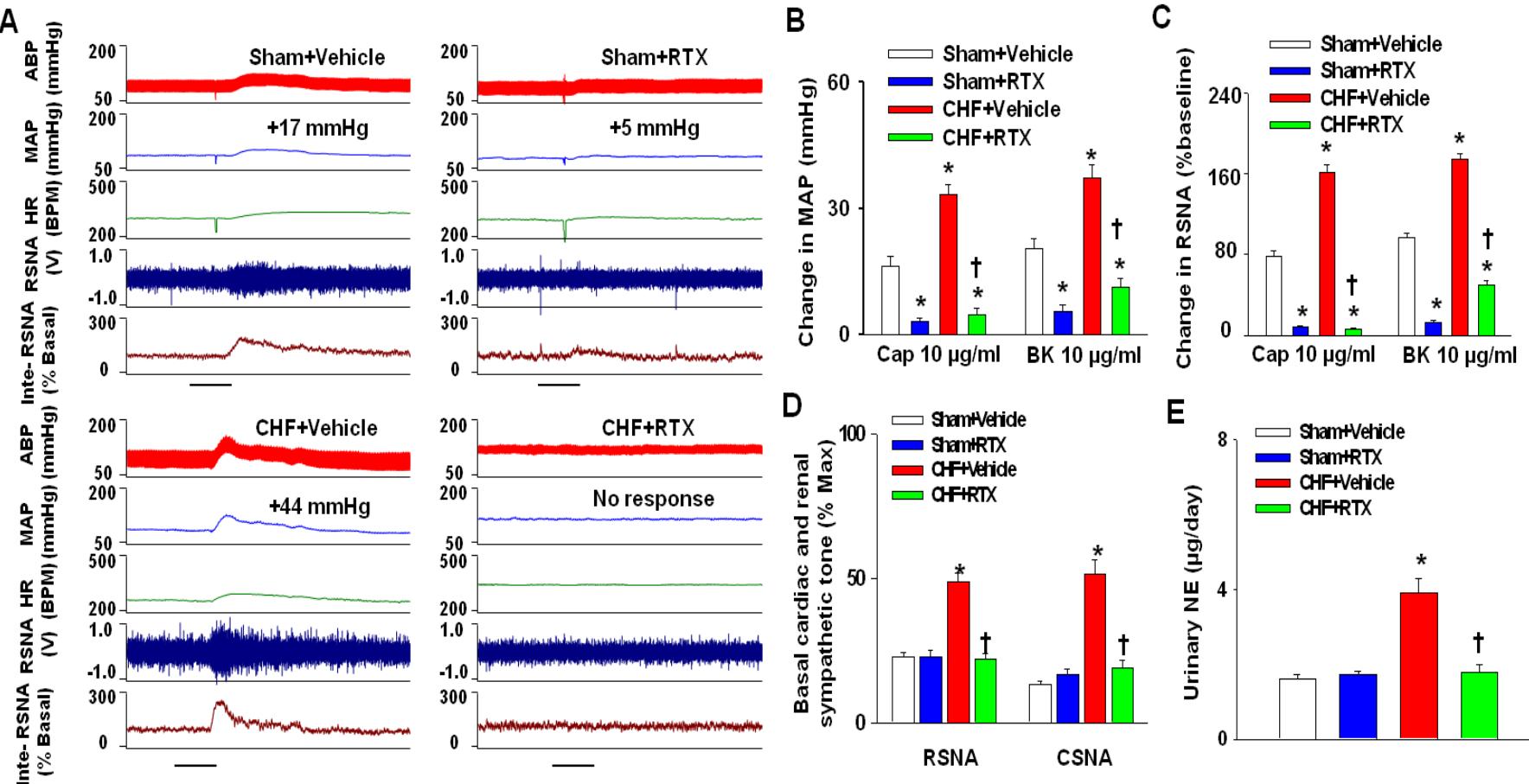


Merge



Sham+RTX



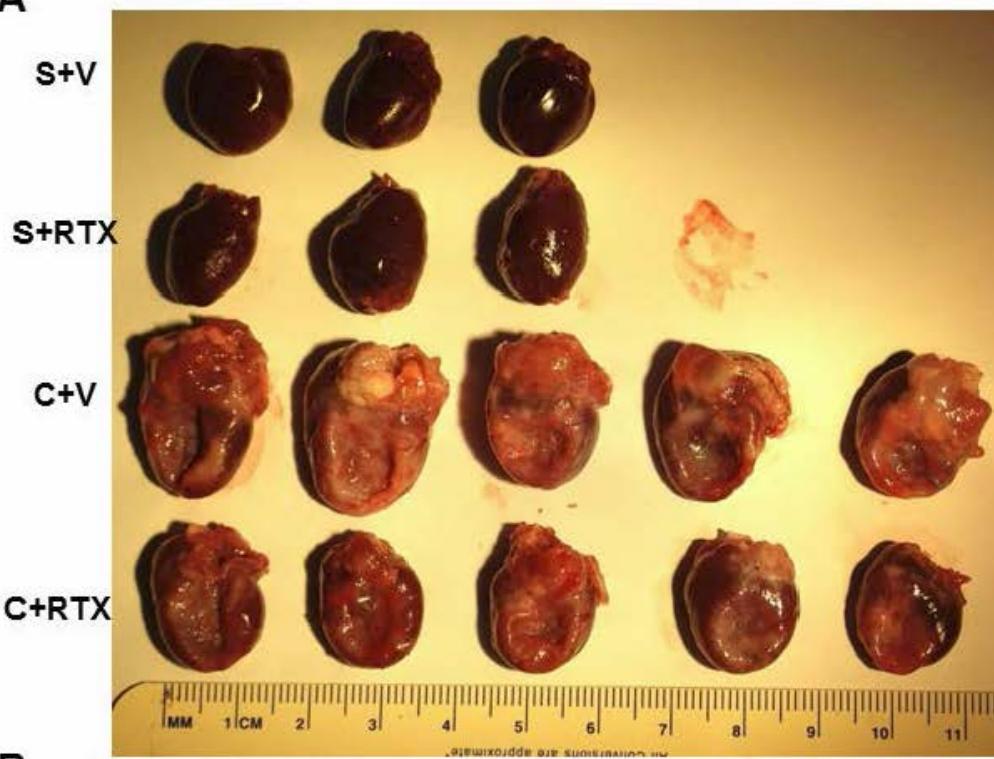
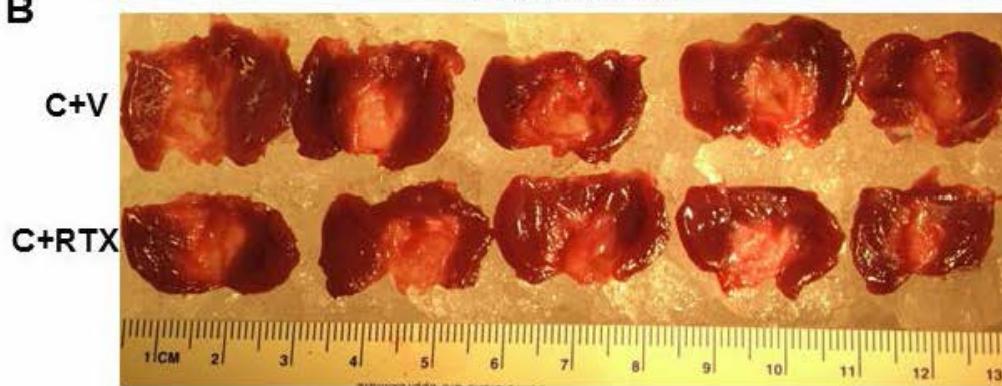


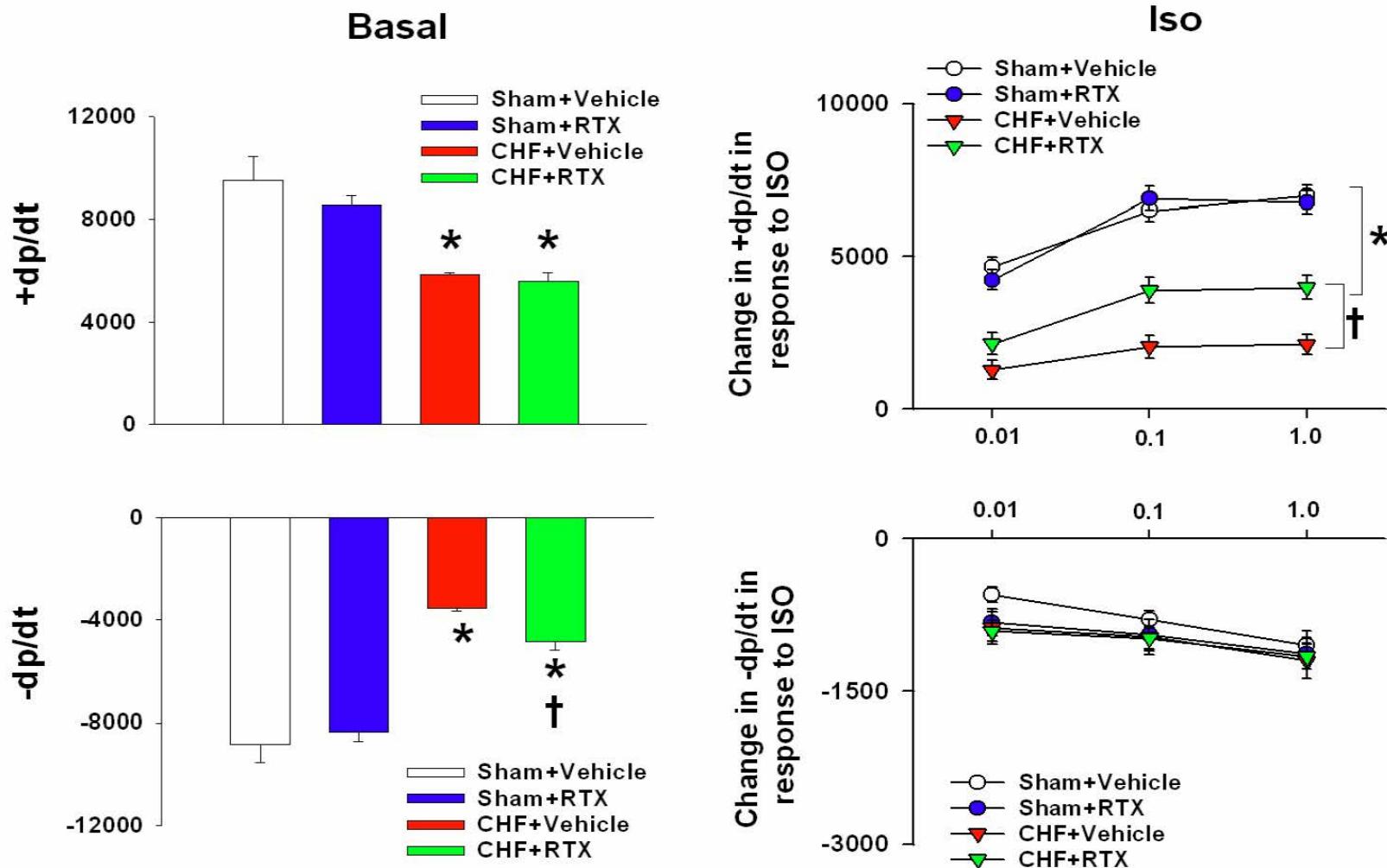
* $P<0.05$ vs. sham+vehicle; †, $P<0.05$ vs. CHF+vehicle.

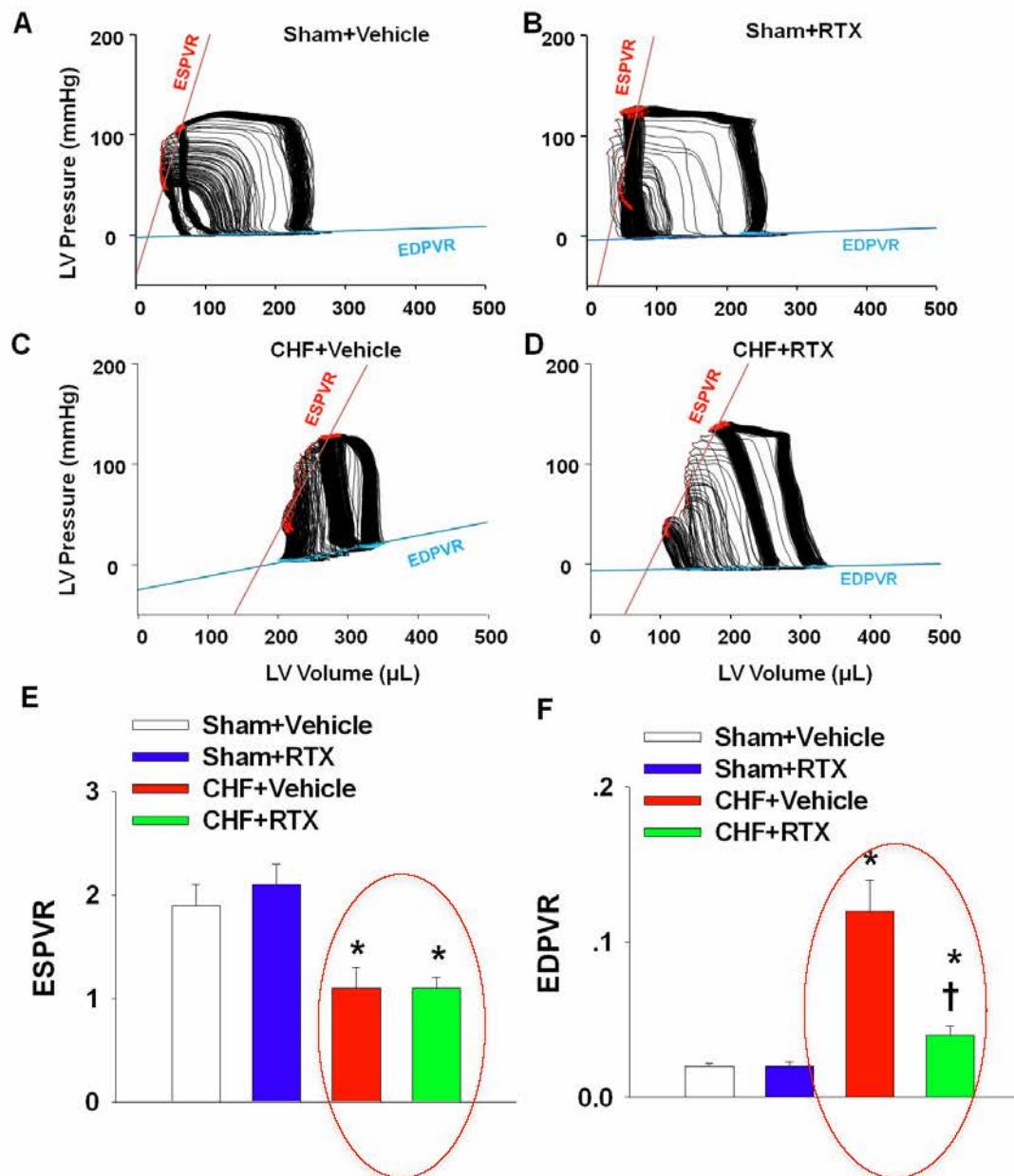
Hemodynamic and morphological data in sham and CHF rats treated with vehicle or RTX

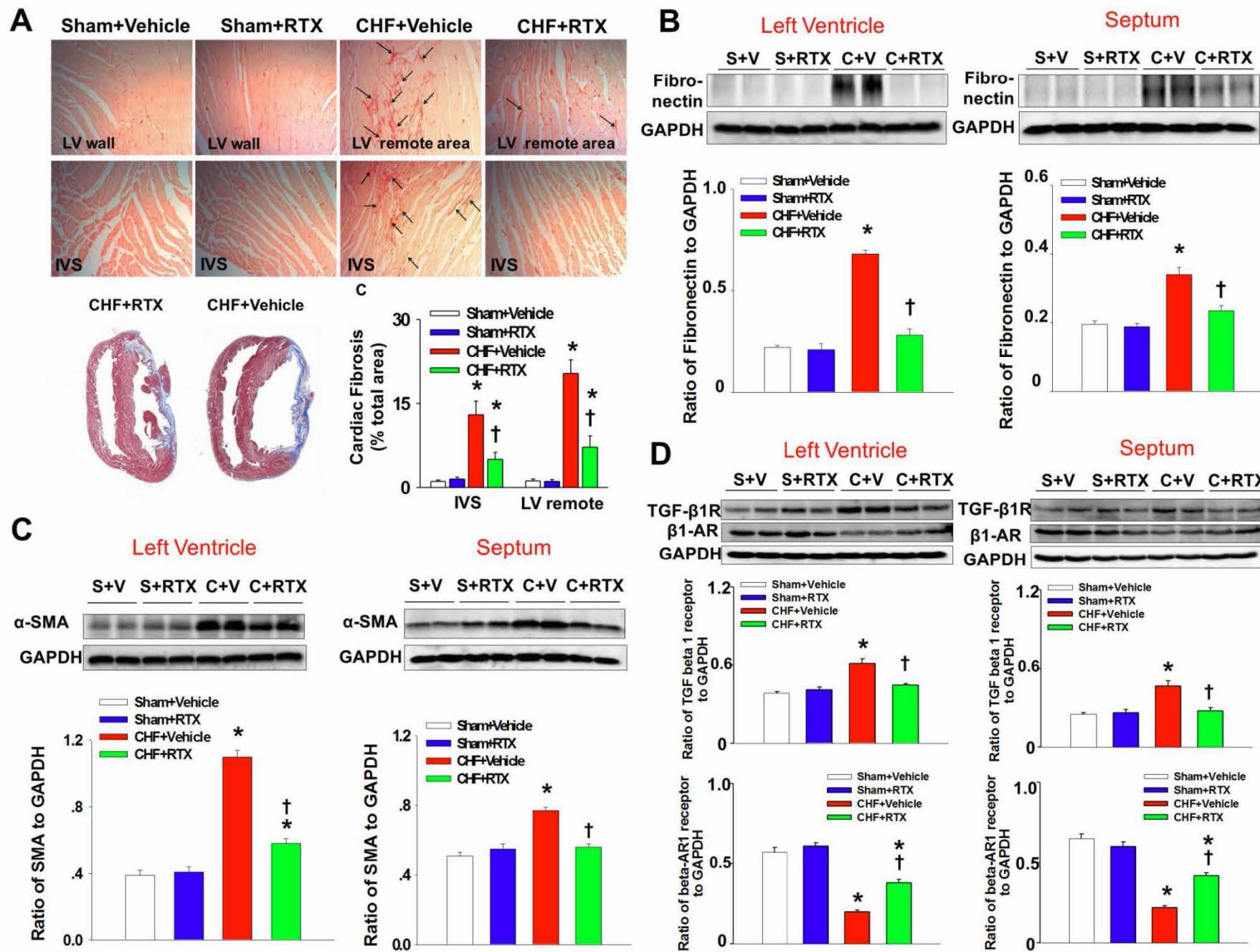
	Sham+Vehicle (n=21)	Sham + RTX (n=20)	CHF+Vehicle (n=23)	CHF + RTX (n=25)
Body weight, g	429 ± 7	430 ± 7	452 ± 8	440 ± 8
Heart weight, mg	1438 ± 28	1430 ± 30	2239 ± 61*	1650 ± 49*†
HW/BW, mg/g	3.4± 0.1	3.3 ± 0.1	5.0 ± 0.1 *	3.8 ± 0.1*†
WLW/BW, mg/g	4.4± 0.1	4.5 ± 0.1	8.7 ± 0.3 *	5.1 ± 0.2*†
MAP, mmHg	103.5 ± 2.4	105.0 ± 3.1	96.7 ± 2.0*	101.3 ± 2.1
LVEDP mmHg	5.0± 0.4	4.8± 0.4	21.3± 1.0*	8.3± 0.7*†
HR, bpm	357.3 ± 6.1	362.0 ±6.8	368.9 ± 5.1	348.3± 5.5†
dp/dt _{max}	9108±324	8601±224	5137 ± 180 *	5446 ± 173*
dp/dt _{min}	-8458±235	-8088±196	-3452±113*	-4643±149*†
Infarct size, %	0	0	42.5± 1.4 *	39.1 ± 1.2 *

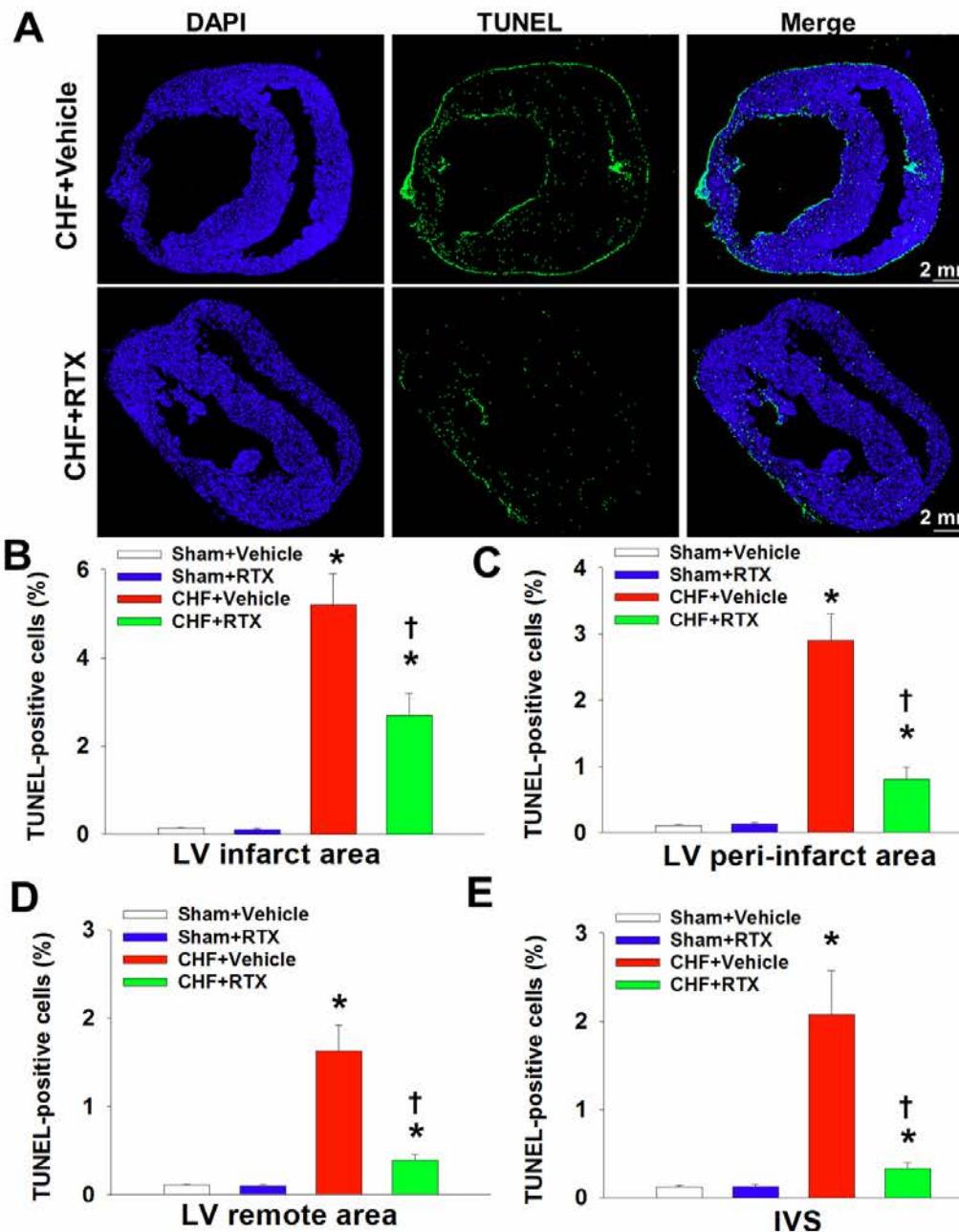
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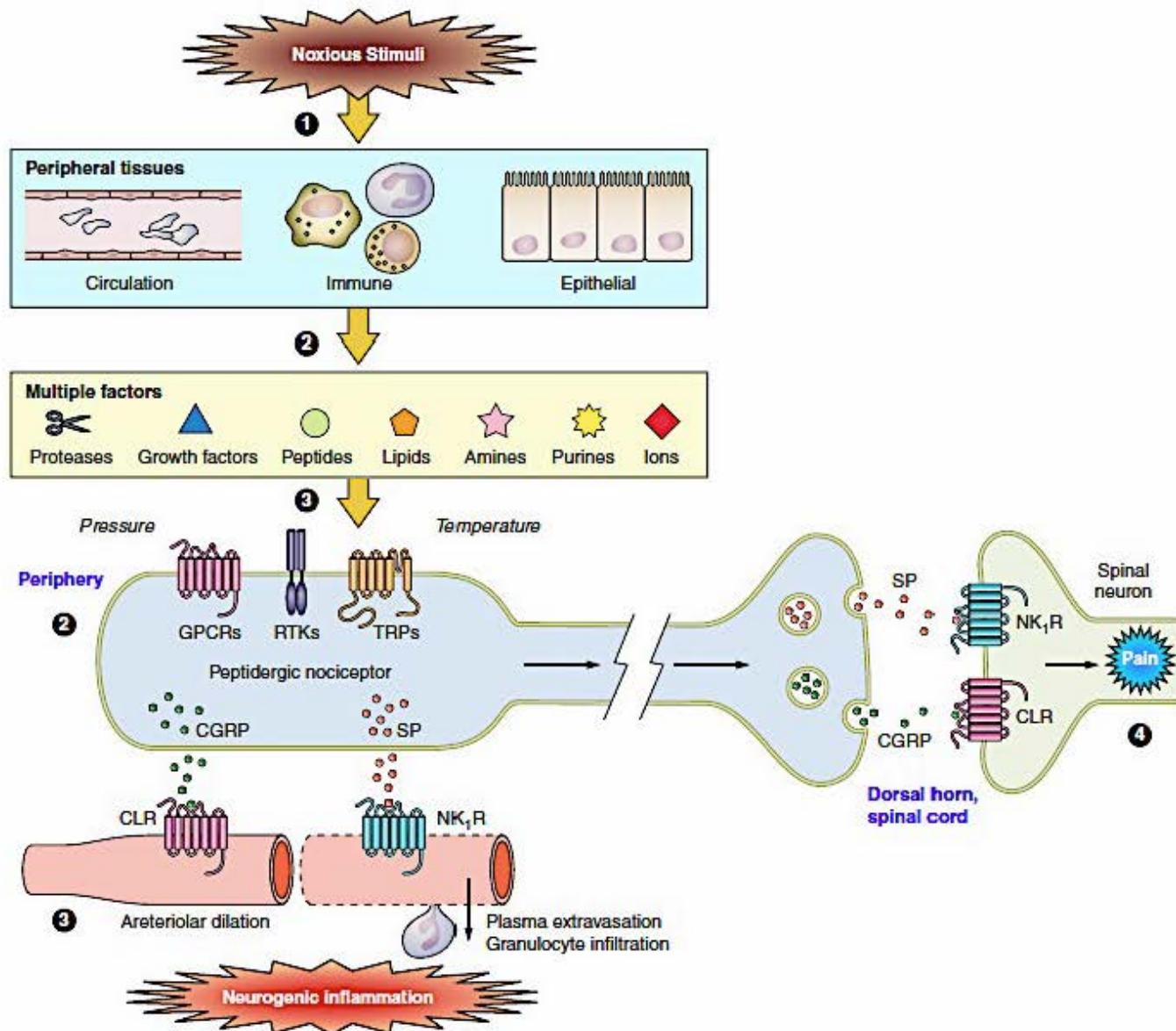
A**B**



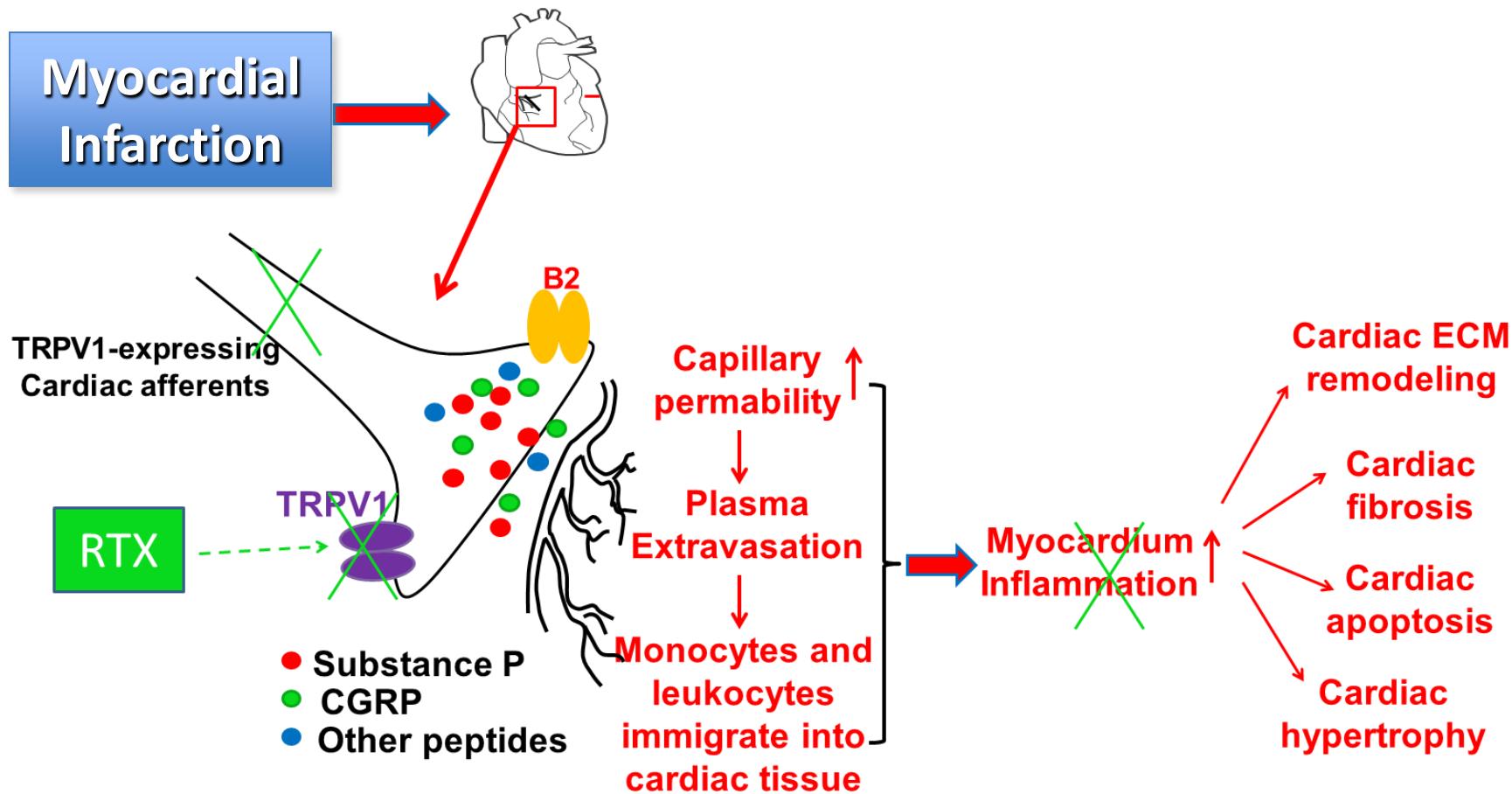


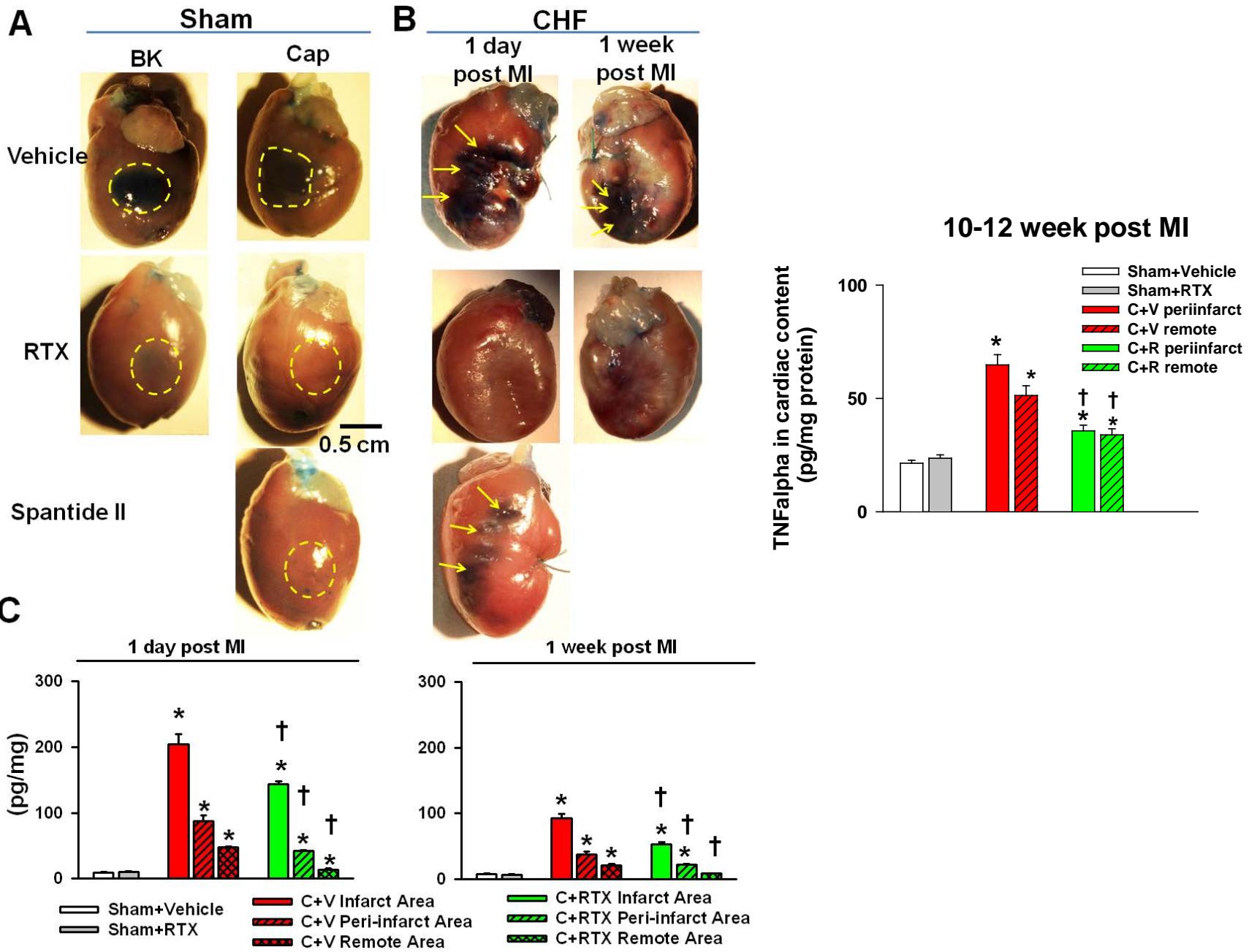


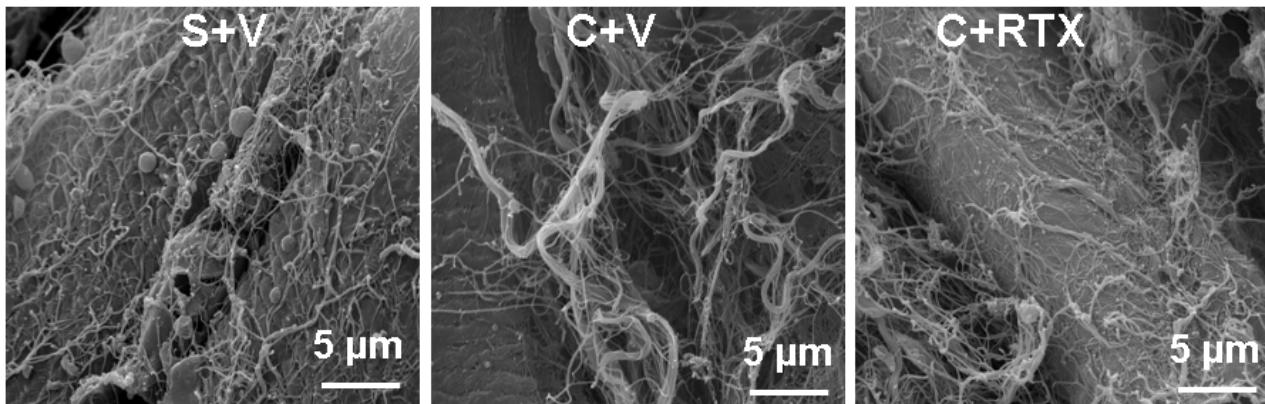
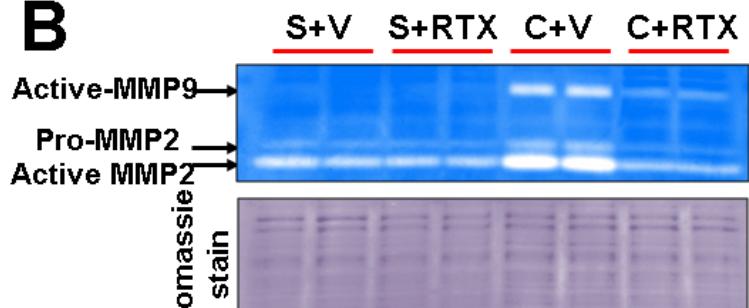




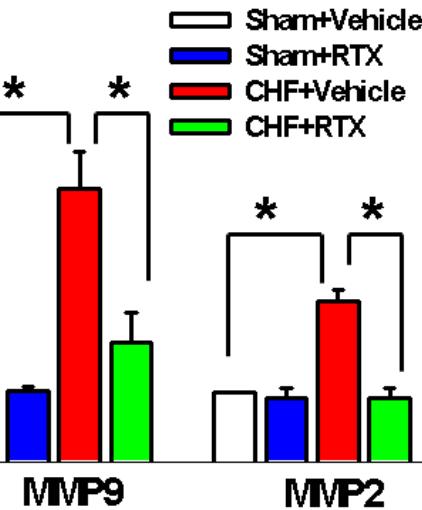
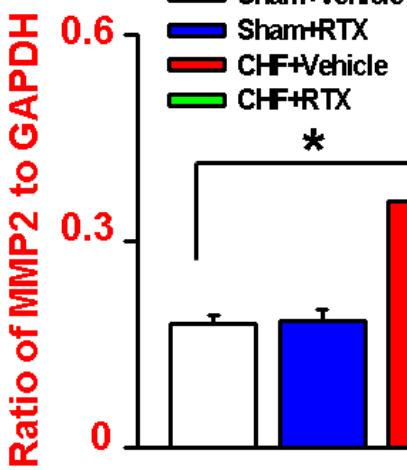
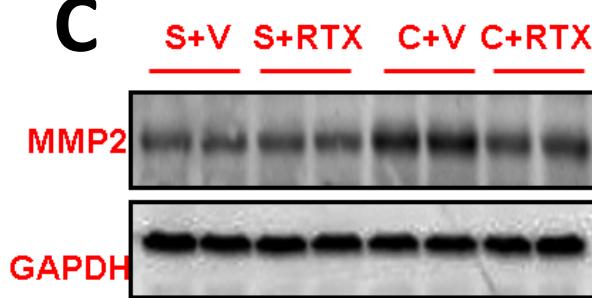
Hypothesis: Local CSAR afferent endings containing pro-inflammatory neuropeptides play a critical role in deleterious cardiac remodeling in CHF



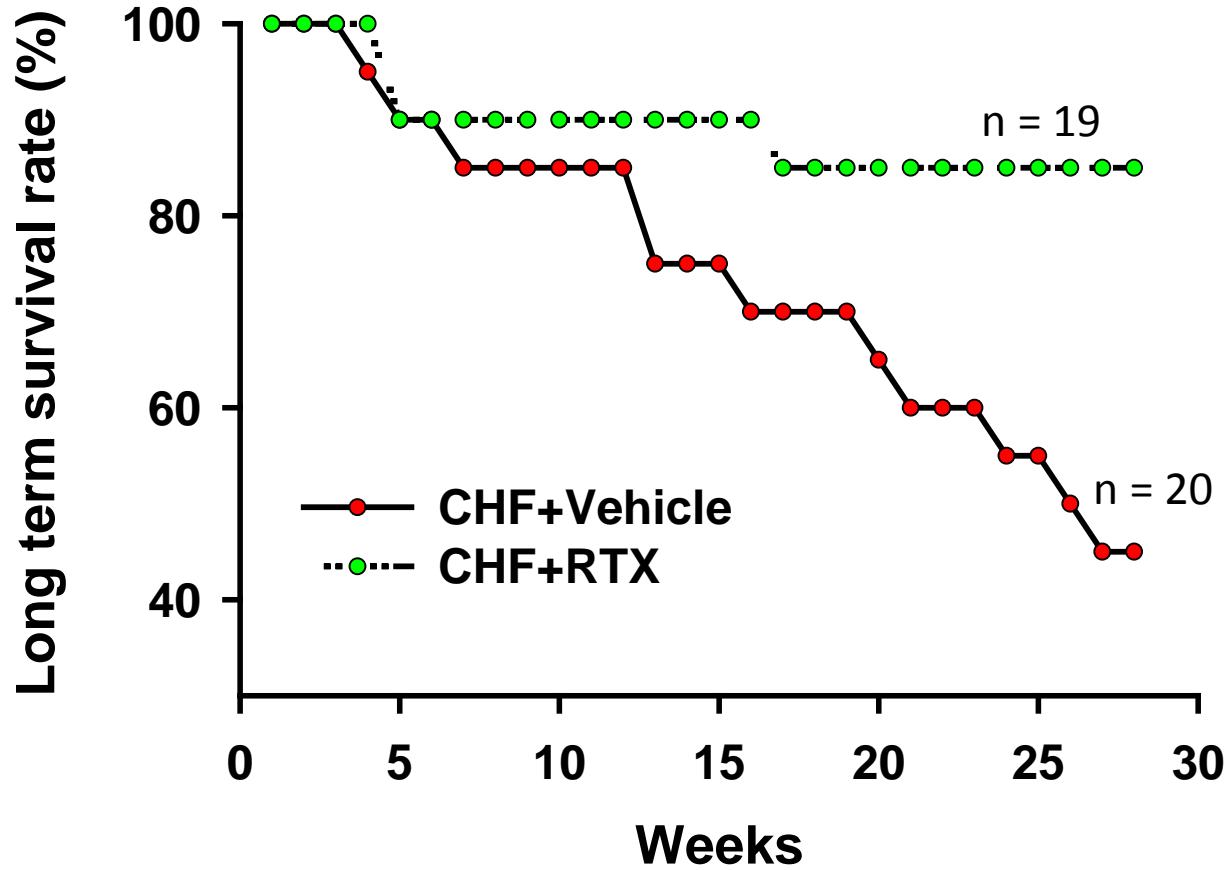


A**B**

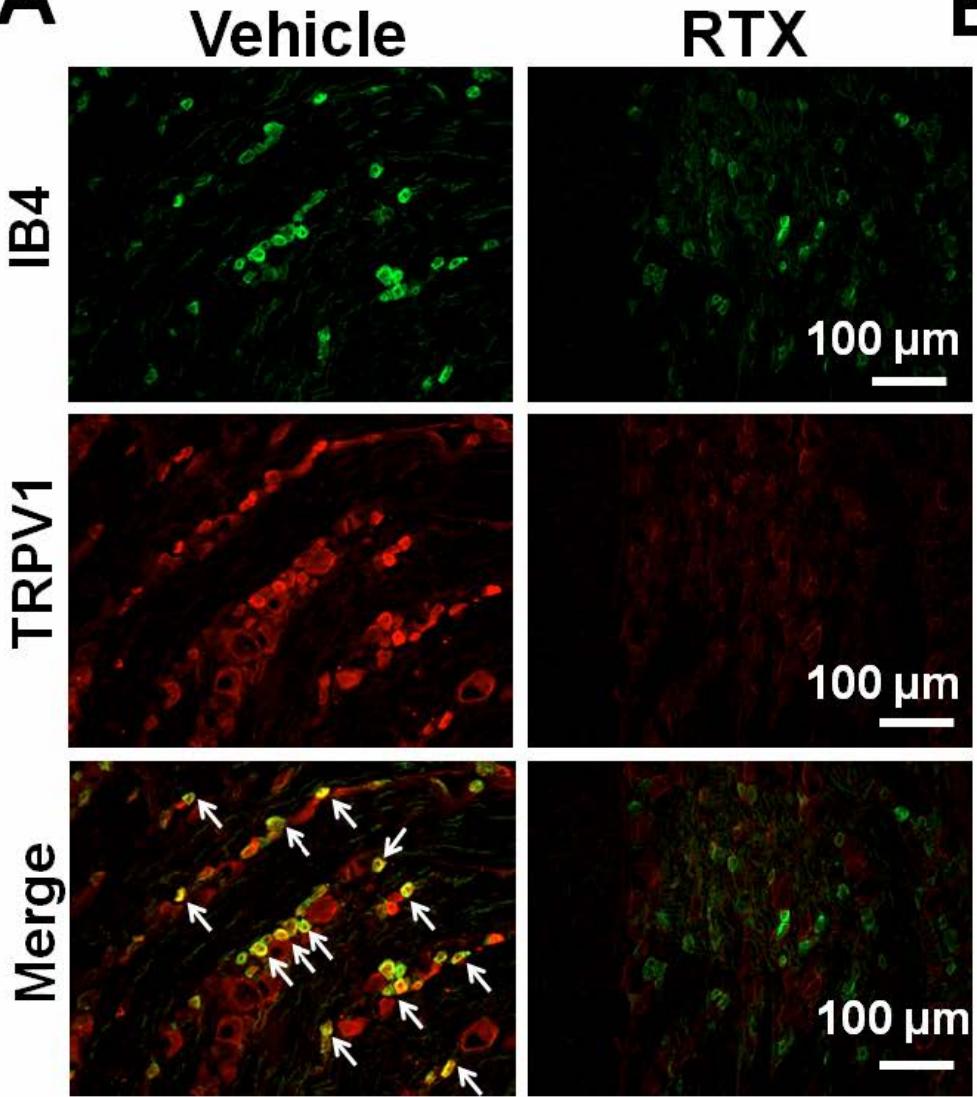
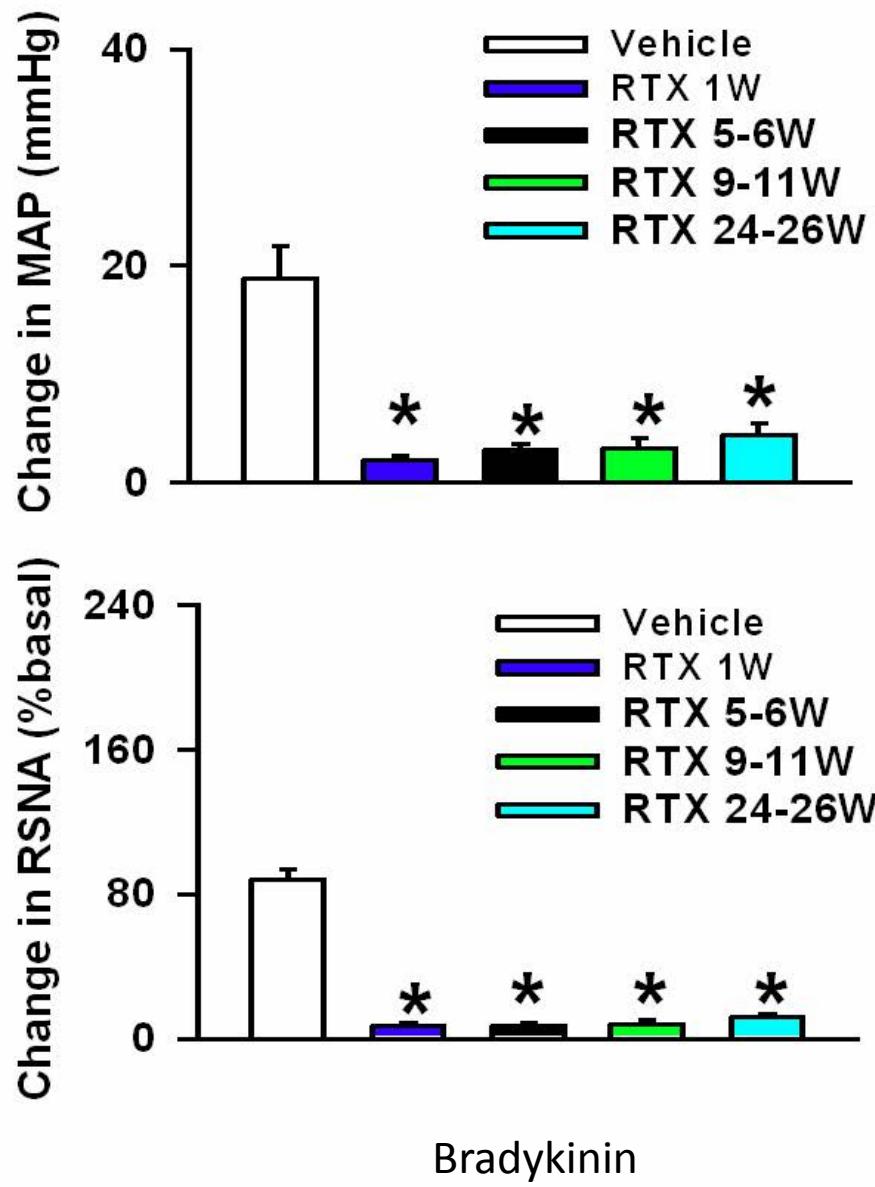
MMP 2 and MMP 9 activities
(Fold Change)

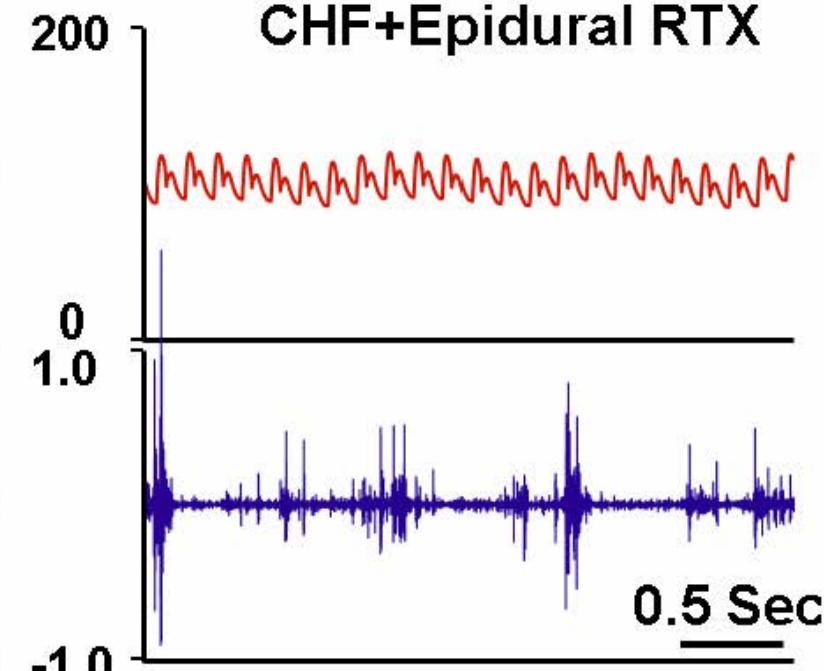
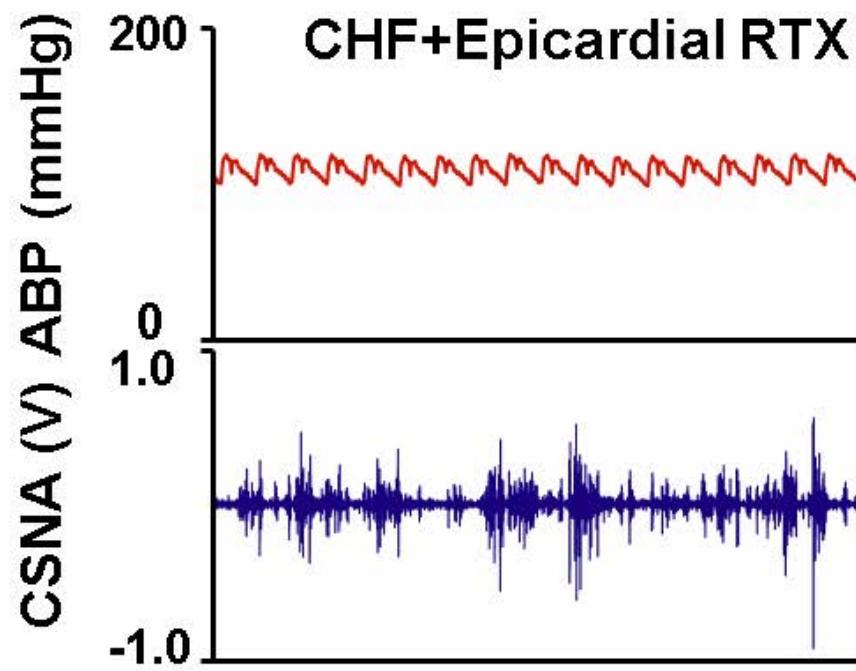
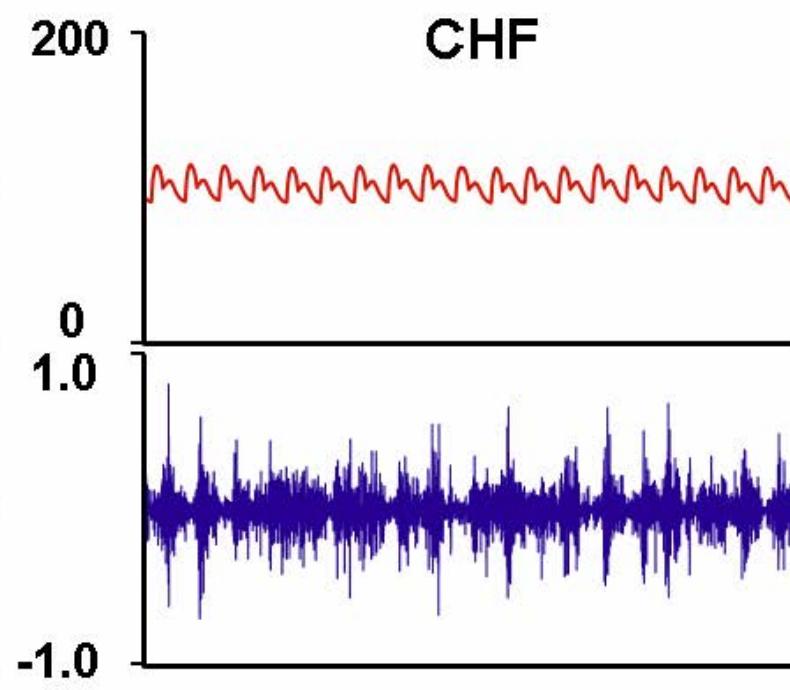
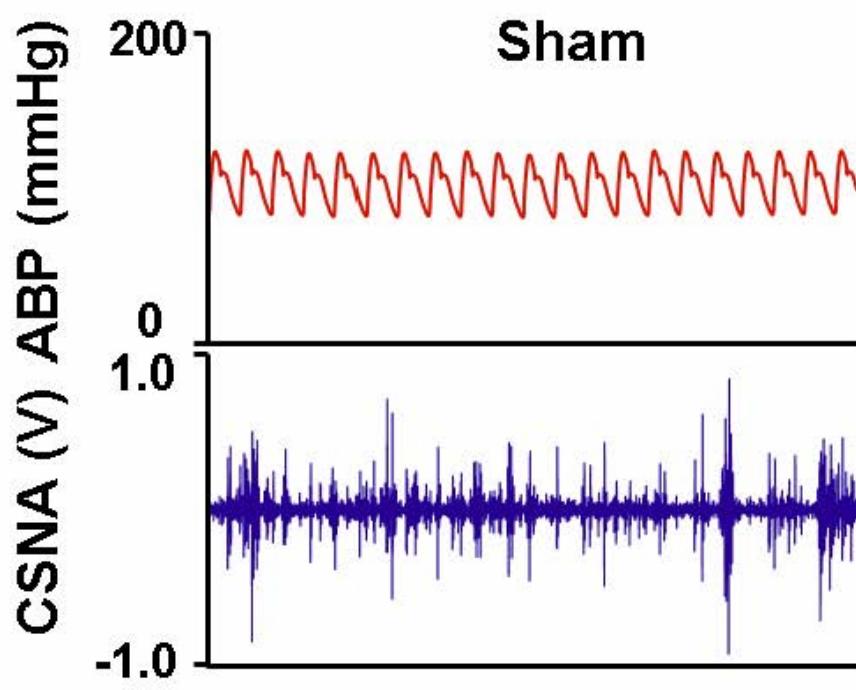
**C**

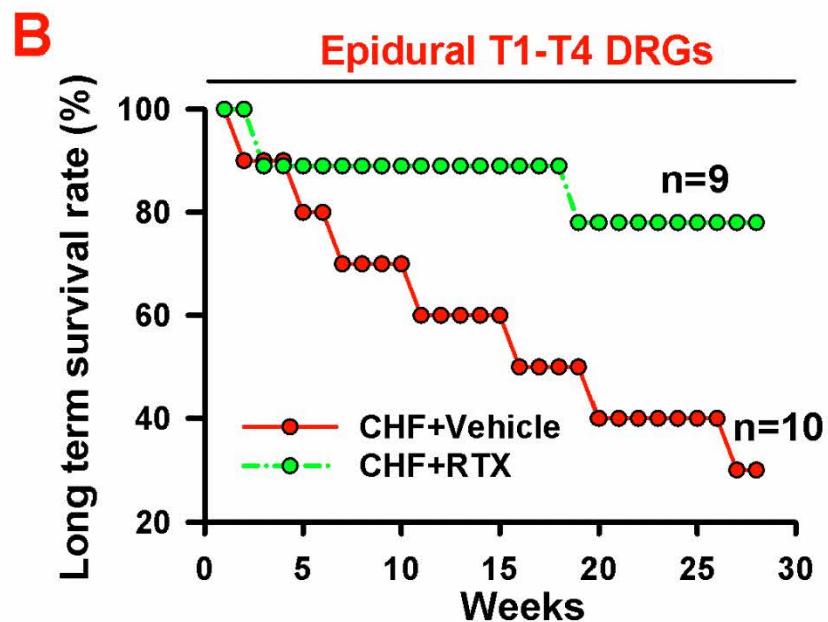
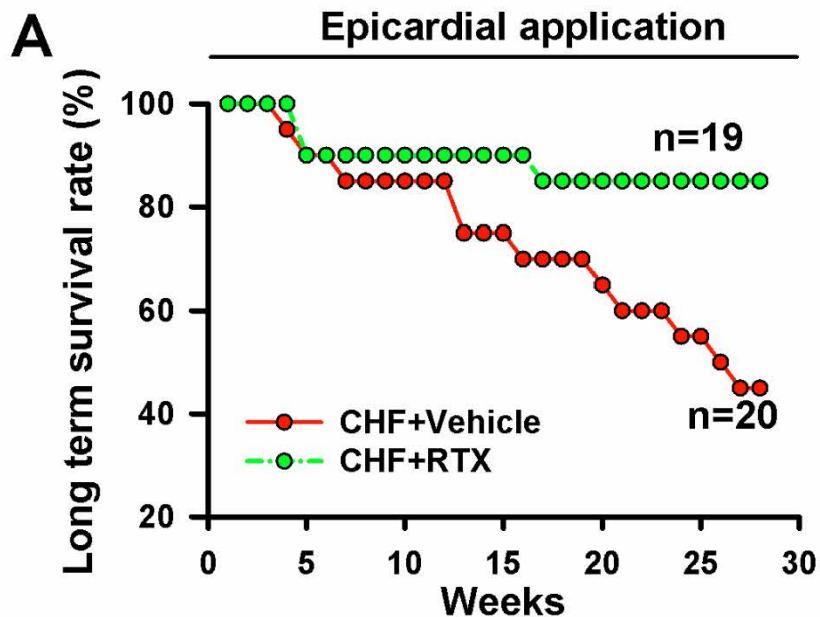
Survival

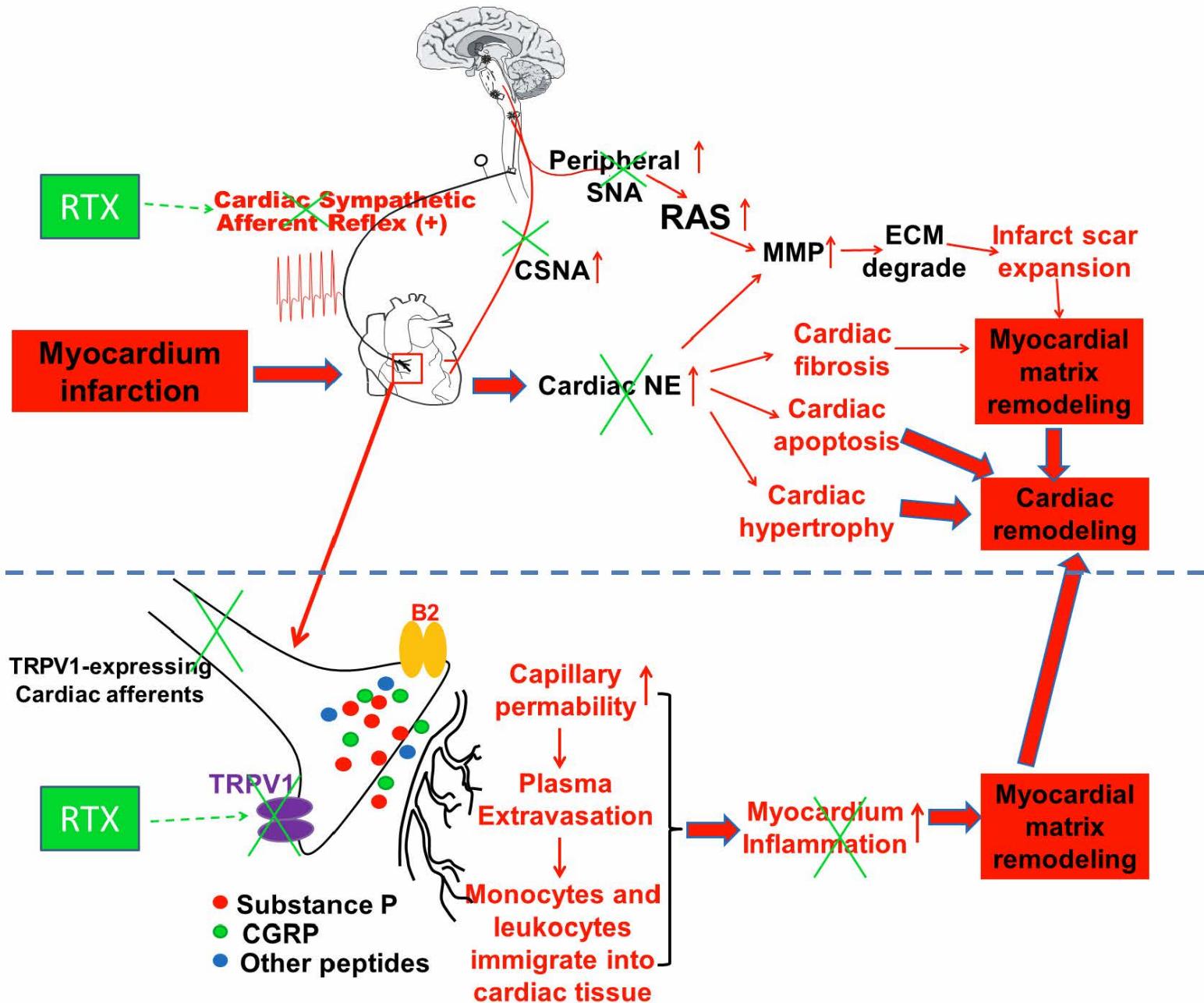


Epidural T1-T4 DRG application
of RTX

A**B**







Future Directions

Animal Models

- Ischemic
- Non-ischemic (cardiomyopathy)
- Diastolic Heart Failure (HFpEF)
- Large animal models (pig, dog)

Proof of Principle strategies

- Modulation of DRG neuronal activity
 - Channel Rhodopsin
 - Halo Rhodopsin
 - Substance P antagonism

Specificity

- Thoracic DRG
- Lumbar DRG
- Epicardial

Therapeutic windows

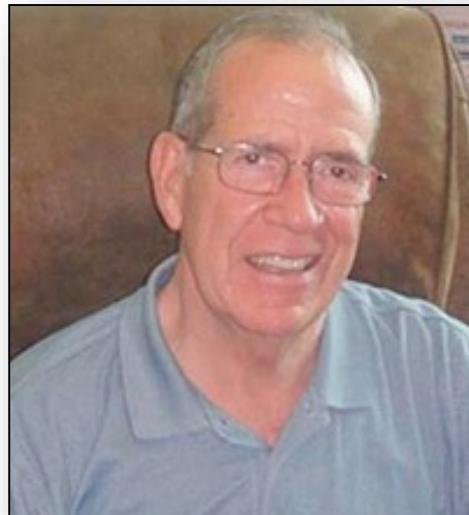
Mechanisms

- Central pathways mediating sympatho-excitation in response to sympathetic afferent activation.
- Molecular regulation of TRPV1 protein in DRG
- Cardiac sympathetic afferent activation and arrhythmogenesis
- Mechanisms of afferent neuropeptide regulation of cardiac remodeling
- Understanding of the “physiological role” of cardiac sympathetic afferents
- Autonomic regulation
- Permeability
- Inflammation
- Blood flow regulation

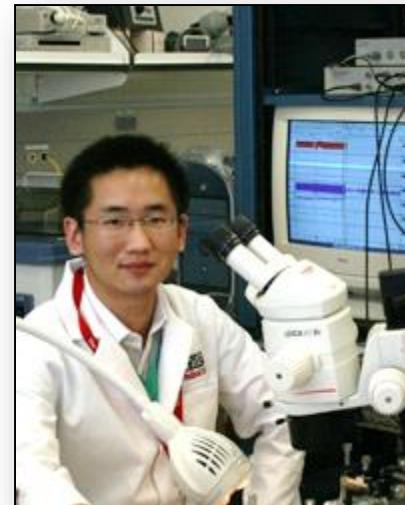
Clinical Studies

Acknowledgements

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Richard Robinson



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Hanjun Wang, M.D.



National Heart, Lung,
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Sorrento Therapeutics, Inc.



American Heart Association