Targeting the cardiac nervous system in treatment of heart disease

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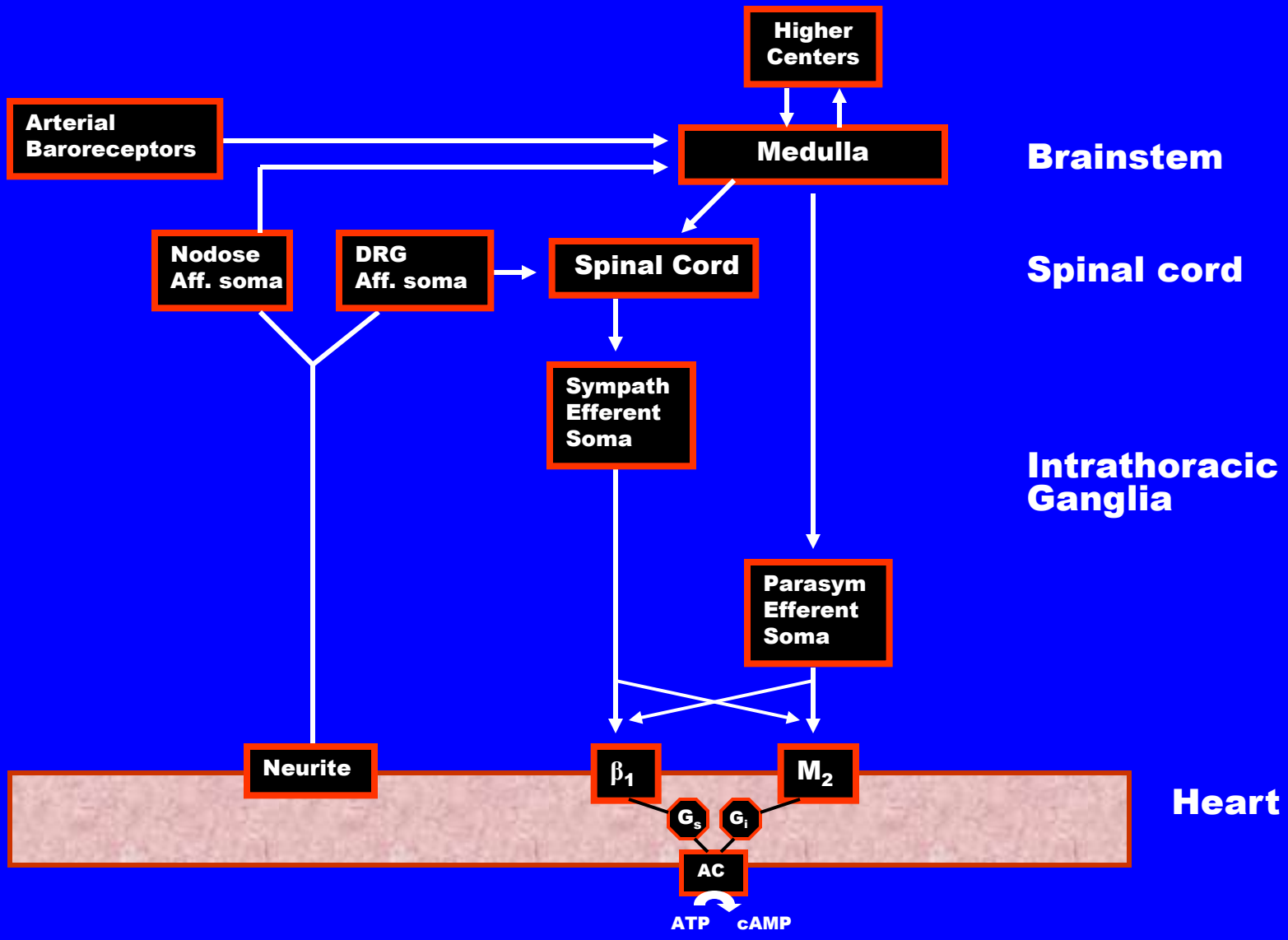
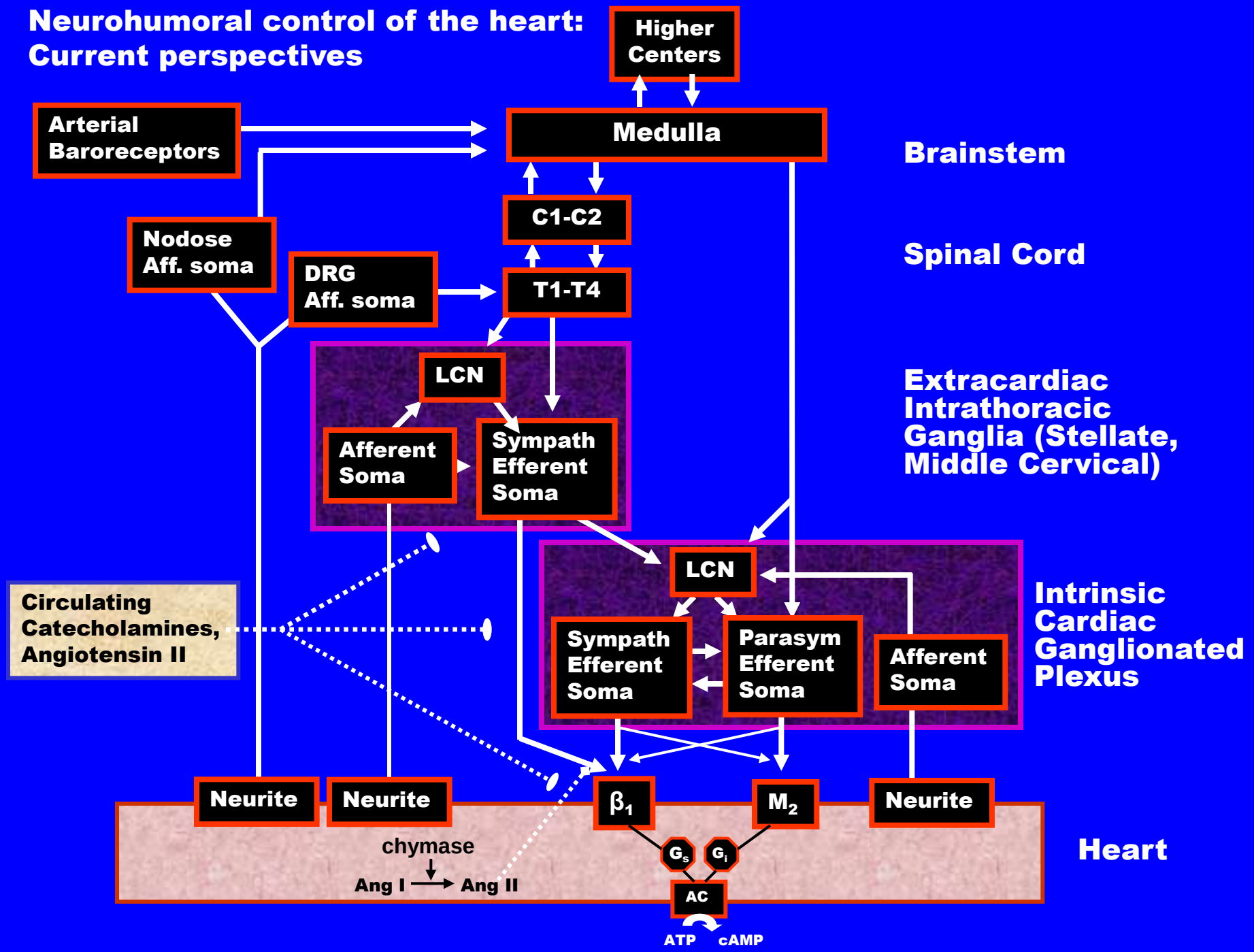
Background

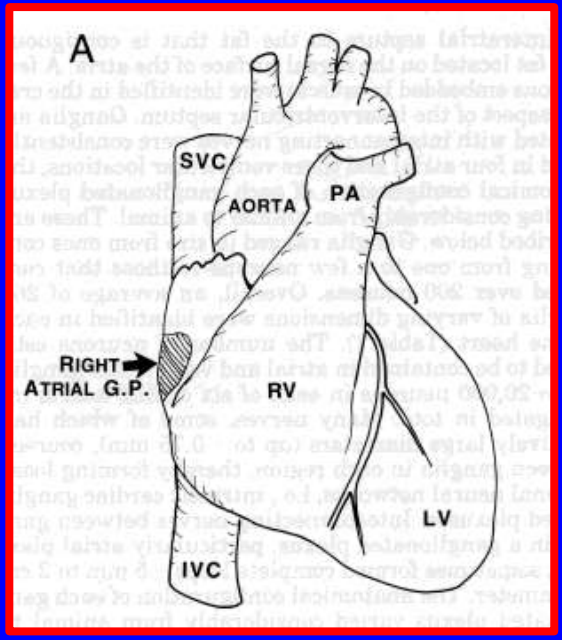
Neural control of regional cardiac function is dependent upon the interactive behavior of neurons within the intrathoracic autonomic neuronal hierarchy and those in the central nervous system. Local factors (hormones, metabolites, etc) act on this neuronal substrate.

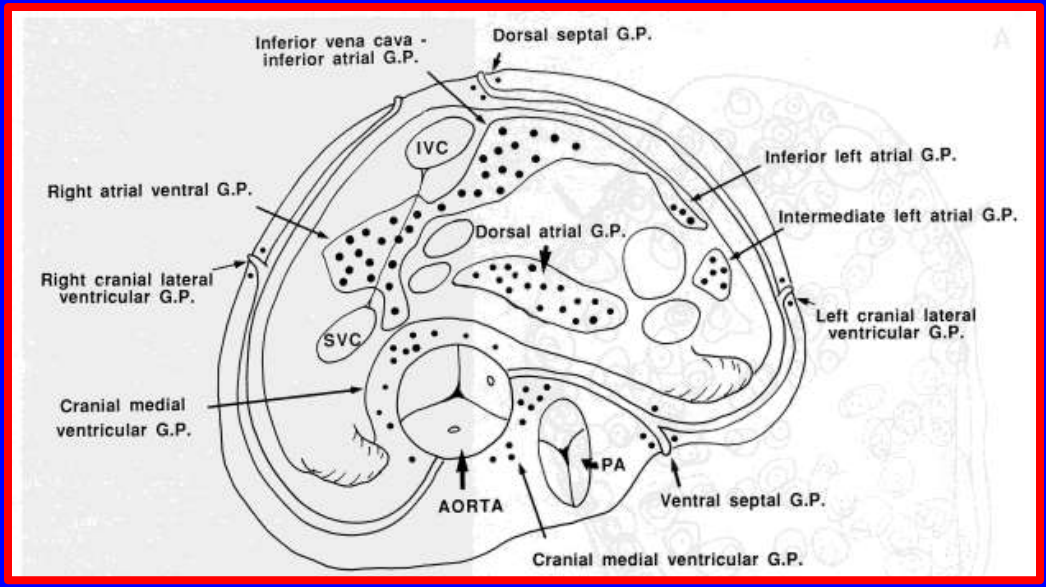
Neural Control of the heart: Historical perspective

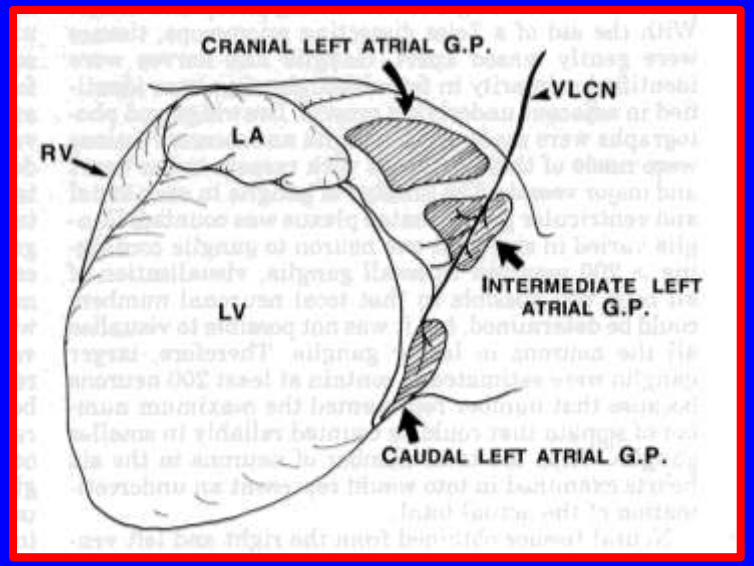



Neurohumoral control of the heart:
Current perspectives
Higher Centers
Arterial Baroreceptors
Medulla
Brainstem
C1-C2
Spinal Cord
Nodose Aff. soma
DRG Aff. soma
T1-T4
LCN
Afferent Soma
Sympath Efferent Soma
Extracardiac Intrathoracic Ganglia (Stellate, Middle Cervical)
Circulating Catecholamines, Angiotensin II
LCN
Sympath Efferent Soma
Parasym Efferent Soma
Afferent Soma
Intrinsic Cardiac Ganglionated Plexus
Neurite
Neurite
β1
M2
Neurite
chymase
Ang I
Ang II
Gs
Gi
AC
ATP
cAMP
Heart

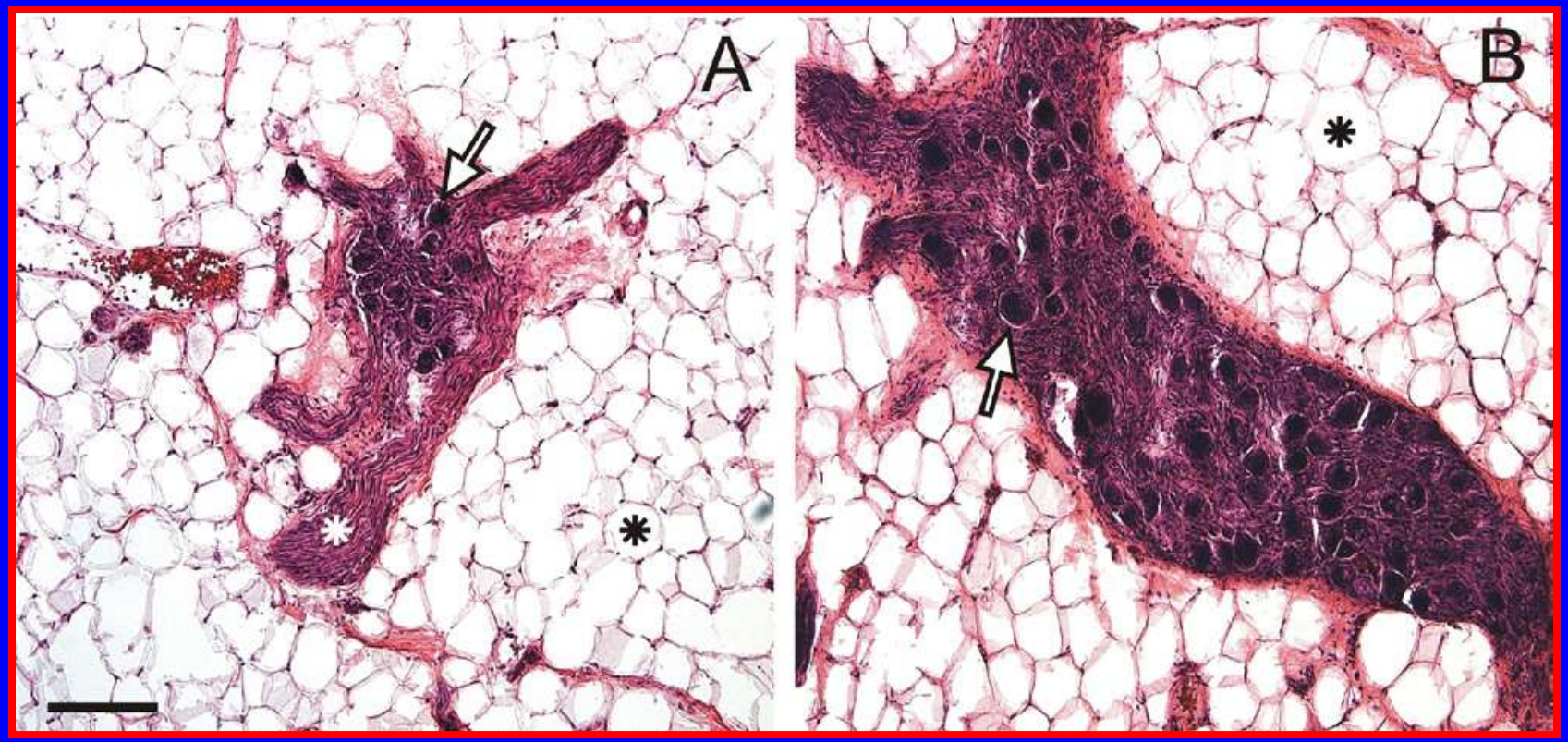
Location of aggregates of atrial and ventricular neurons contained within the intrinsic cardiac ganglionated plexus.





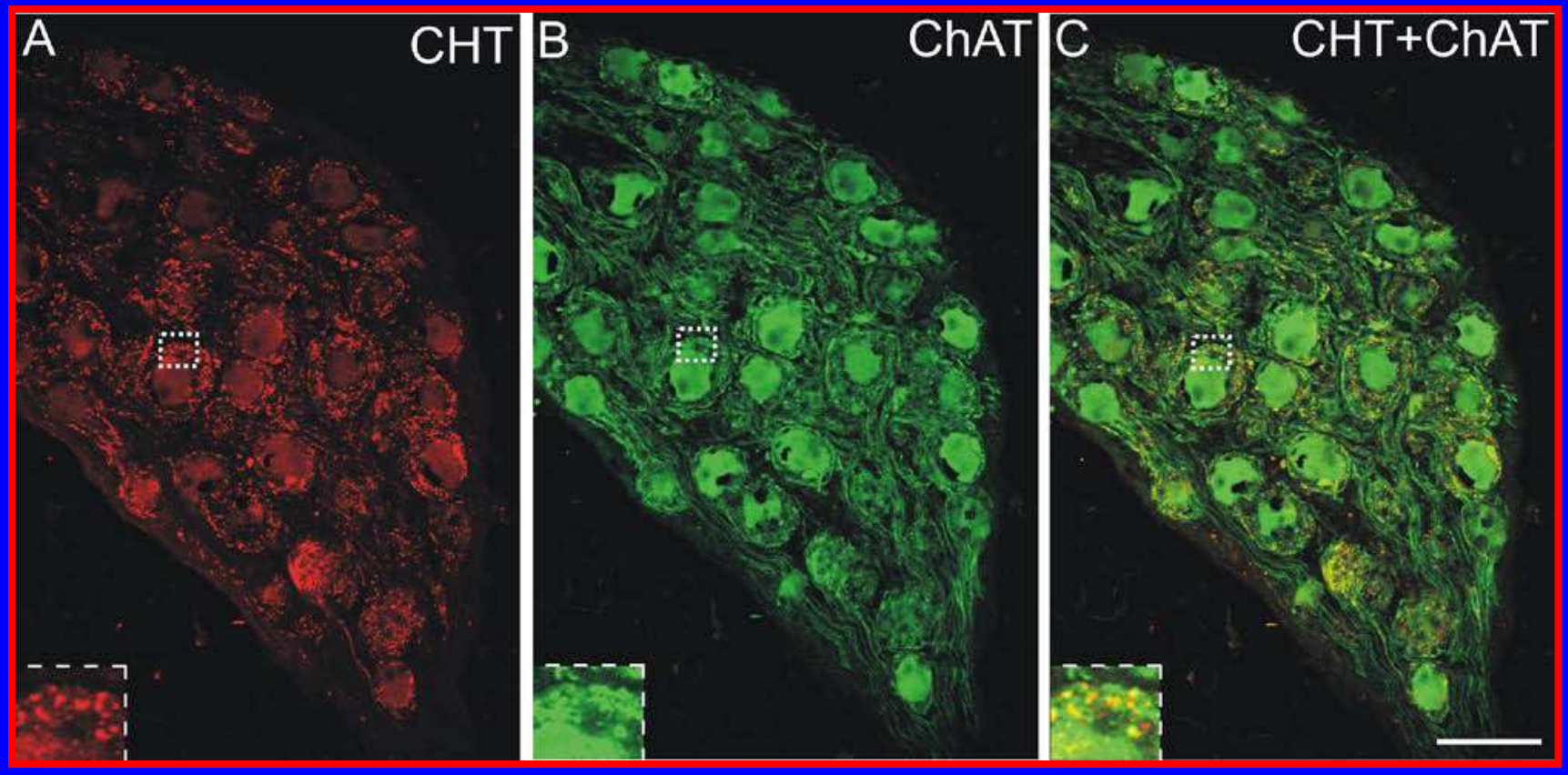


Intrinsic cardiac ganglia and nerve bundles are surrounded by adipose tissue



Hoover, et al, Neurosci, 164, 2009

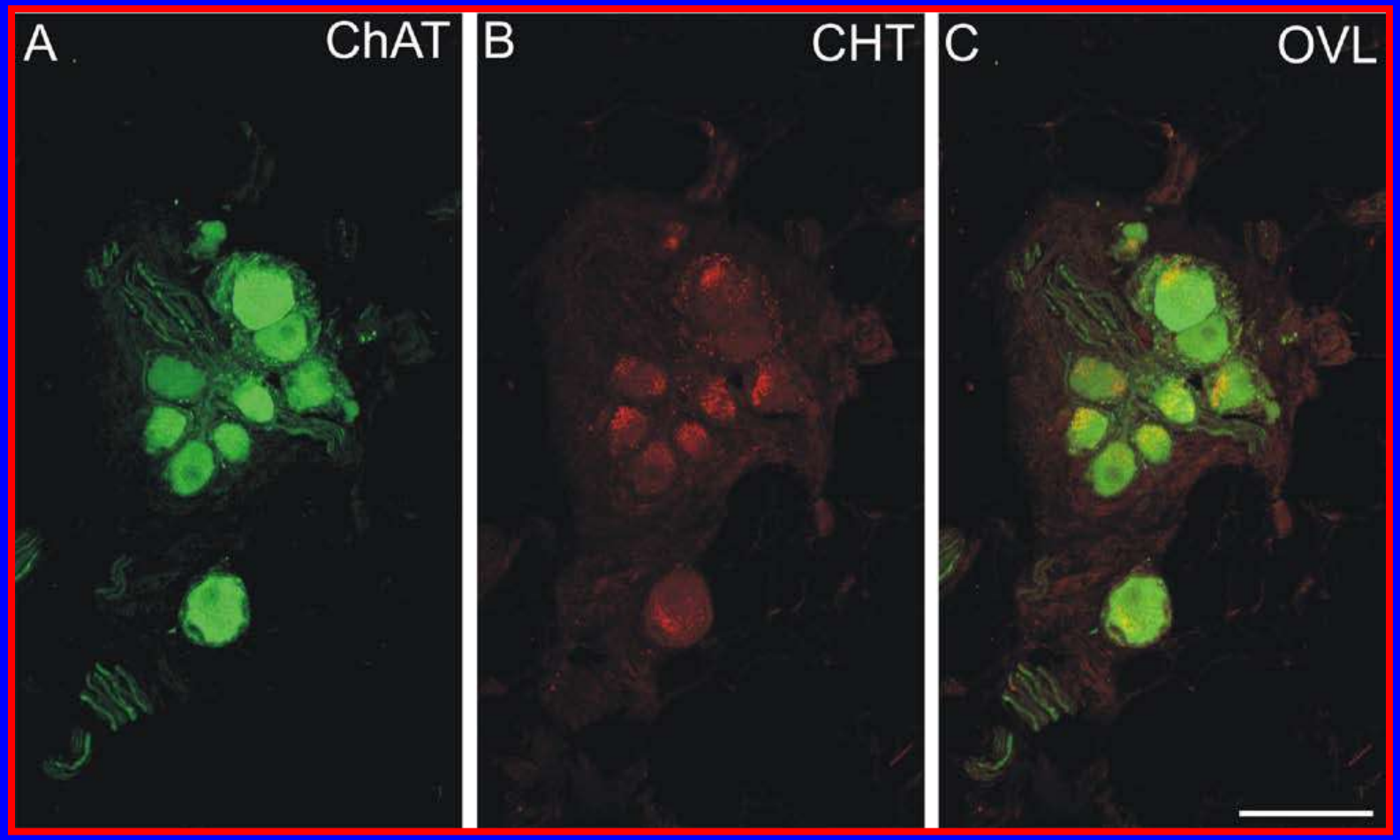
Human intrinsic cardiac neurons show the cholinergic phenotype and receive cholinergic input.



ChAT – choline acetyltransferase
CHT – high affinity choline transporter

Hoover, et al, Neurosci, 164, 2009

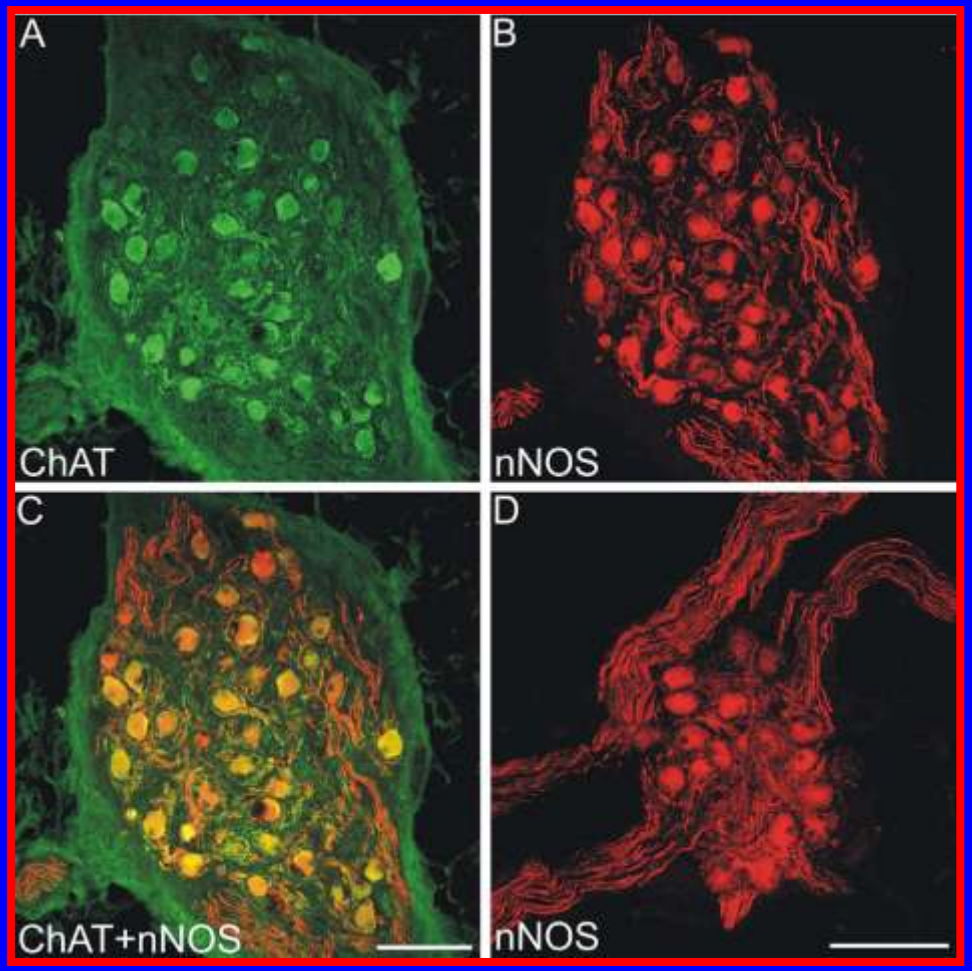
Some human intrinsic cholinergic neurons lack cholinergic inputs



ChAT – choline acetyltransferase
CHT – high affinity choline transporter

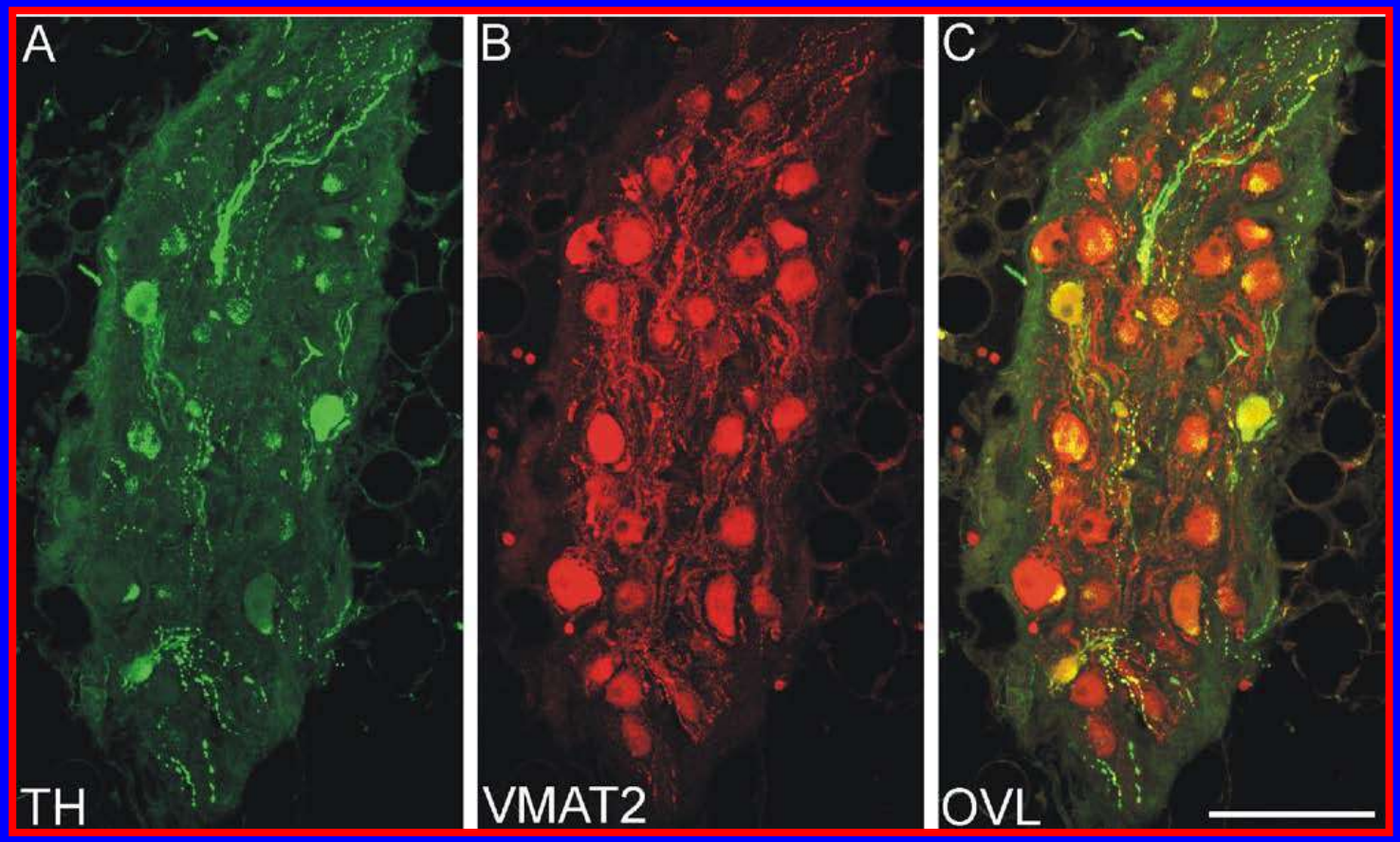
Hoover, et al, Neurosci, 164, 2009

Nitrergic marker nNOS is localized to most cholinergic neurons and to non-cholinergic nerve fibers within the human ICN ganglia and nerve bundles.



Hoover, et al, Neurosci, 164, 2009

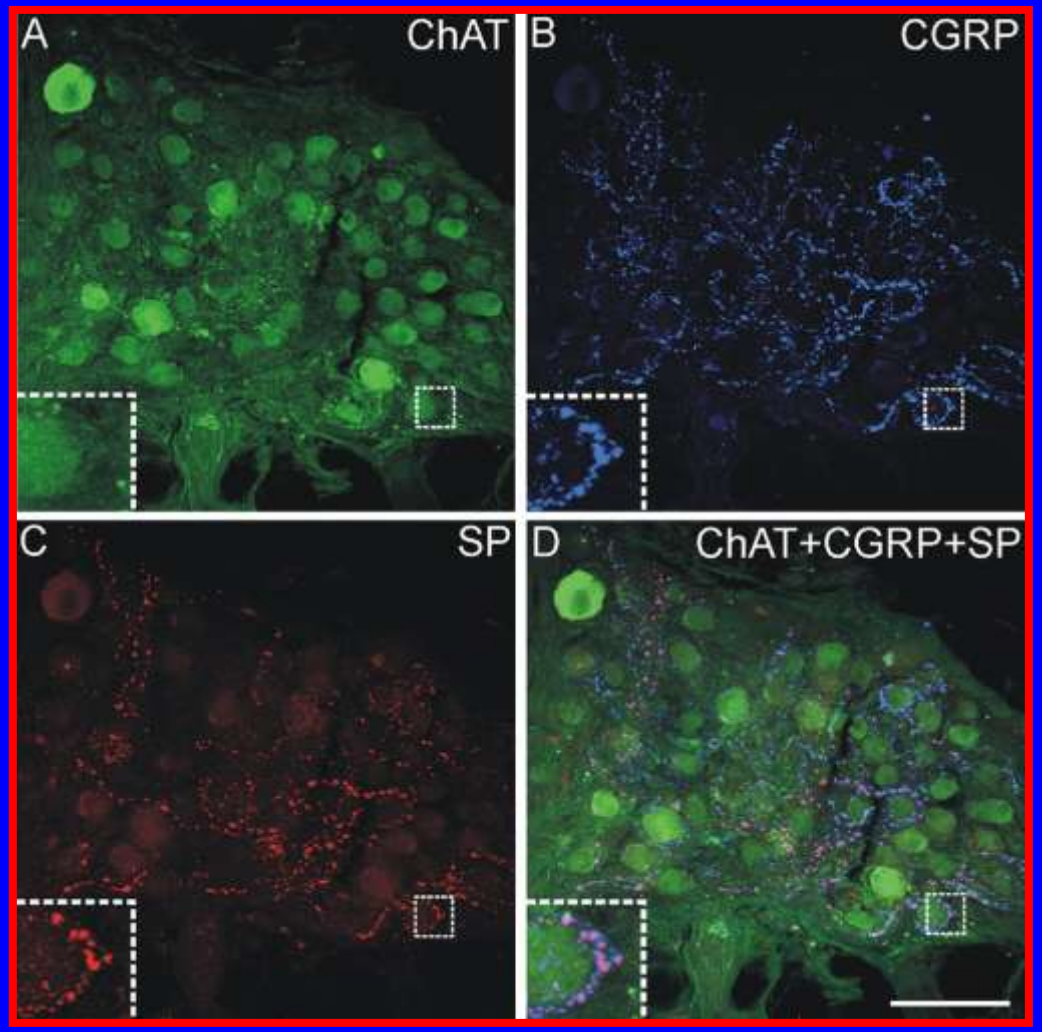
Subpopulations of human intrinsic cardiac neurons have the capacity to synthesize, store and release catecholamines



TH – tyrosine hydroxylase
VMAT2 – vesicular monamine transporter type 2

Hoover, et al, Neurosci, 164, 2009

Various neuropeptides are localized to nerve fibers innervating subpopulations of intrinsic cardiac neurons



Human tissue

ChAT – choline acetyltransferase
CGRP – calcitonin gene-related peptide
SP – substance P

Hoover, et al, Neurosci, 164, 2009

Conclusions

The intrinsic cardiac nervous system demonstrates a complex neurochemical anatomy.

Many of the intrinsic cardiac neurons receive dual cholinergic/nitrergic phenotype innervation.

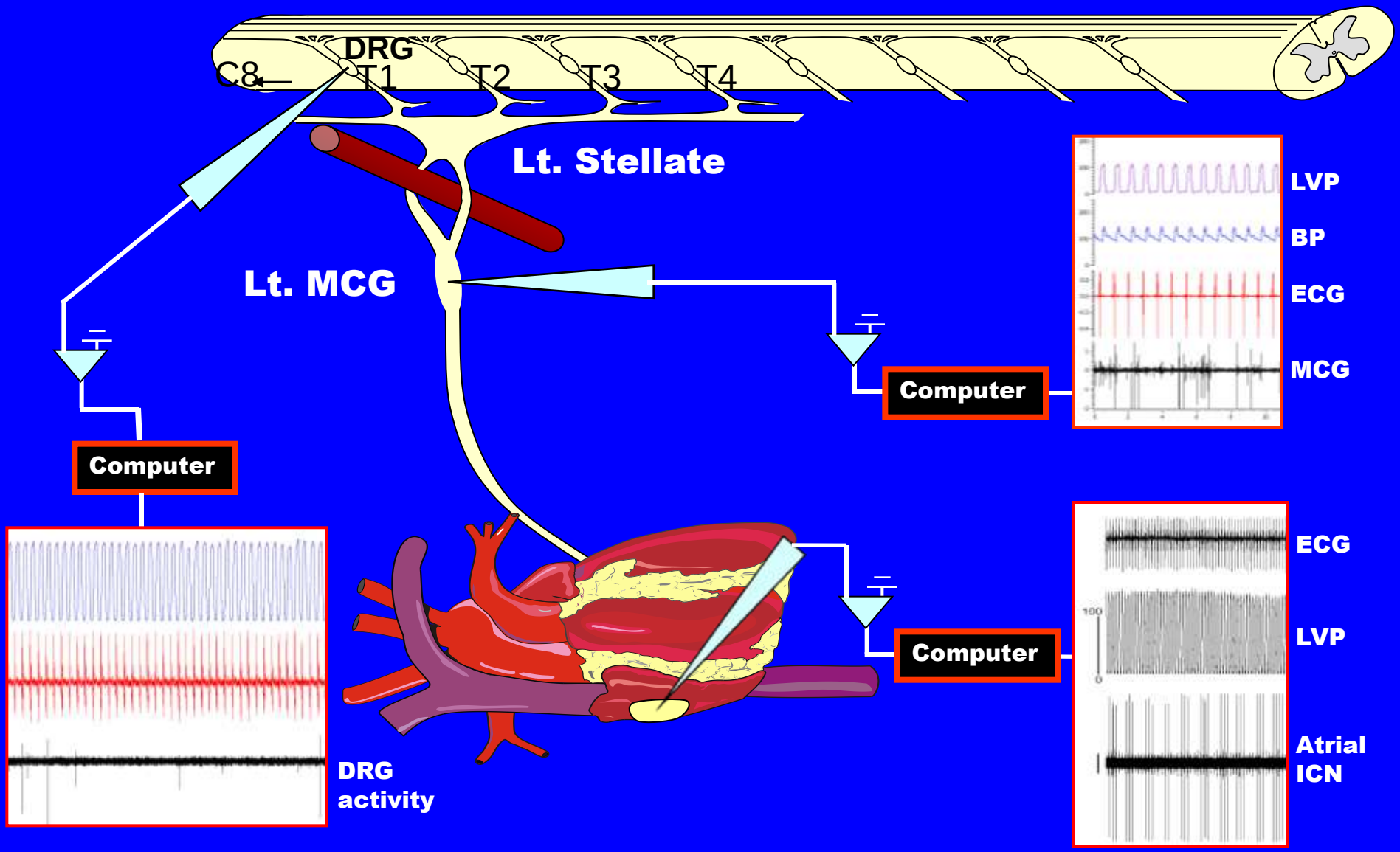
A subpopulation of intrinsic cardiac neurons exhibit an noradrenergic phenotype.

Intrinsic cardiac neurons are innervated a host of neurochemical distinct neurons.

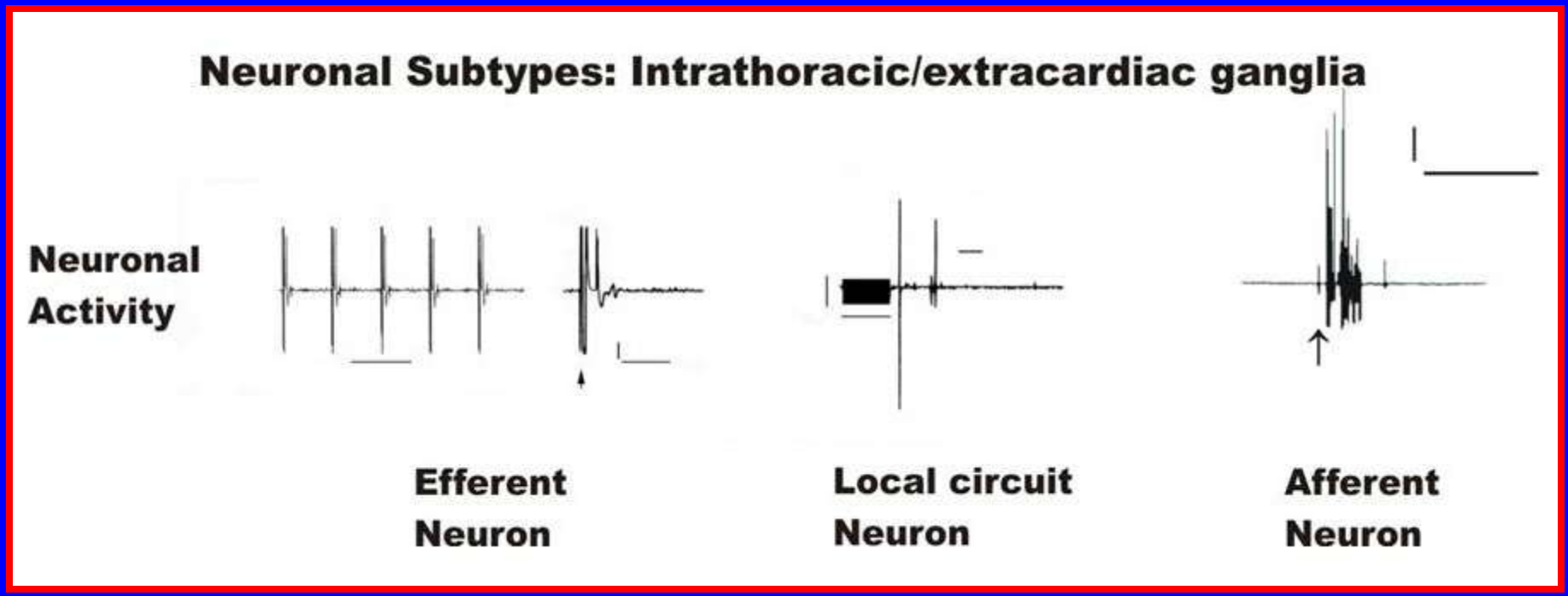
The actions of these multiple neurotransmitters in control of cardiac neurons and the heart tissues they innervate remodel with the progression of cardiac disease.

As such, the cardiac nervous system represents a novel target for management of the diseased heart.

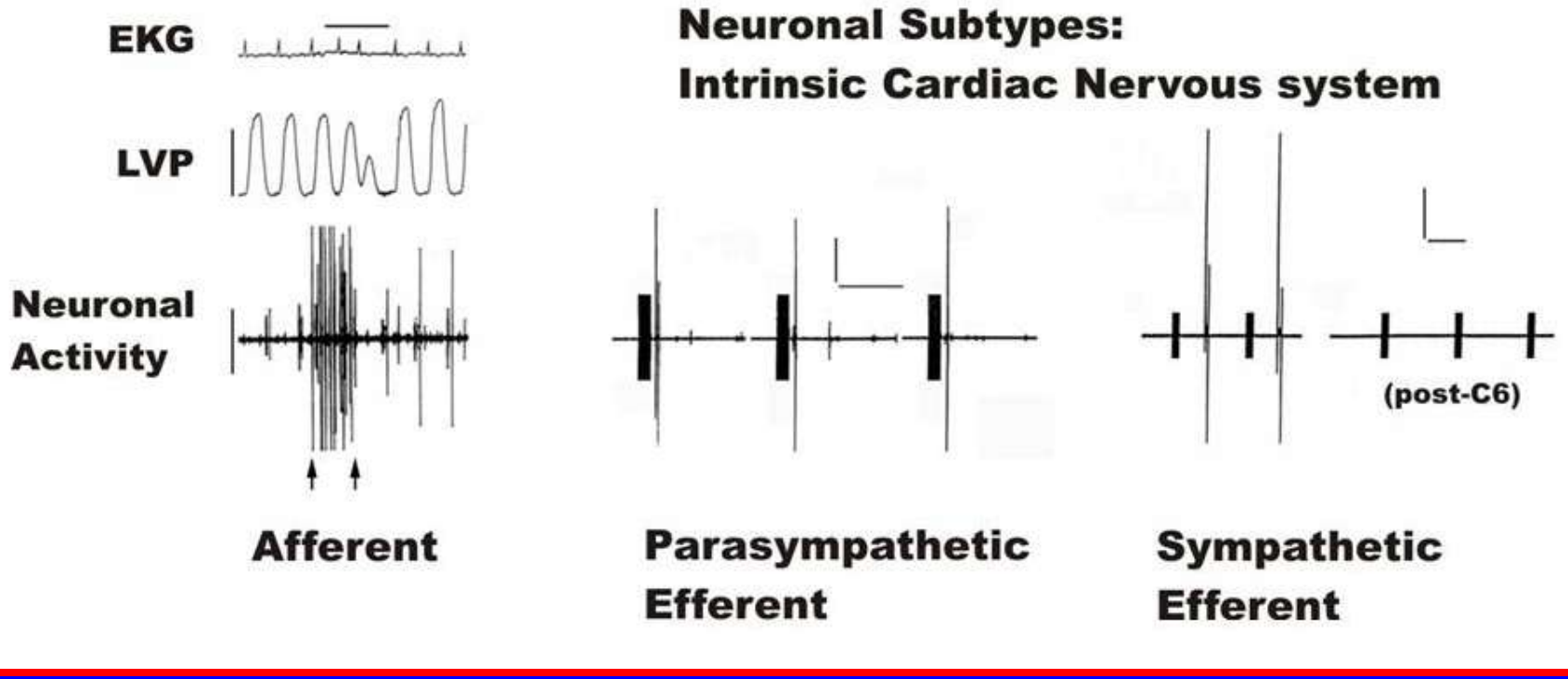
Neurophysiology methods



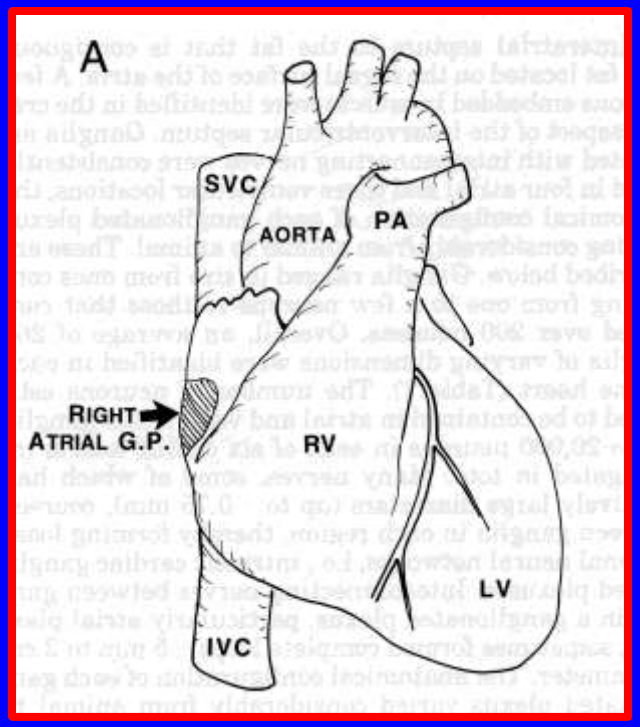
Intrathoracic autonomic ganglia are not passive relay stations. They are complex neural networks capable of reflex processing alone and in coordination with other levels of the cardiac nervous system.

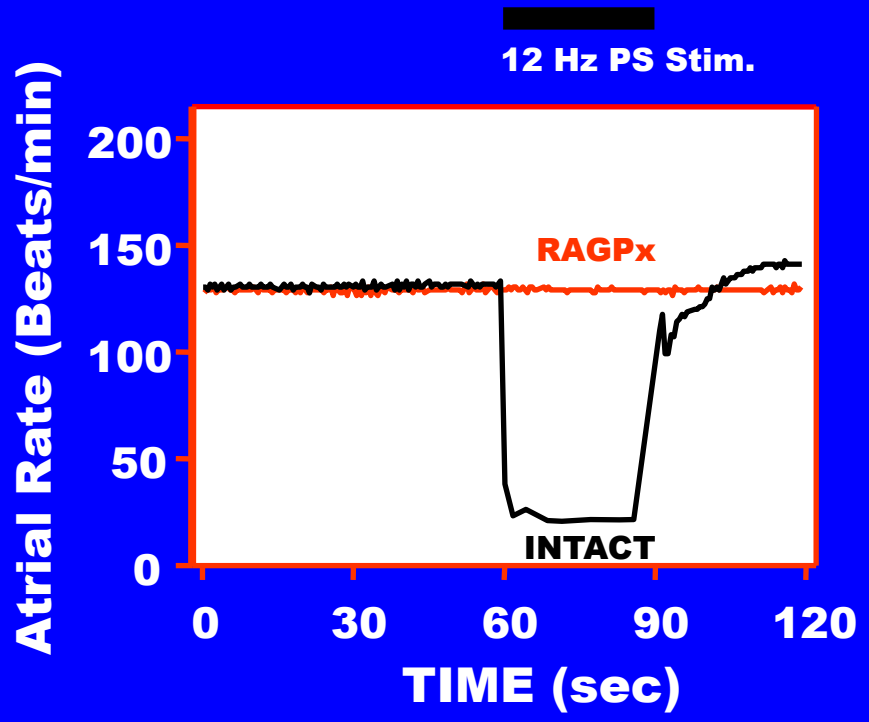


The intrinsic cardiac nervous system provides the foundation for reflex control (and coordination) of regional cardiac function

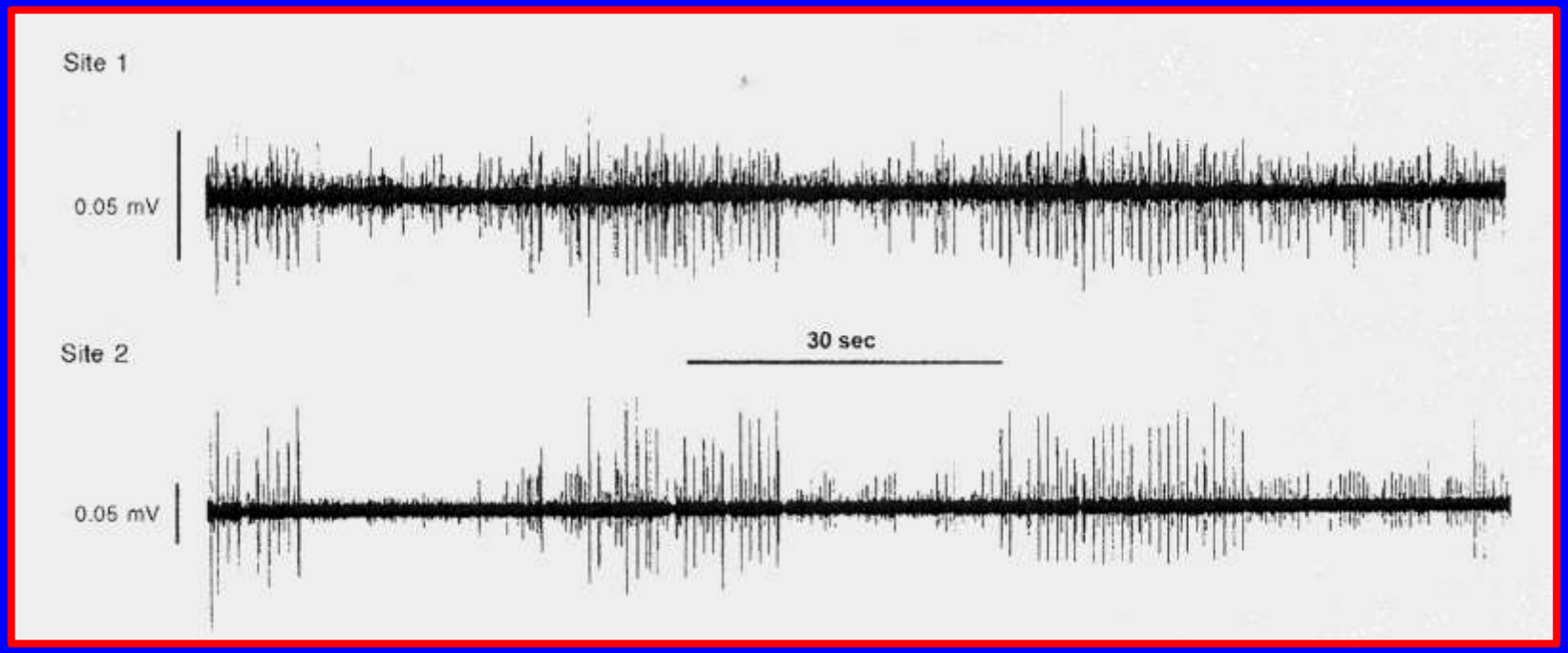


Functional interdependence of neurons contained within a single intrinsic cardiac ganglionated plexus



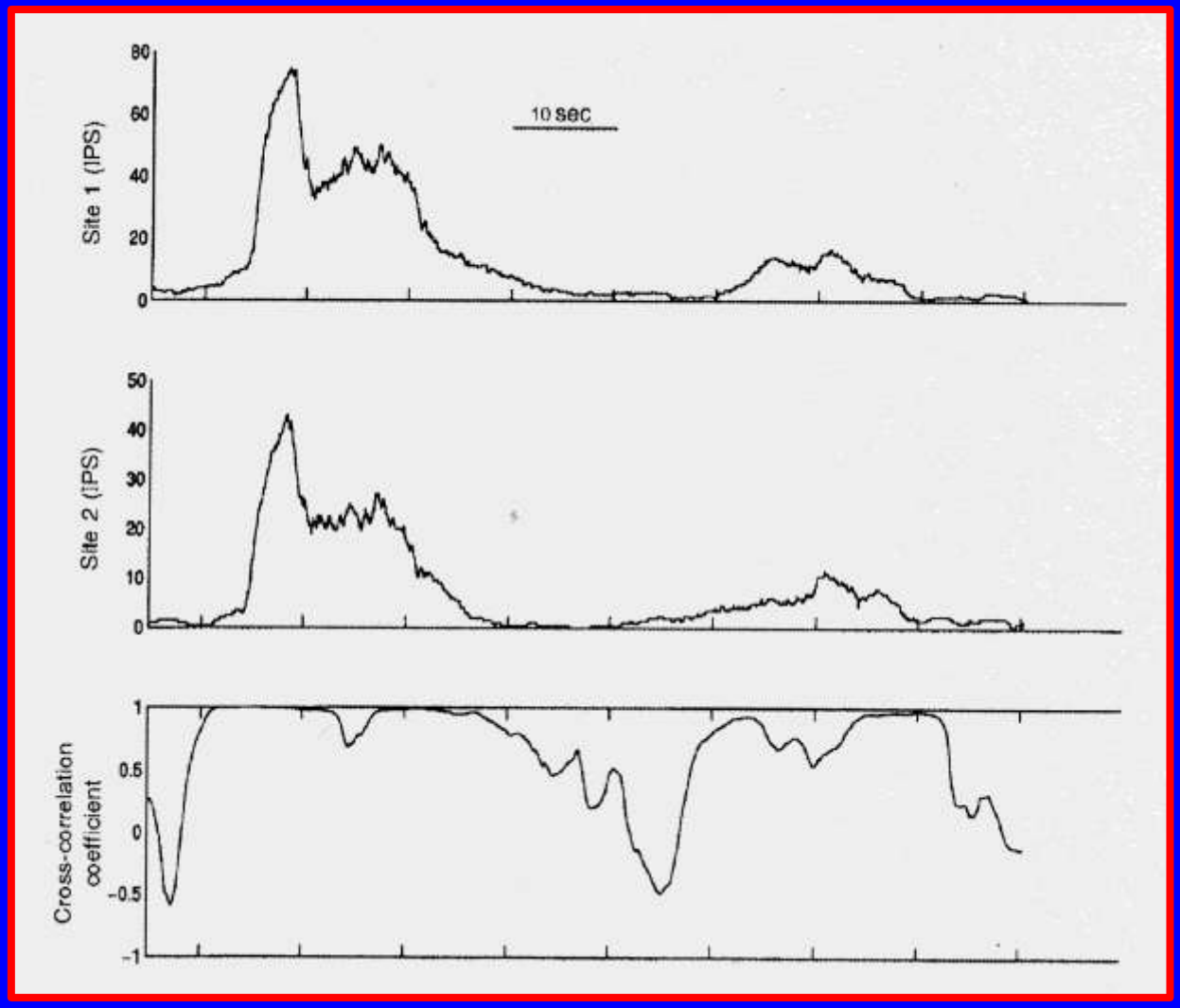


Spontaneous activity recorded from two different populations of intrinsic cardiac neurons contained within a single cardiac ganglia

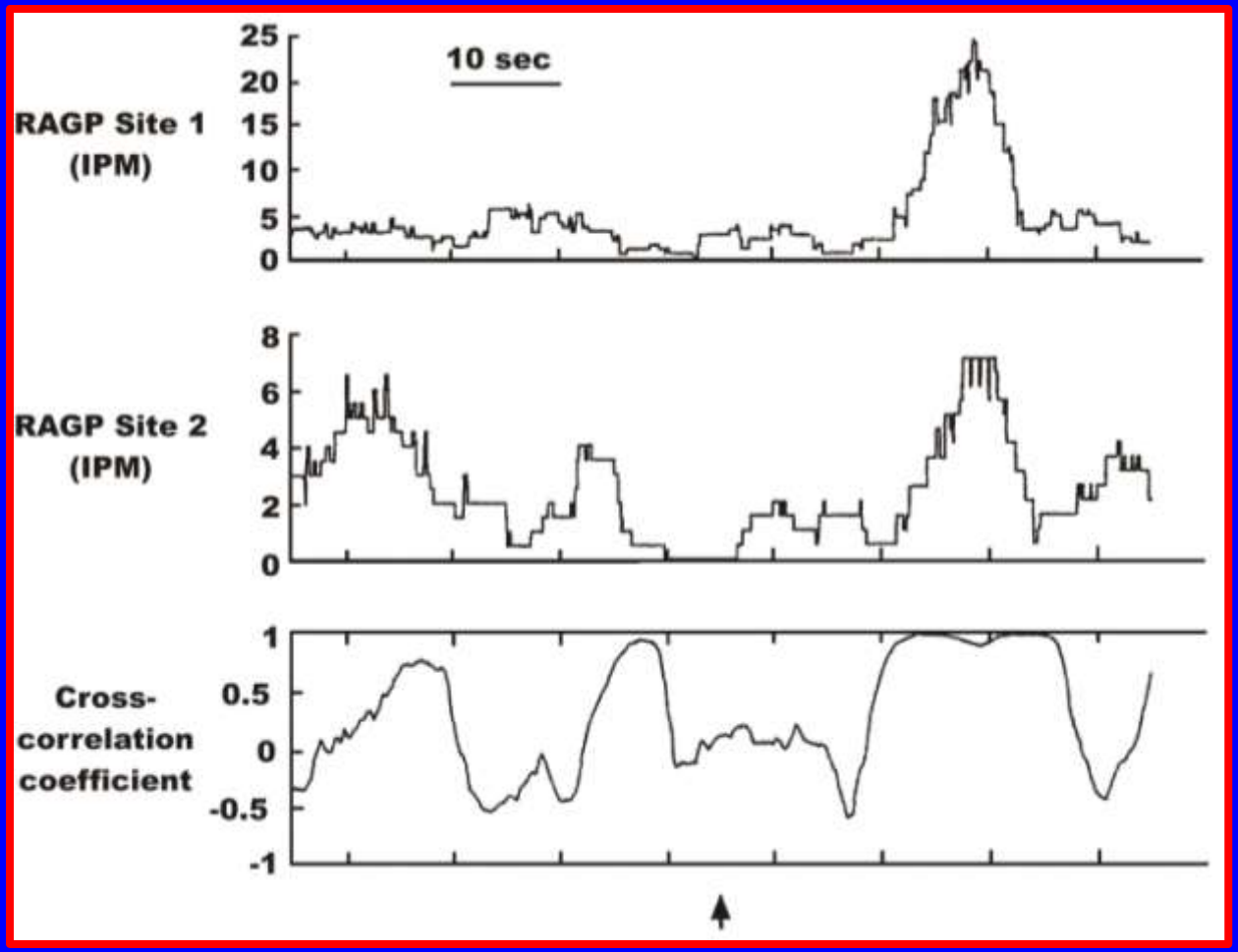


Note cyclic nature of spontaneous activity that is “in phase”.

Separate populations of neurons within one intrinsic cardiac ganglia can exhibit coherent activity



Activation of inputs to a given intrinsic cardiac ganglia can enhance coherence of activity



Veratridine to RV
sinus epicardium

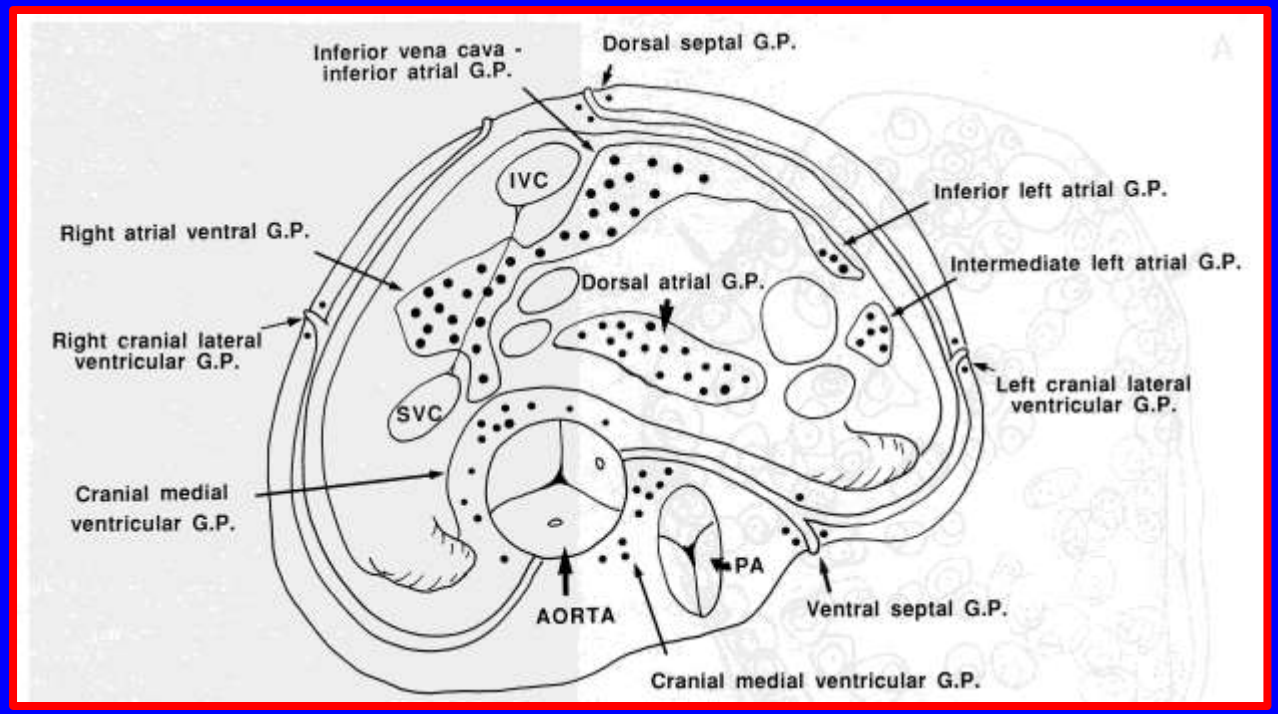
Conclusions

For neurons within a single intrinsic cardiac ganglionated plexus, coordination of activity depends upon

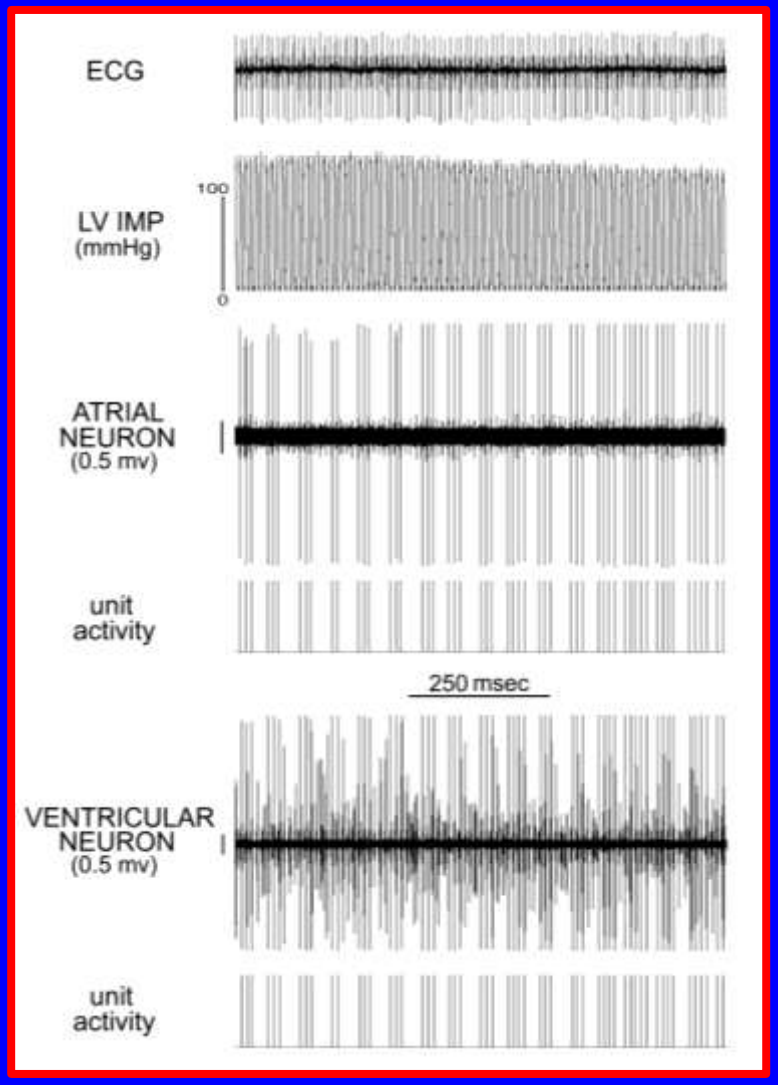
1. Descending projections from higher centers
2. Common shared afferent inputs
3. Intraganglionic network interactions mediated via local circuit neurons

Such neural interactions form the basis for integrated control of regional cardiac control.

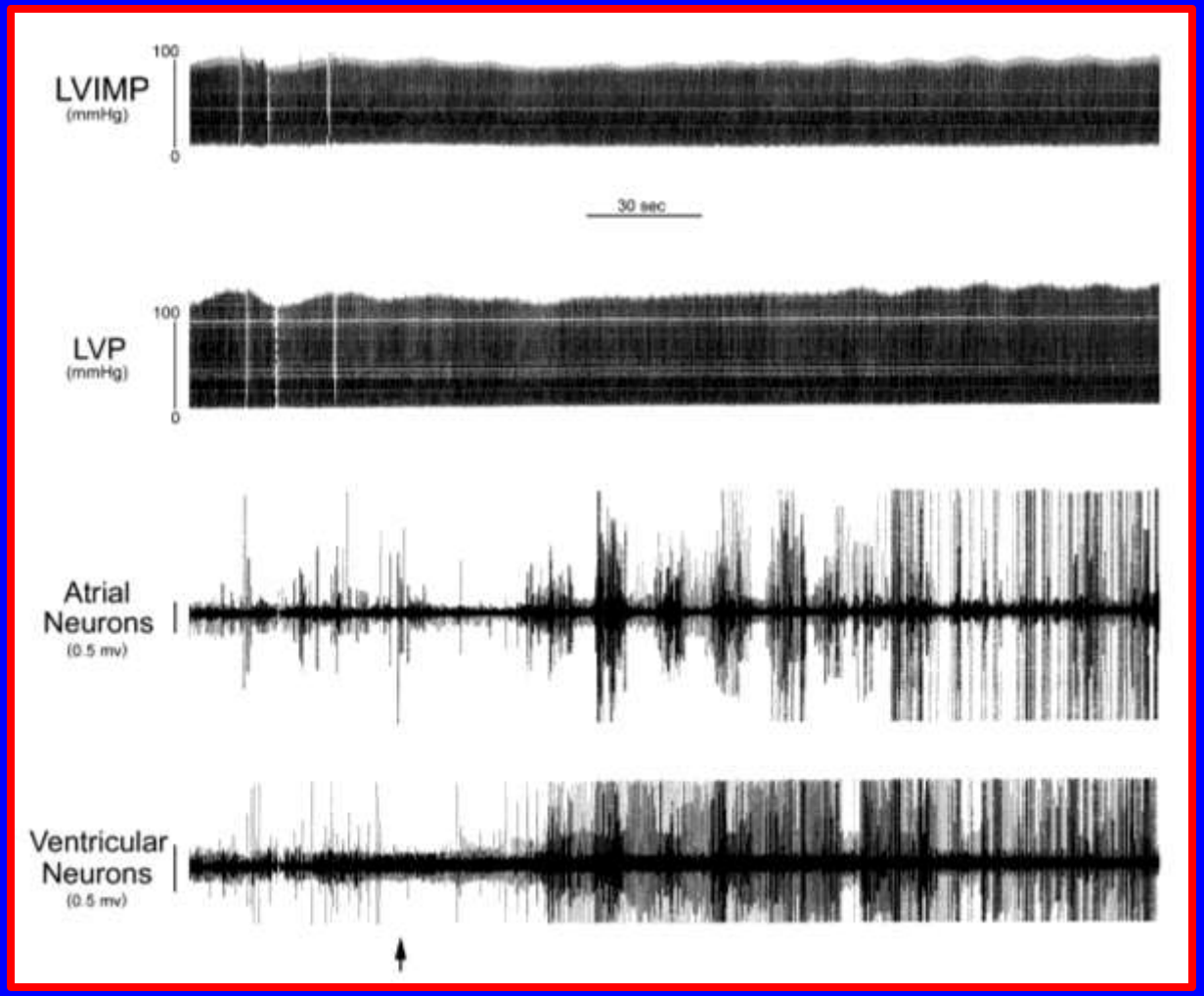
Stochastic behavior of neurons in separate (atrial and ventricular) intrinsic cardiac ganglia



Between separate intrinsic cardiac ganglia, a small subpopulation of mechano-sensitive neurons demonstrate tightly coupled activity



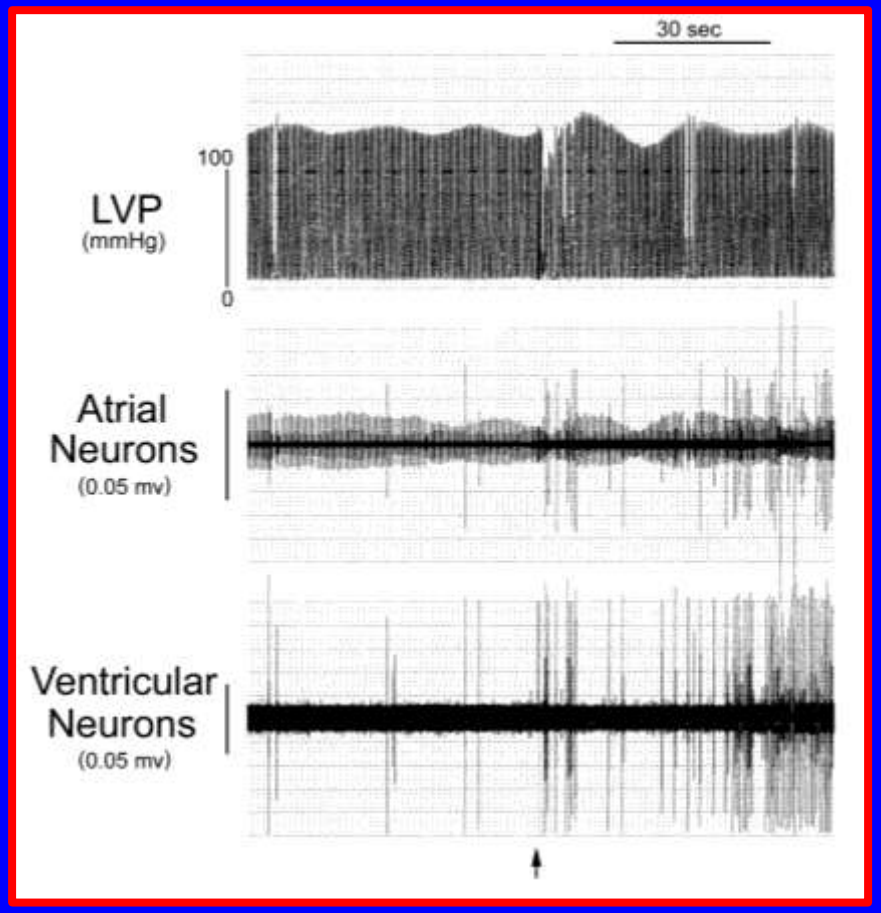
Majority of atrial and ventricular neurons transduce multimodal stimuli to display stochastic behavior



Bradykinin (LV epicardium)

Cross-correlation coefficient, r = .21

Stochastic behavior between separate population of intrinsic cardiac neurons is likewise evident in reflex response to endogenous stressors

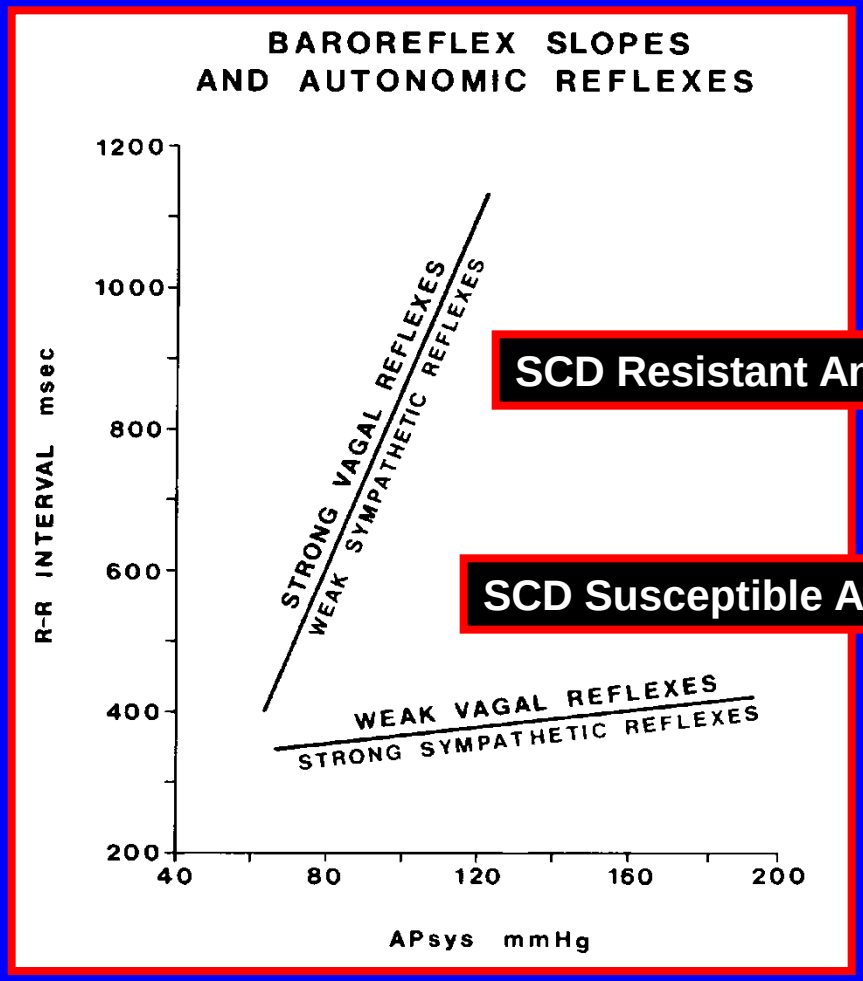


Occlude Left Anterior Descending coronary artery

Acute myocardial ischemia and the cardiac nervous system

Background

There are inherent and acquired differences within the cardiac nervous system that impact on the transduction of myocardial ischemia/infarction to affect risk for cardiac mortality post-MI.



SCD Resistant Animals

SCD Susceptible Animals

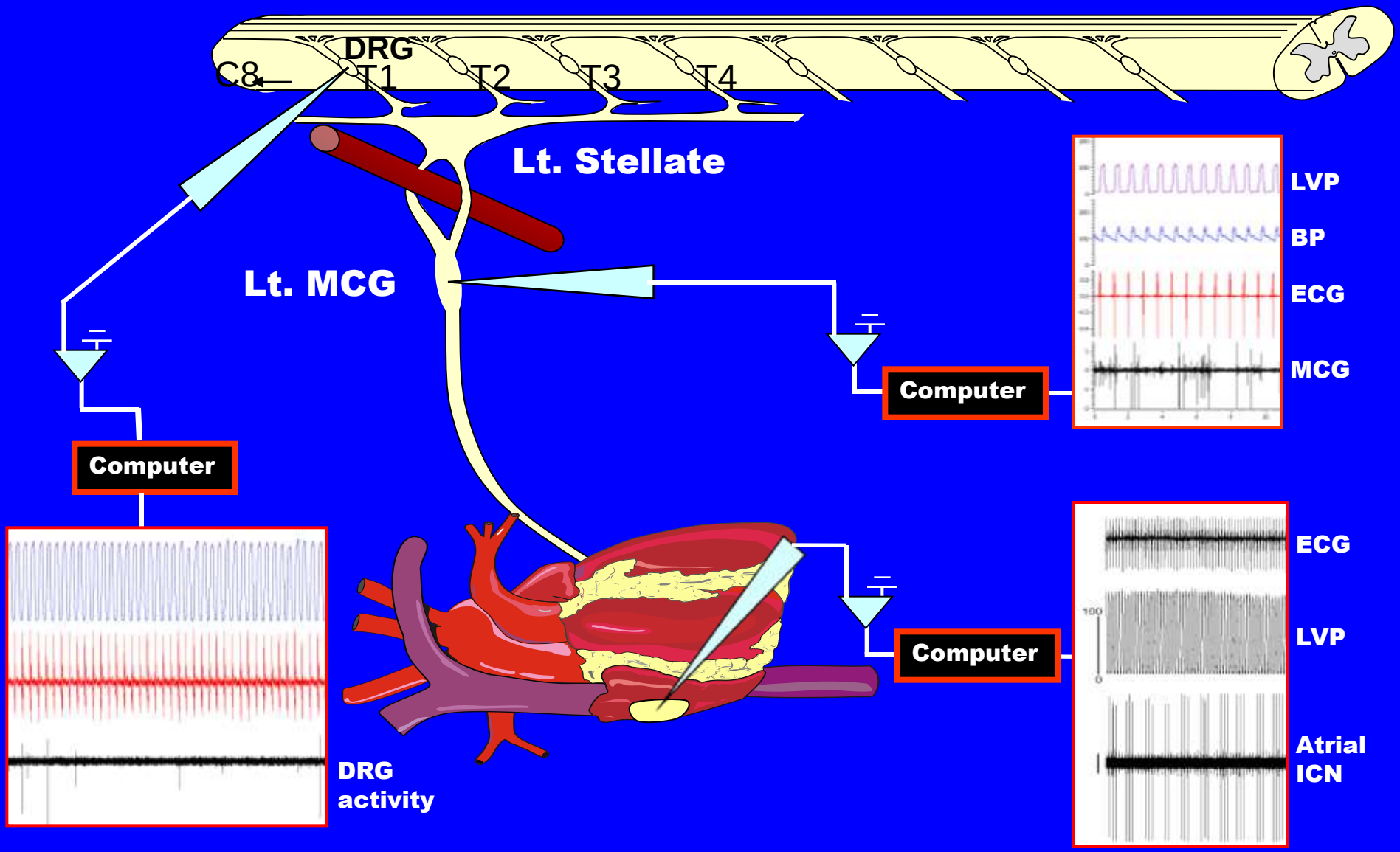
Background

Neural control of regional cardiac function involves the dynamic interplay of peripheral and central reflex control loops.

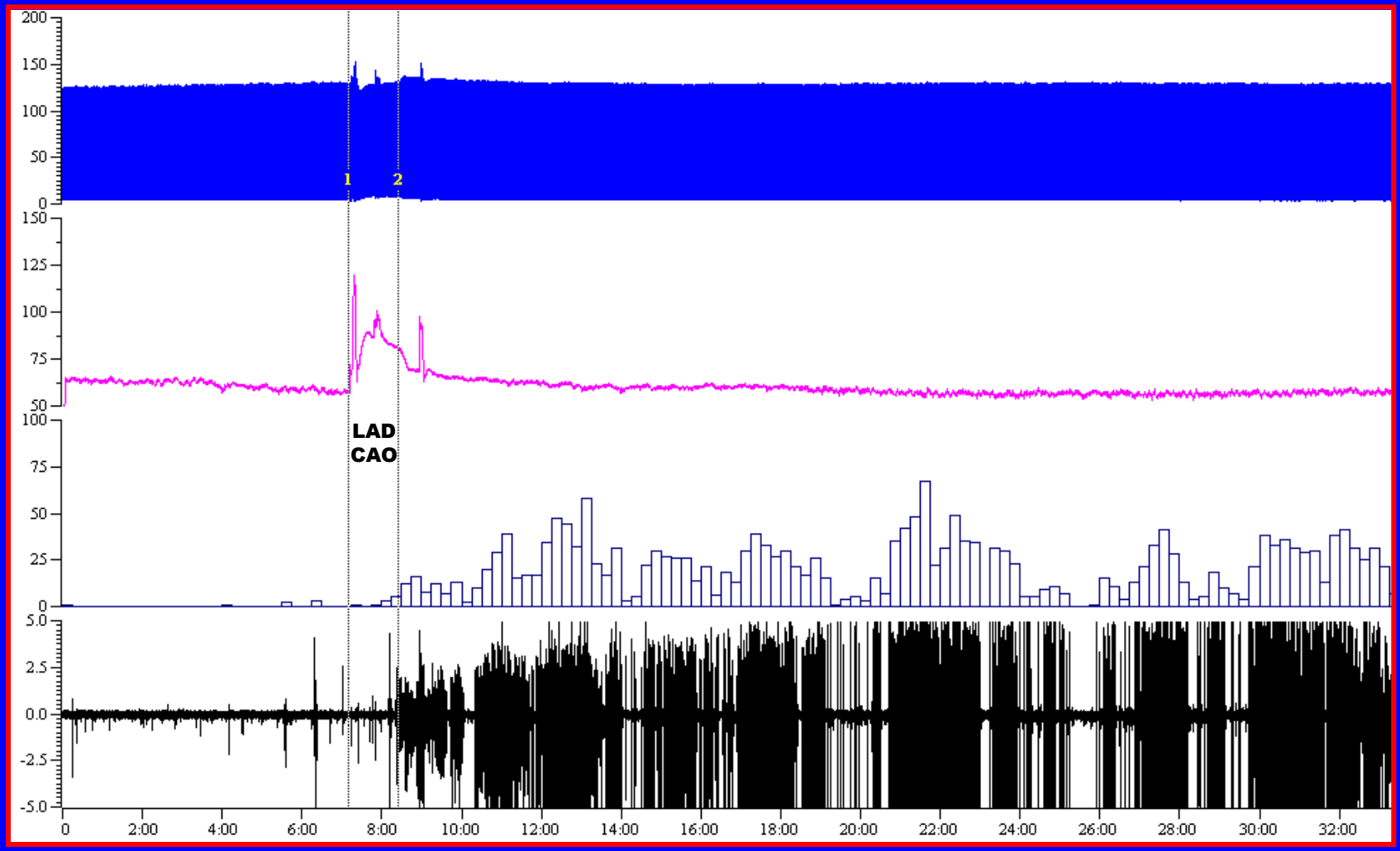
Myocardial ischemia (MI) induces an asymmetric activation of cardiac afferent neurons that feedback to peripheral and central aspects of the cardiac nervous system to modulate efferent neuronal output.

How this information is reflexly processed by various levels of the cardiac nervous system is critical to the ultimate outcome to the imposed stressor.

Neurophysiology methods



Transient myocardial ischemia induces long-lived changes in cardiac dorsal root ganglia sensory neurons



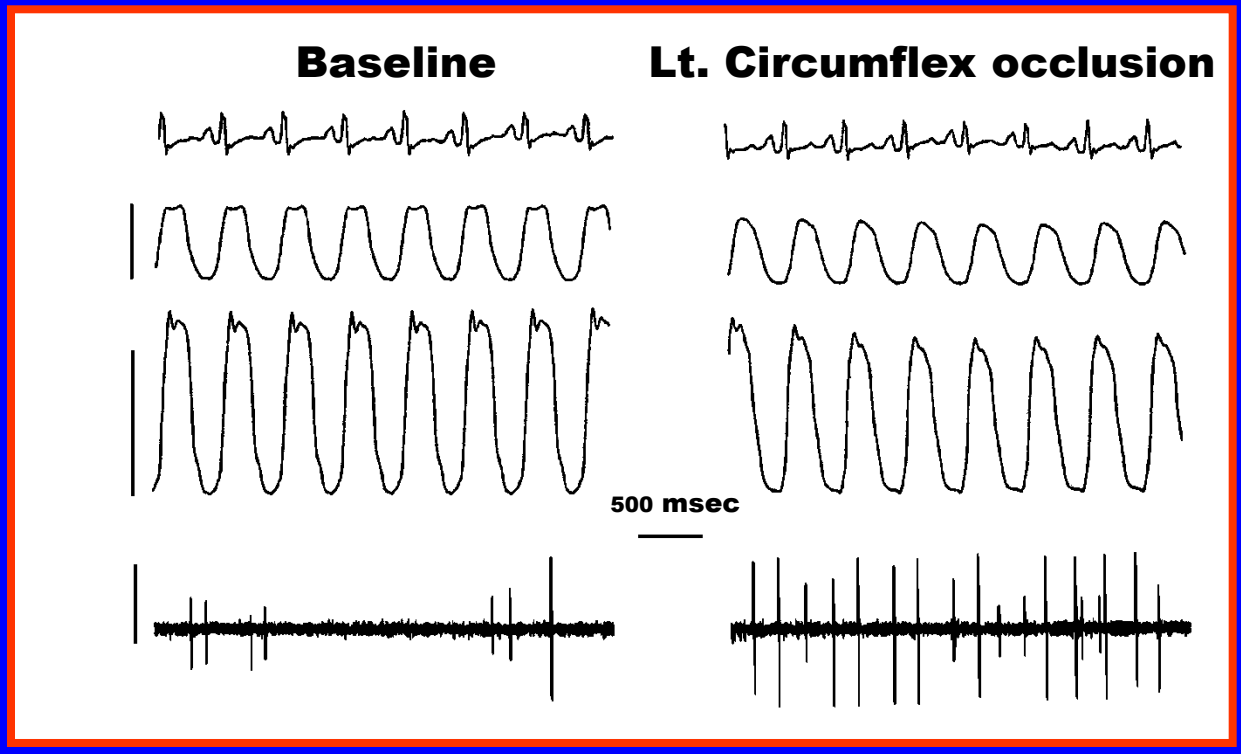
Coronary artery occlusion increases ICN activity

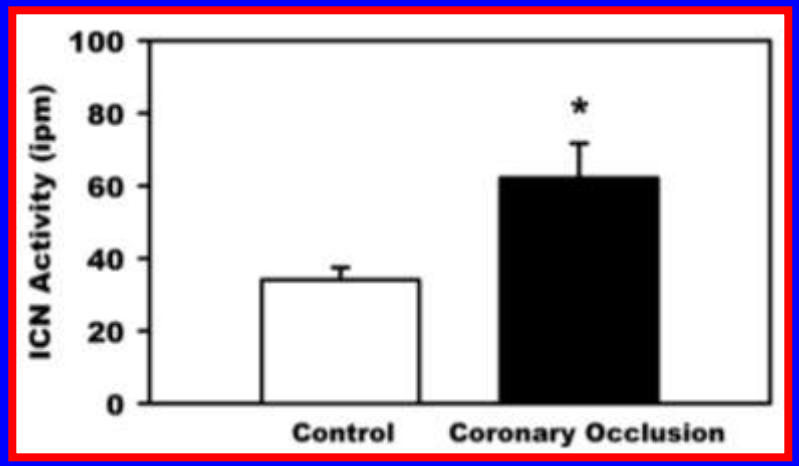
ECG

LV IMP

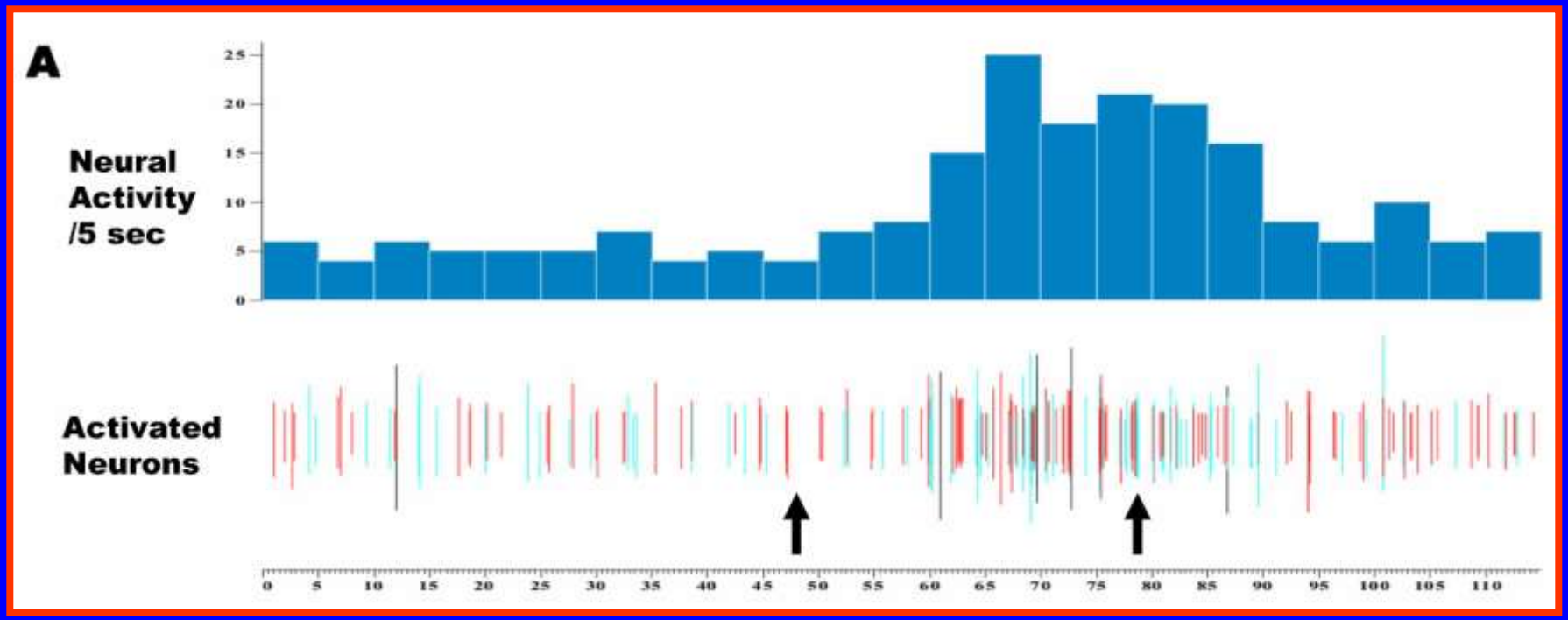
LVP

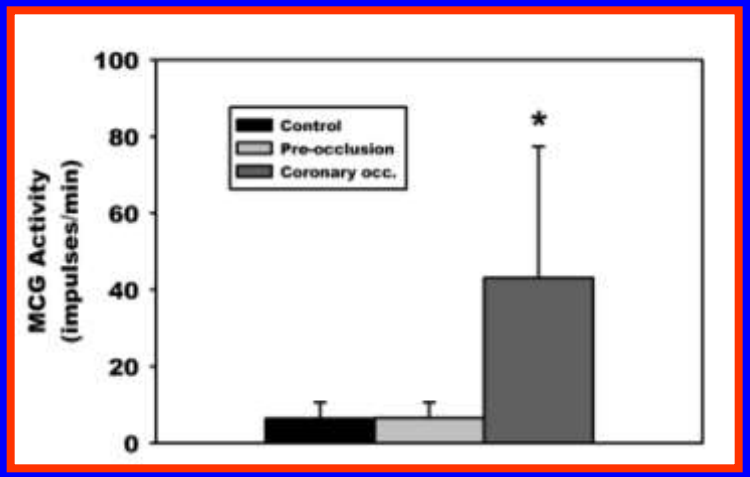
ICN Activity





Myocardial ischemia-induced increases in cardiac afferent inputs reflexly increases MCG activity

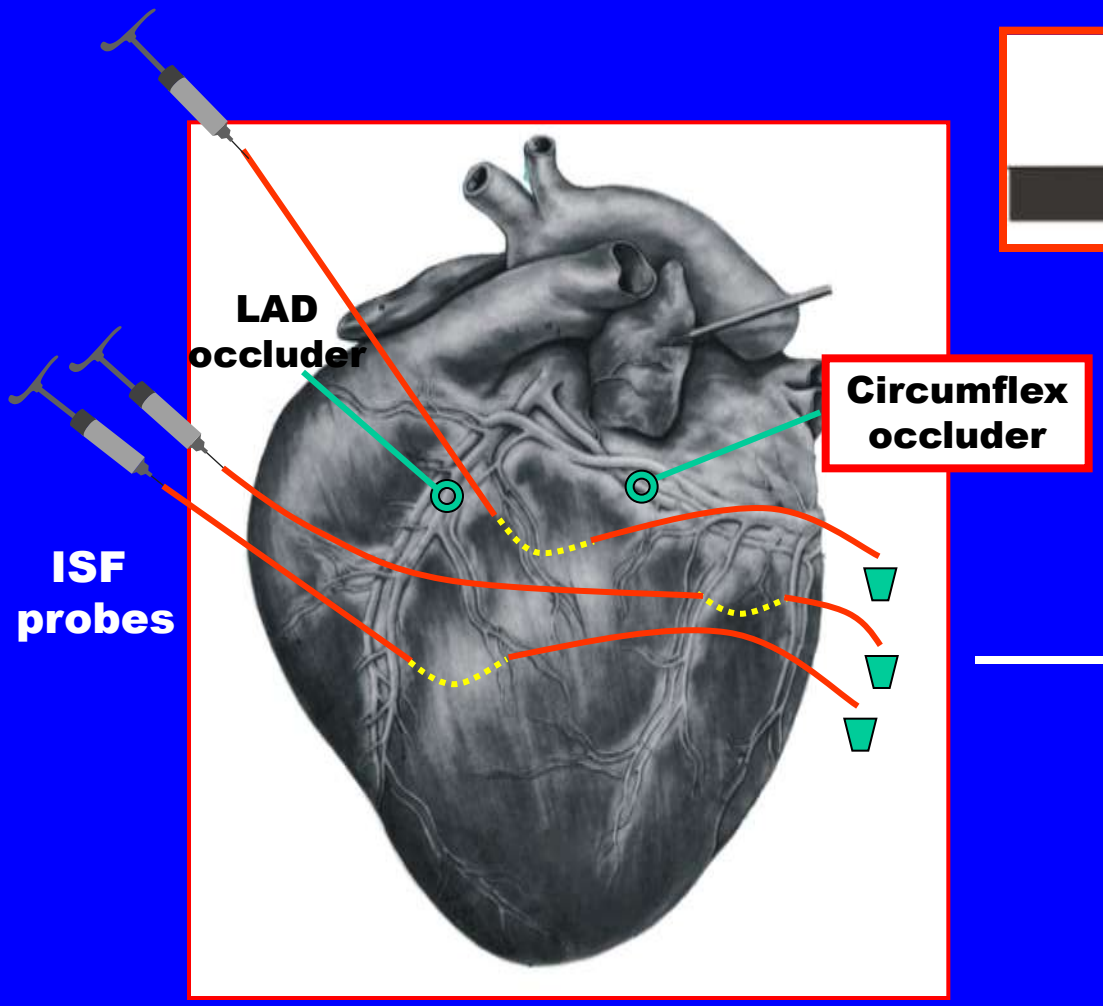


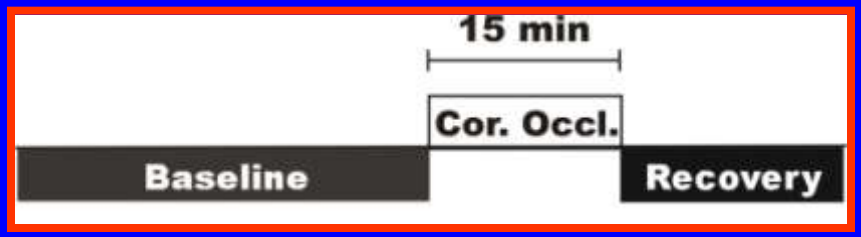


30” LAD CAO

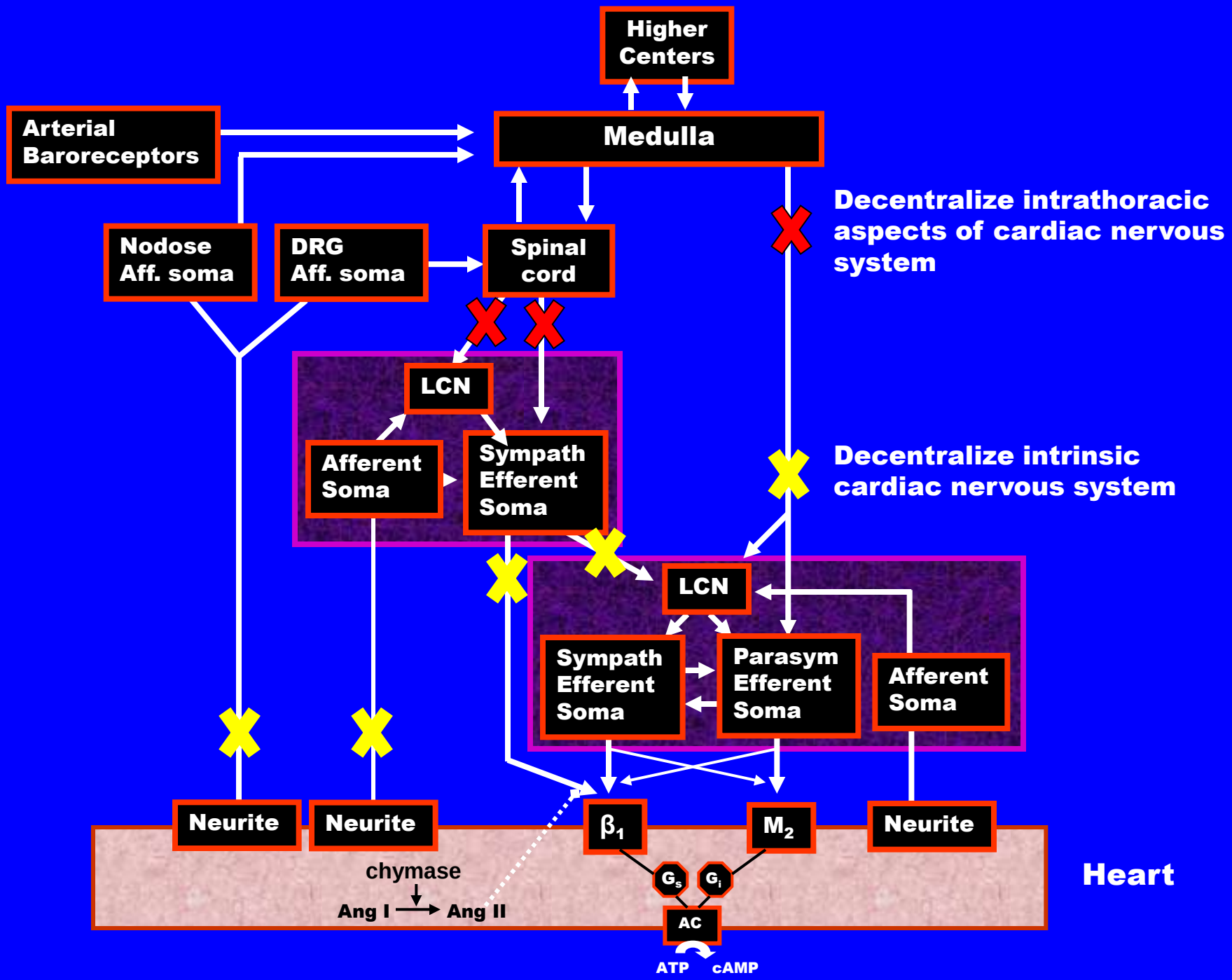
It is proposed that heterogeneity of MI reflex-evoked responses among different levels of the cardiac nervous system induces heterogeneity of catecholamine release into the interstitium of the left ventricle to exacerbate the substrate for ventricular arrhythmia formation.

Methods





ISF and Plasma NE


Higher Centers
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Decentralize intrathoracic aspects of cardiac nervous system
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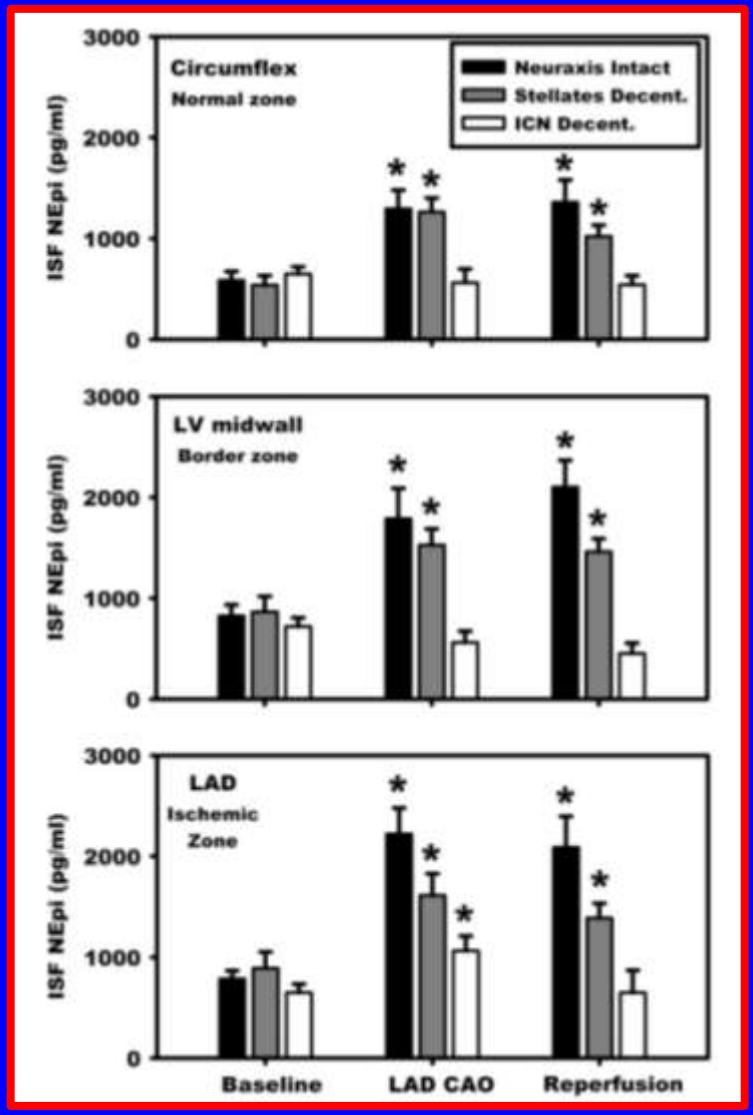
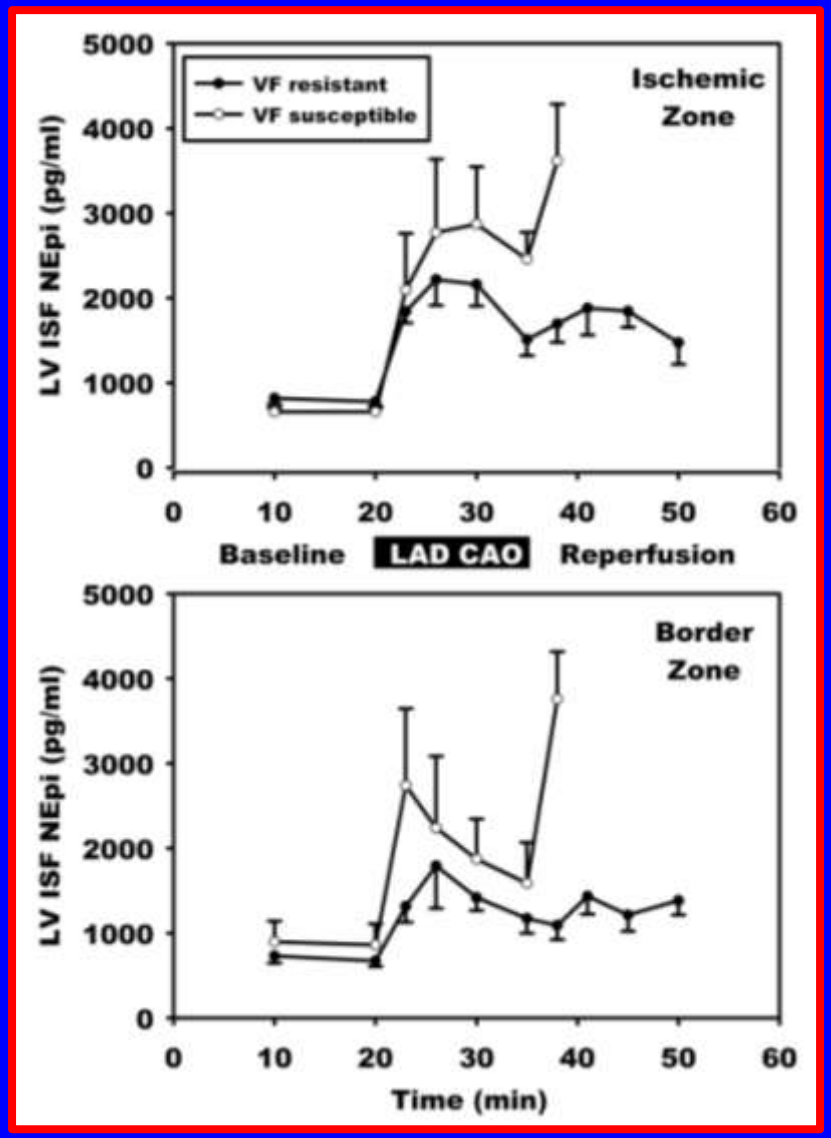
Heart

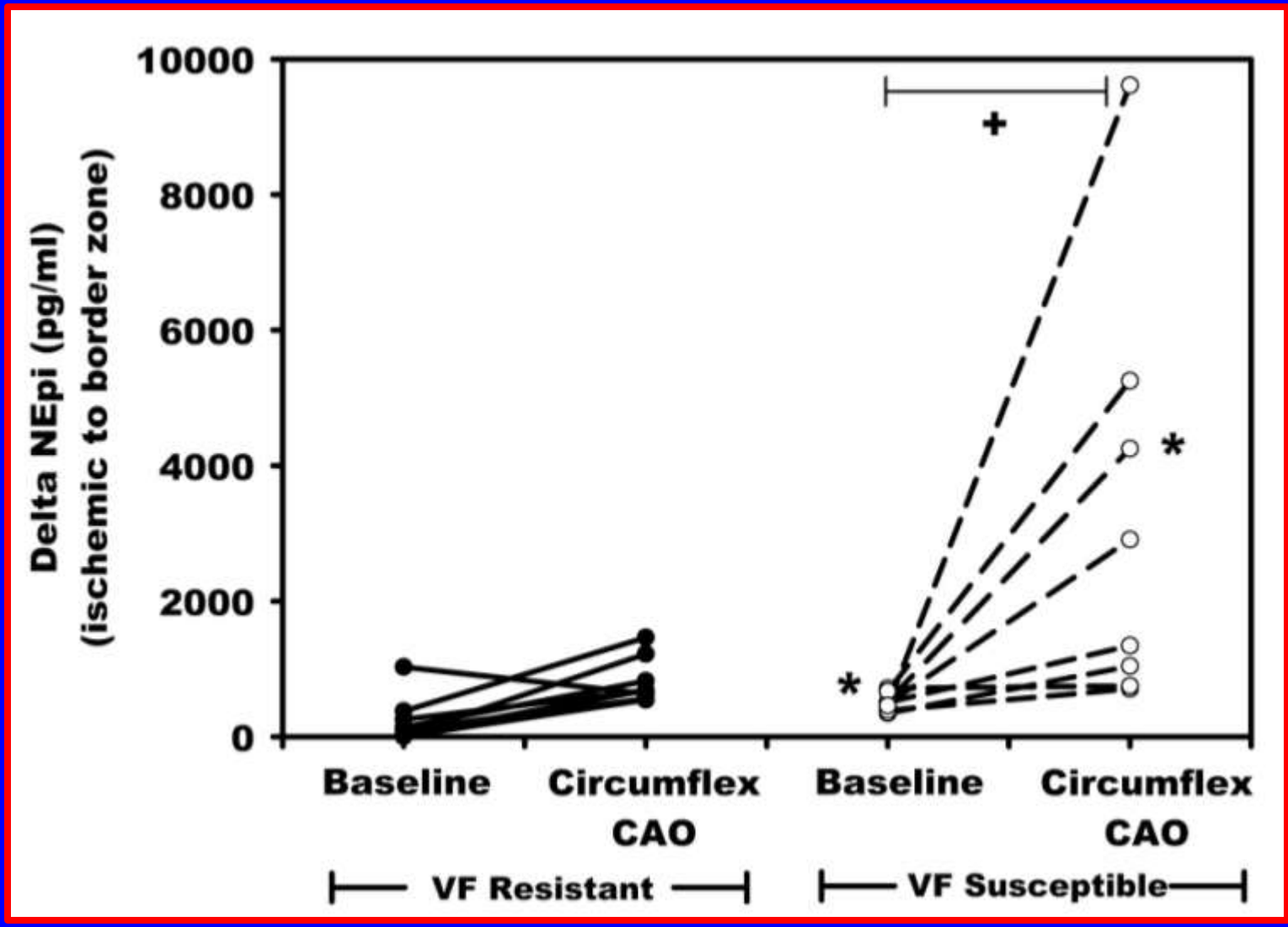
Reflex control of the heart involves interdependent interactions of central and peripheral neurons



Inherent differences within the cardiac nervous system impact on the transduction of myocardial ischemia to affect risk for cardiac sudden cardiac death



Increased dispersion in MI-induced NEpi release is associated with increase risk for sudden cardiac death



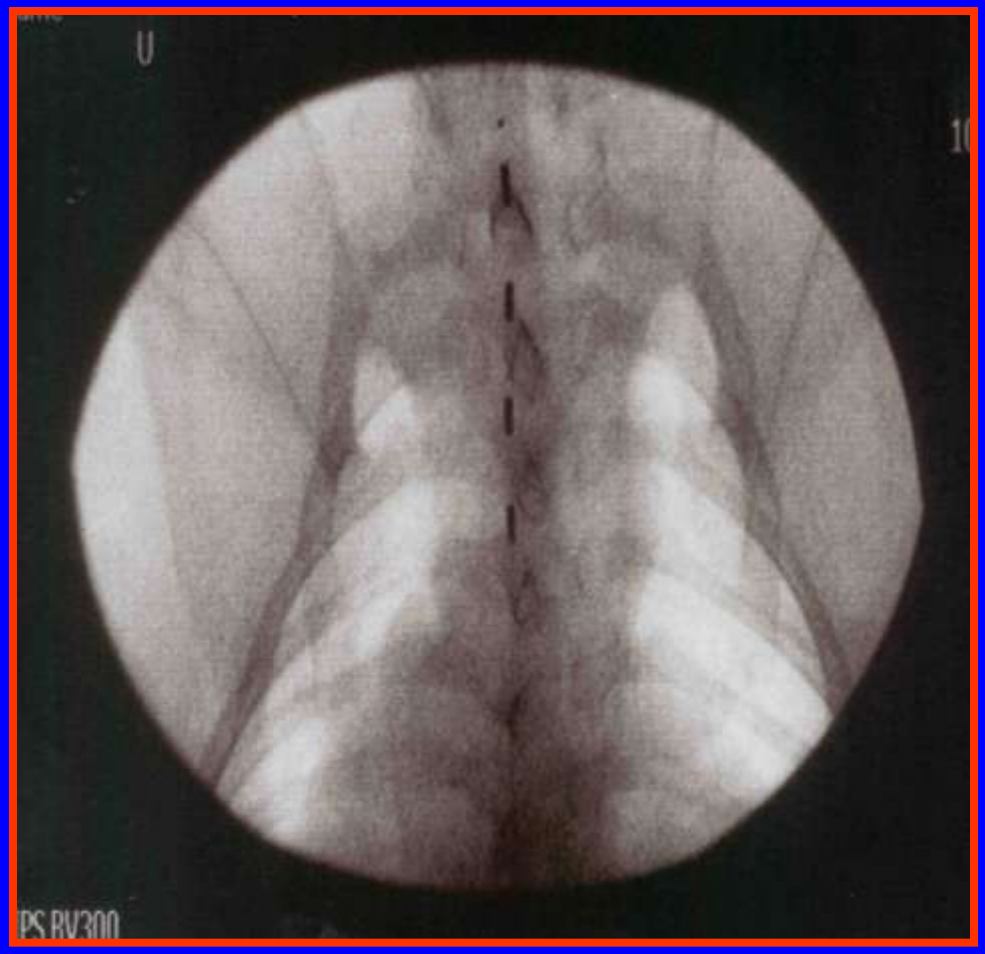
Hypotheses

We hypothesize that inherent differences within the cardiac nervous system impact on the transduction of myocardial ischemia/infarction to affect risk for cardiac mortality post-MI.

We hypothesize that subpopulations of CNS (spinal cord) neurons act to stabilize elements within the intrathoracic cardiac neuronal hierarchy to reduce arrhythmia susceptibility.

It is proposed that appropriate activation of subpopulations of neurons within the T1-T3 spinal segments of the spinal cord stabilizes, via activated descending projections, reflex processing of ischemia events within intrathoracic extracardiac and intrinsic cardiac ganglia.

Methods: Spinal Cord Stimulation



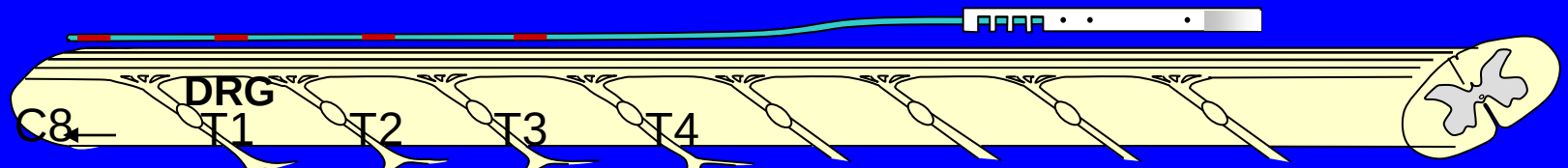
1. Epidural space is entered with a Touhy-needle in the lower thoracic region.

2. Using fluoroscopy, a 4-pole electrode is introduced into the epidural space and positioned to the left of the midline with the cranial pole at the T1-level and the caudal pole at the T3-level.

3. Electrical current (50 Hz, 200 µsec) is delivered via a Grass stimulator connected to the cranial (negative) and caudal (positive) poles of the electrode. Intensity is set to 90% of that inducing any motor changes.

Neurophysiology methods

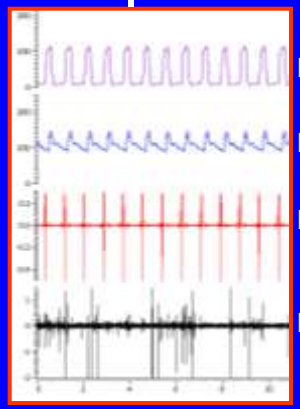
Grass S88 Stimulator



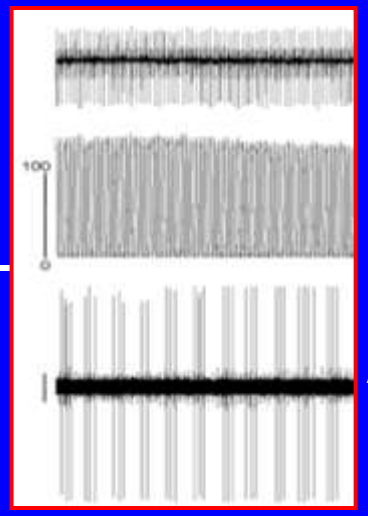
Lt. Stellate

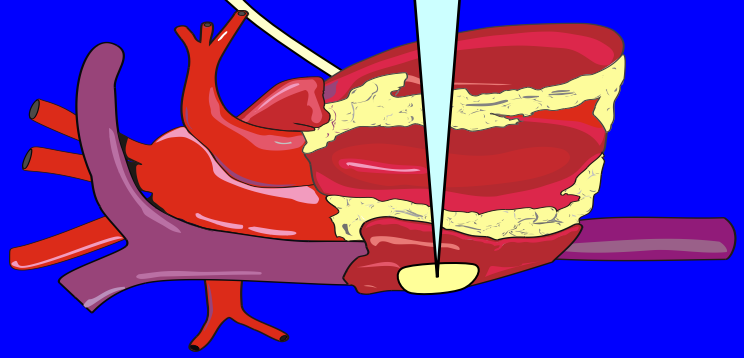
Lt. MCG

Computer



Computer

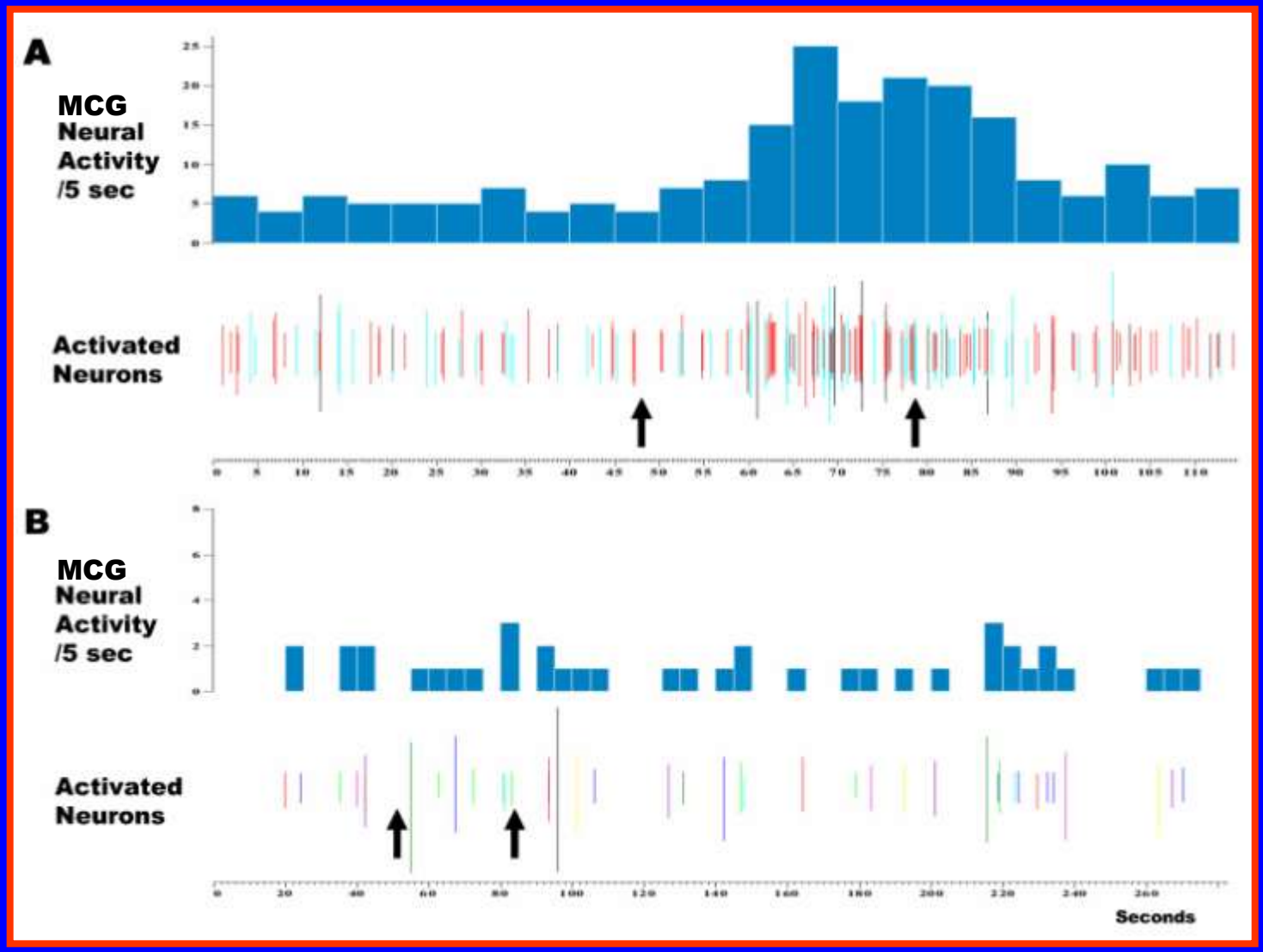




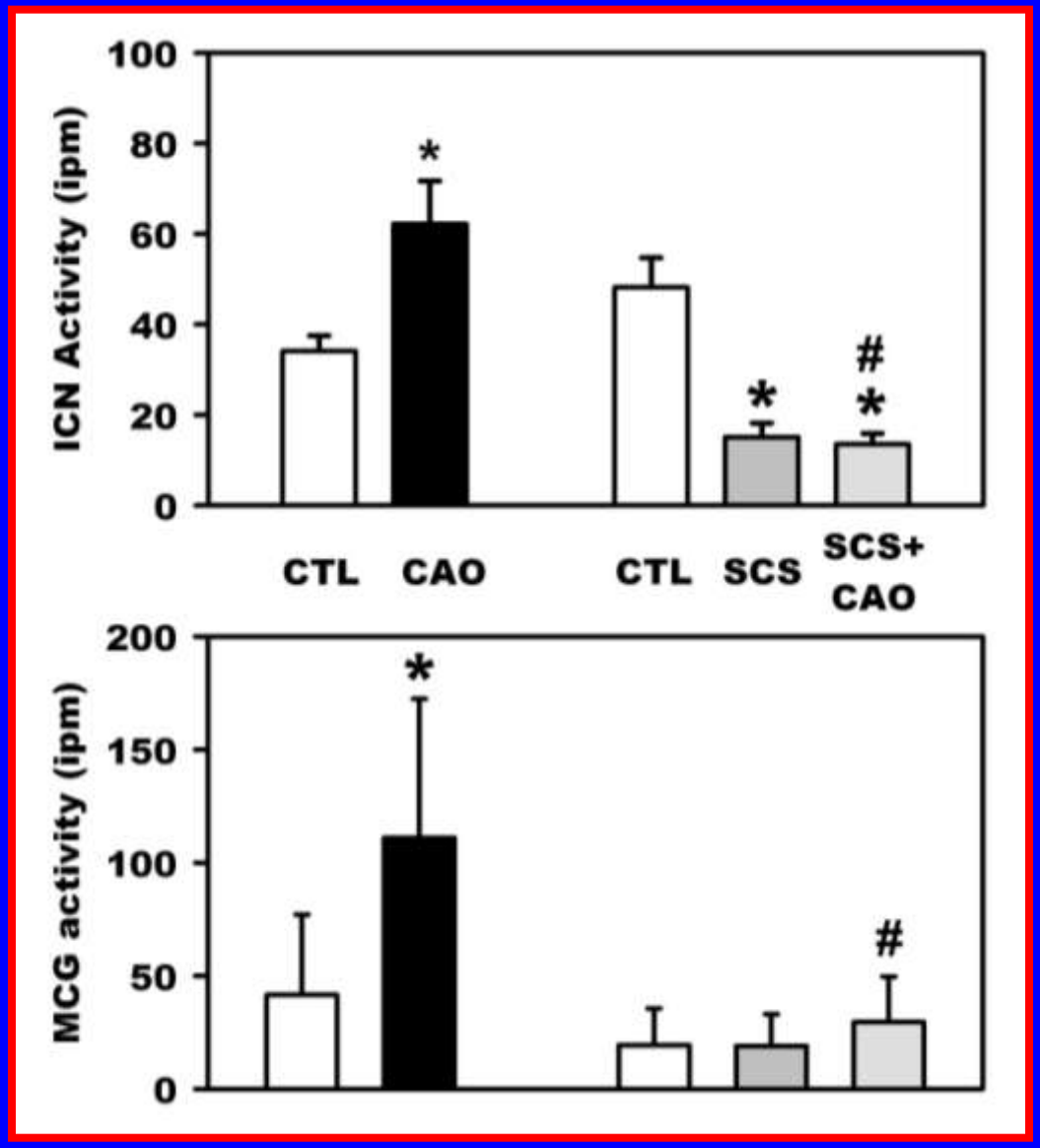
Pre-emptive SCS blunts the reflex increase in sympathetic (MCG) activity associated with transient myocardial ischemia

Untreated

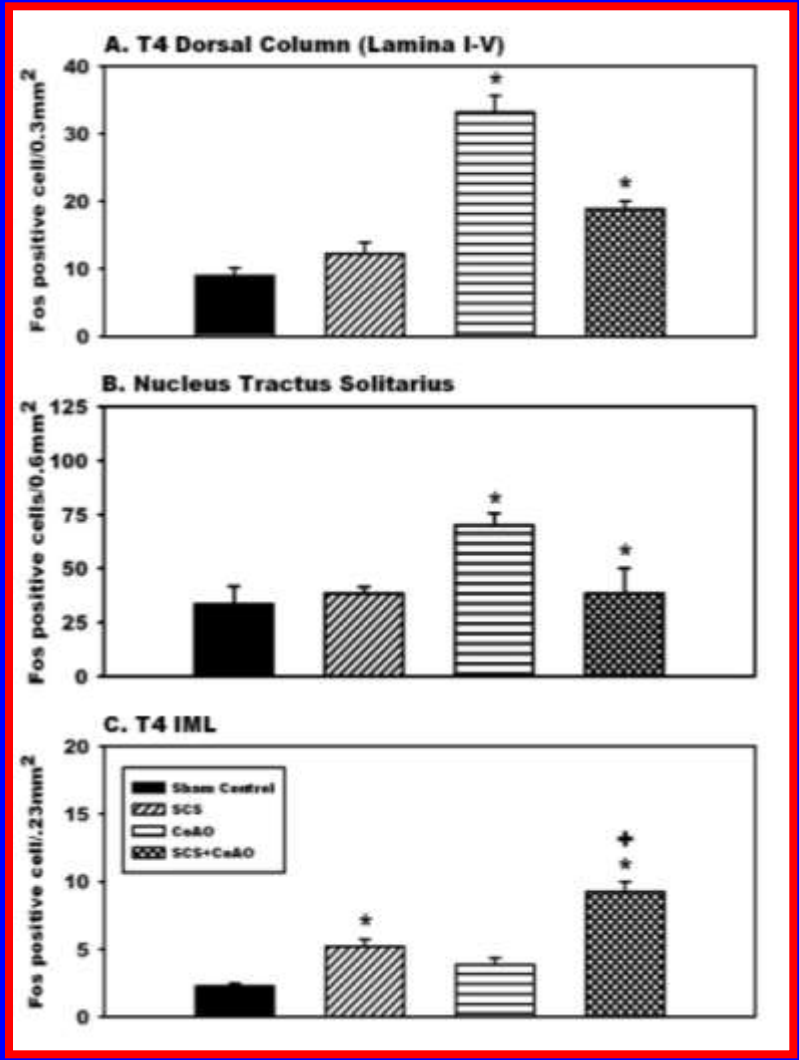
Pre-emptive T1-T3 SCS



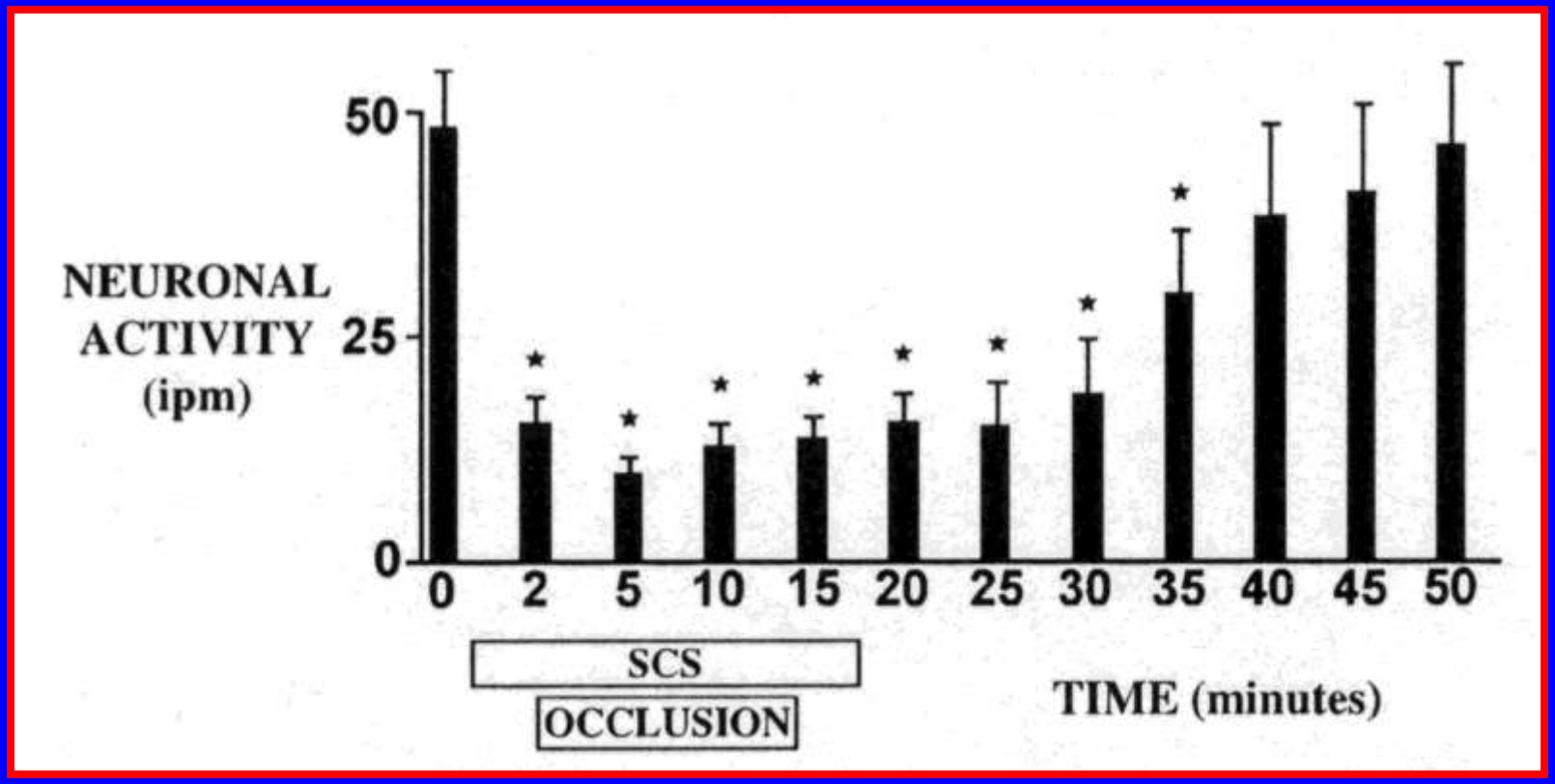
SCS neuromodulation blunts myocardial ischemia-reflex induced activation of intrathoracic autonomic ganglia



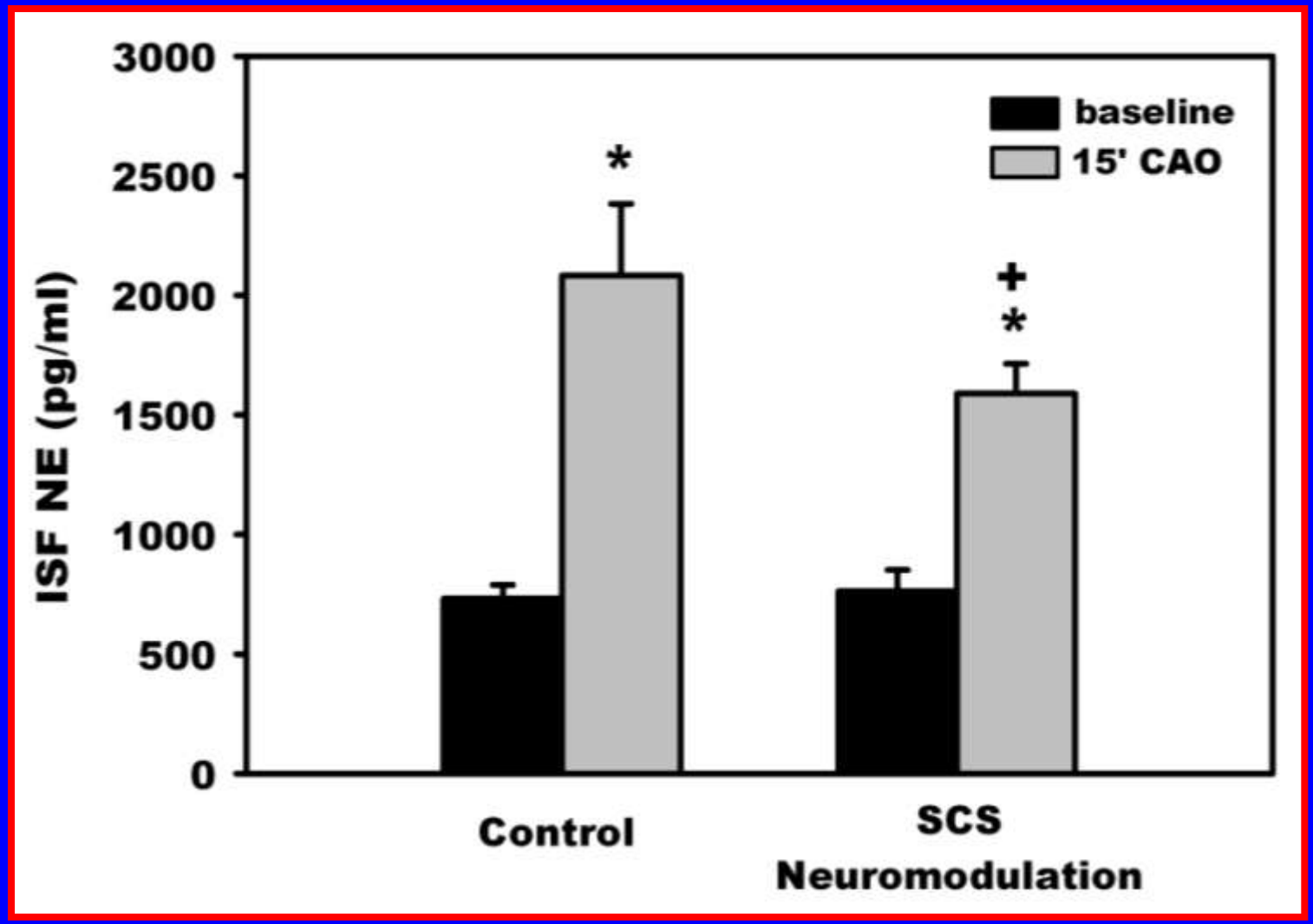
SCS neuromodulation blunts myocardial ischemia reflex induced activation of spinal and supraspinal components of the cardiac nervous system



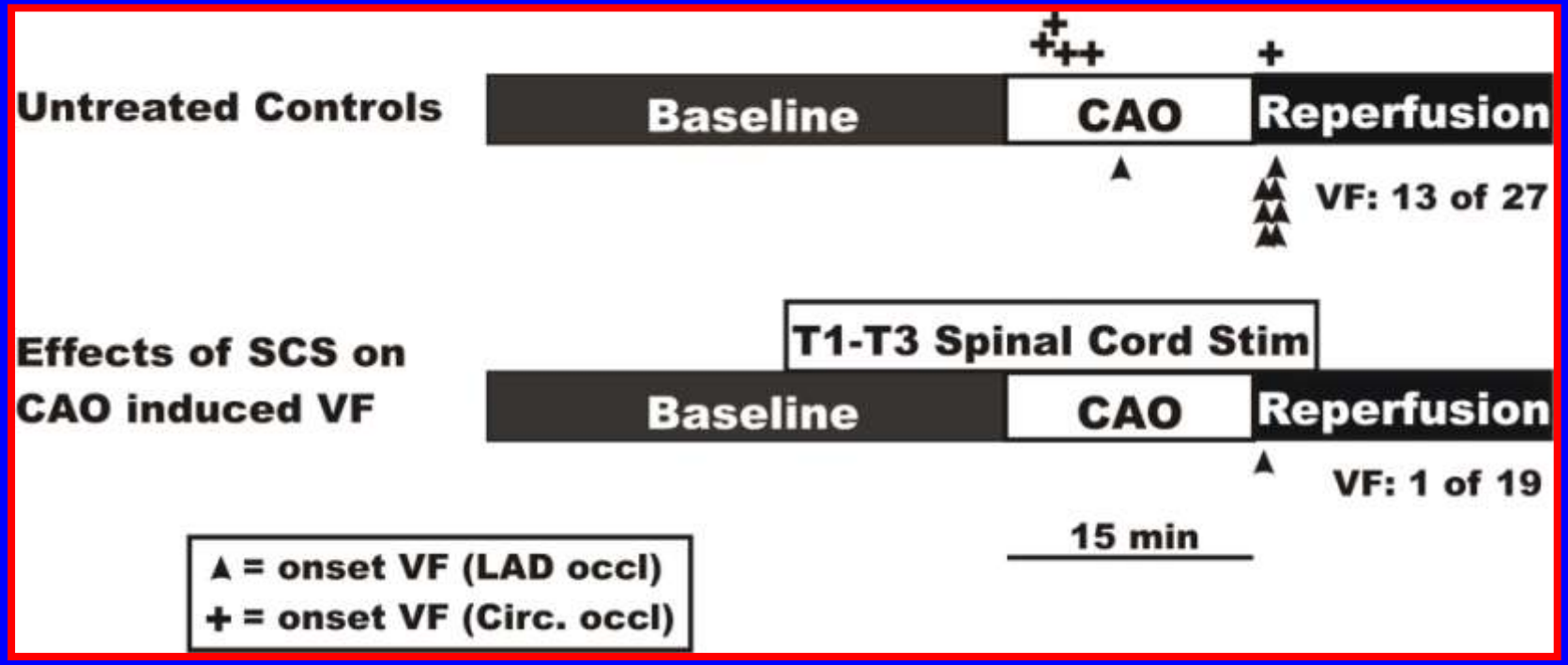
Effects of SCS on peripheral ganglia function demonstrate persistence



SCS neuromodulation (T1-T3) mitigates NE release in reflex response to transient myocardial ischemia



Pre-emptive SCS reduces the potential for sudden cardiac death in response to transient myocardial ischemia



Conclusions

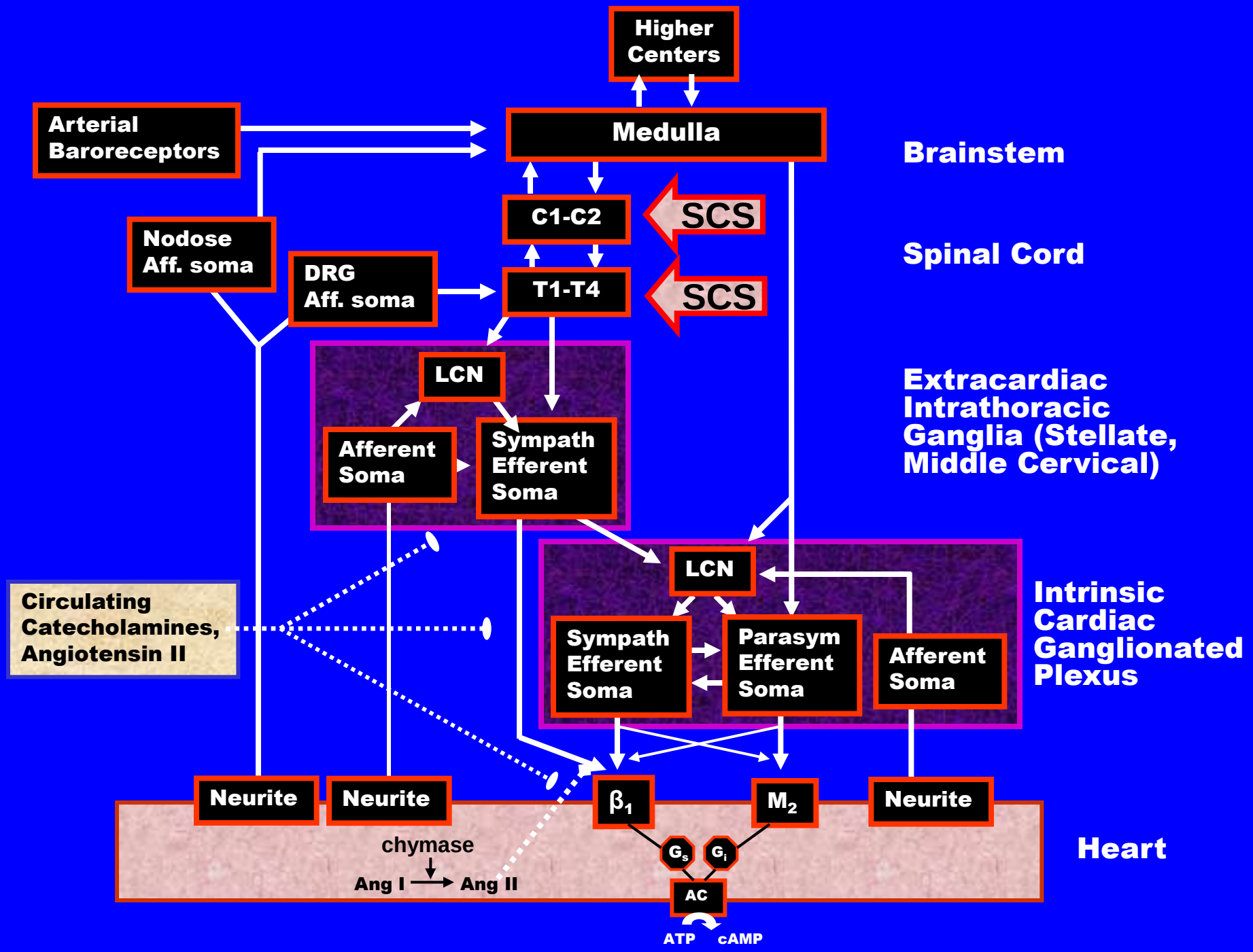
1. Asymmetry of MI-evoked evoked reflex release of norepinephrine into the ventricular interstitium induces arrhythmias.

2. Peripheral reflex processing contributes to MI-induced norepinephrine release.

3. Activation of subpopulations of neurons within the T1-T3 spinal segments of the spinal cord stabilizes, via activated descending projections, reflex processing of ischemia events within intrathoracic extracardiac and intrinsic cardiac ganglia.

4. Stabilization of MI-evoked reflex function within the cardiac nervous system reduces the potential for lethal arrhythmias.

SPINAL CORD STIMULATION AND EFFECTS ON TRANSIENT ISCHEMIA-INDUCED MYOCARDIAL INFARCTION


Higher Centers
Arterial Baroreceptors
Medulla
Brainstem
C1-C2
SCS
Nodose Aff. soma
DRG Aff. soma
T1-T4
SCS
Spinal Cord
LCN
Afferent Soma
Sympath Efferent Soma
Extracardiac Intrathoracic Ganglia (Stellate, Middle Cervical)
Circulating Catecholamines, Angiotensin II
LCN
Sympath Efferent Soma
Parasym Efferent Soma
Afferent Soma
Intrinsic Cardiac Ganglionated Plexus
Neurite
Neurite
β1
M2
Neurite
chymase
Ang I
Ang II
Gs
Gi
AC
ATP
cAMP
Heart

Background

Endogenous myocardial catecholamines are not essential for protection from ischemic preconditioning.

Exogenous catecholamines can protect the heart from transient MI, an effect that is prevented by α_1-receptor blockade.

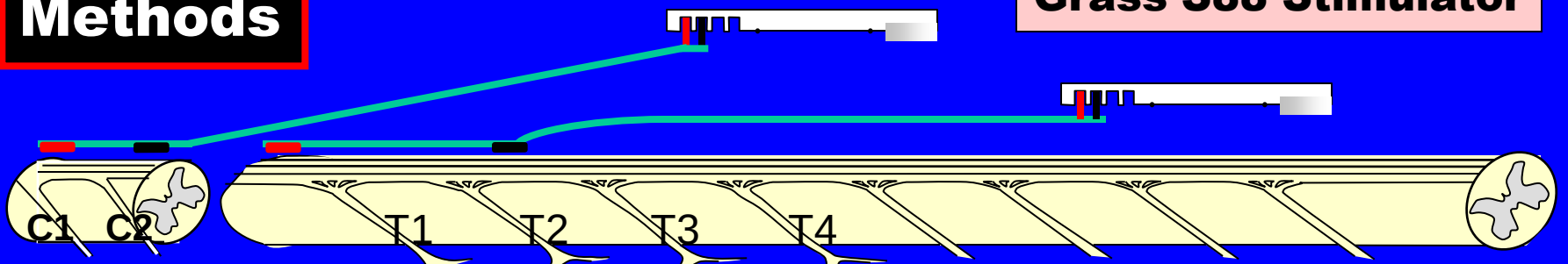
Spinal cord stimulation evokes low level catecholamine release into the ventricular interstitium, while also blunting MI-reflex induced catecholamine release.

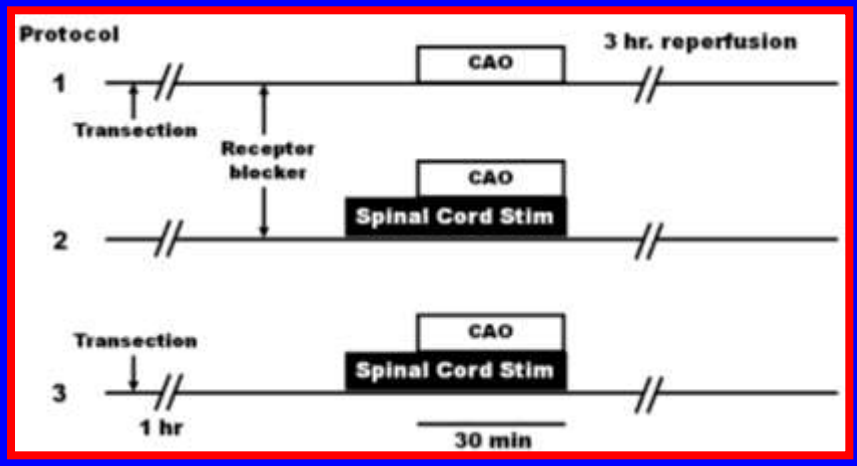
Hypothesis

SCS will reduce myocyte cell death to transient MI and this cardioprotection is mediated via adrenergic receptors.

Methods

Grass S88 Stimulator





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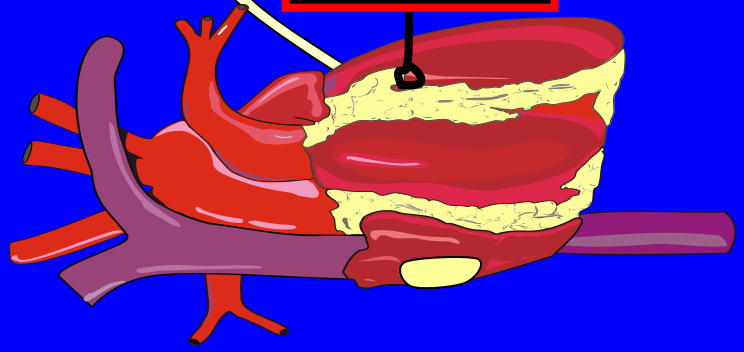
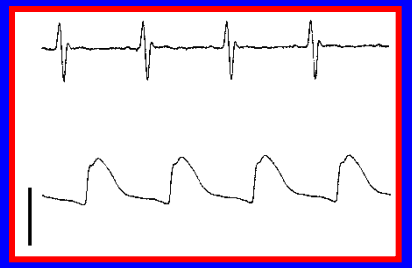


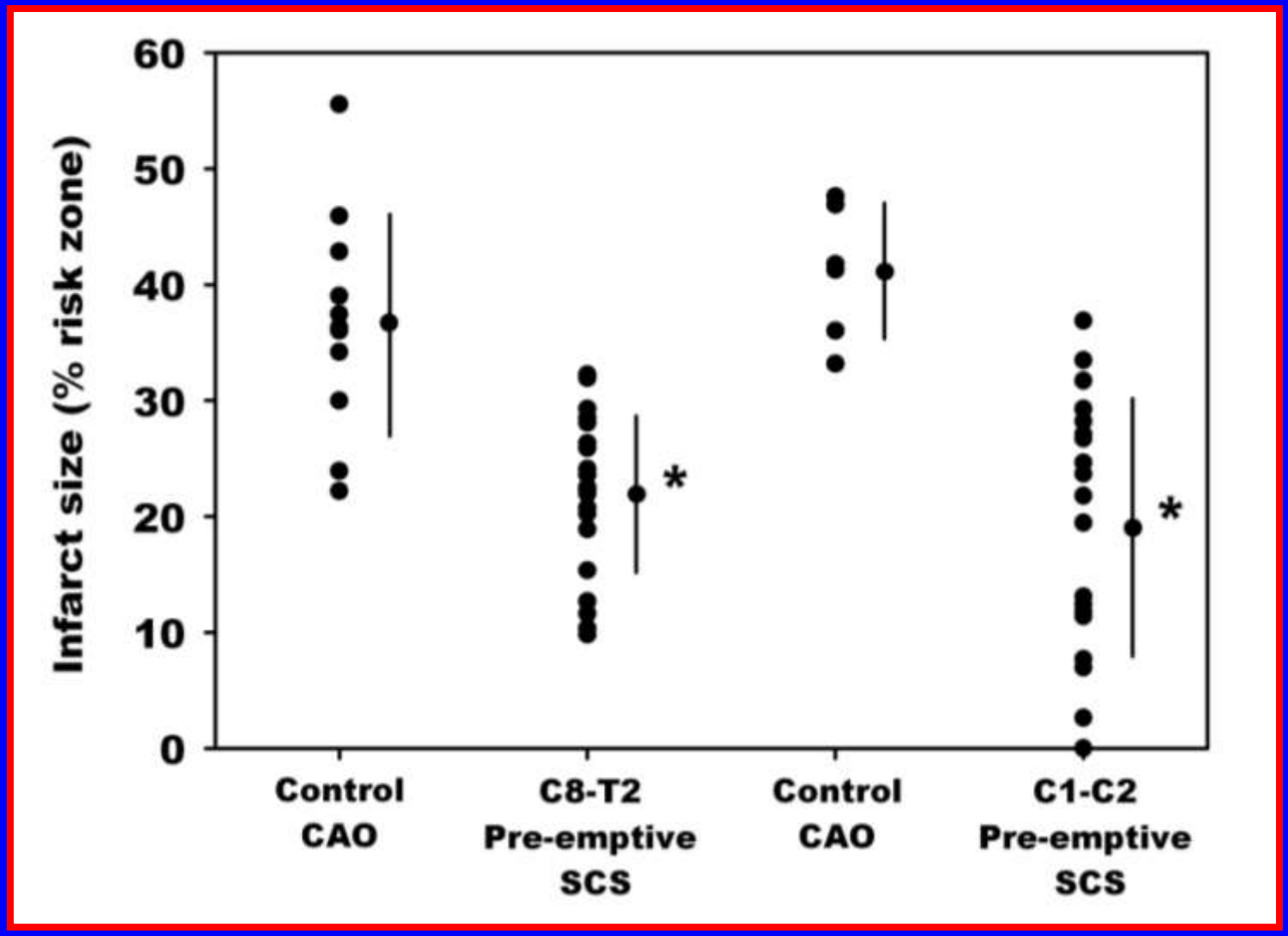
Recorder



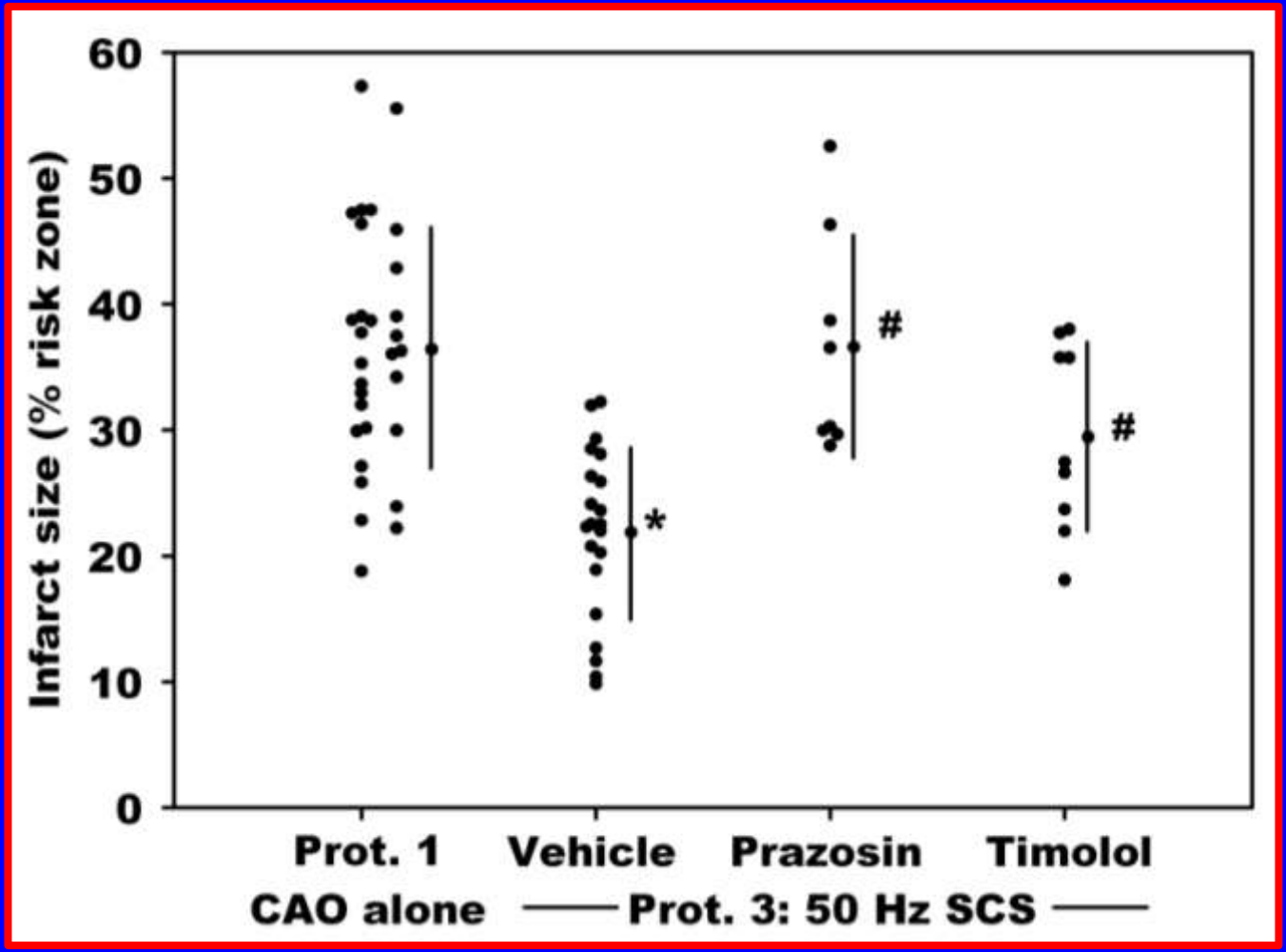
ECG

BP

Both high thoracic and high cervical pre-emptive SCS reduce myocardial infarction to transient coronary ischemia



Effects of pre-emptive T1-T3 SCS to reduce infarct size are attenuated by adrenergic blockade



Conclusions

Pre-emptive SCS reduces the size of infarcts induced by transient CAO; such cardioprotection involves cardiac adrenergic neurons.

In clinical practice, SCS has been shown to be a long-term adjunct therapy for patients with chronic angina pectoris. It should be considered that as an unrecognized benefit to chronic SCS therapy, these patients may experience a relative state of cardioprotection.

Atrial fibrillation and the cardiac nervous system

Background

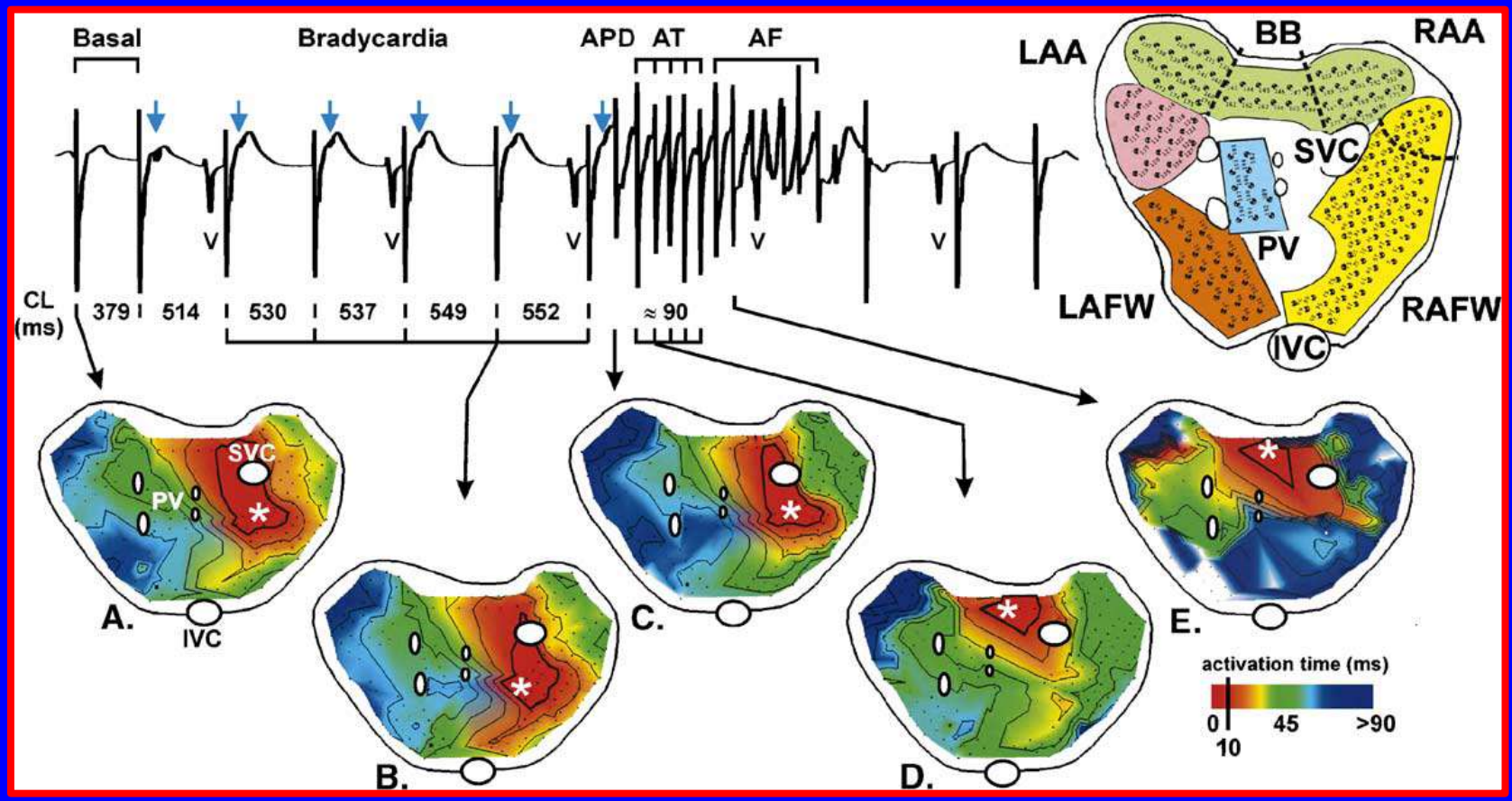
Spinal cord stimulation stabilizes peripheral aspects of the cardiac nervous system

Activating discrete extrinsic inputs to the intrinsic cardiac nervous system can initiate self-terminating episodes of atrial tachyarrhythmia/fibrillation.

Hypothesis

SCS therapy suppresses neuronally induced atrial tachyarrhythmias via its capacity to stabilize excessive inputs to the intrinsic cardiac nervous system.

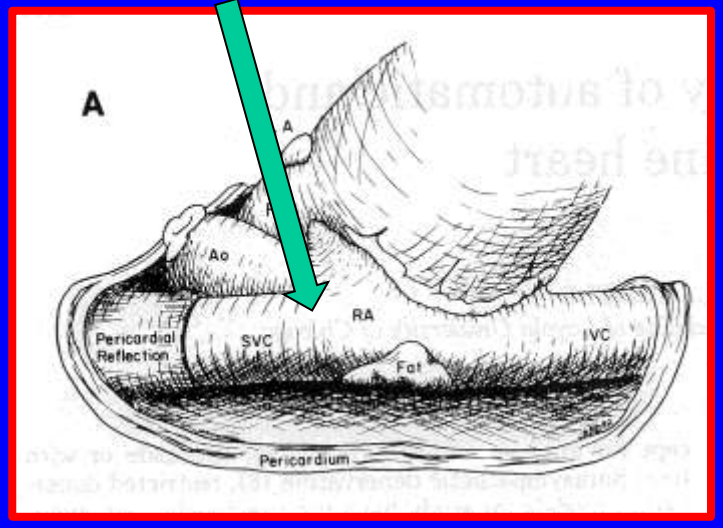
Electrical stimuli delivered to mediastinal nerves during atrial refractory period reproducibly induces (self-terminating) atrial tachyarrhythmias

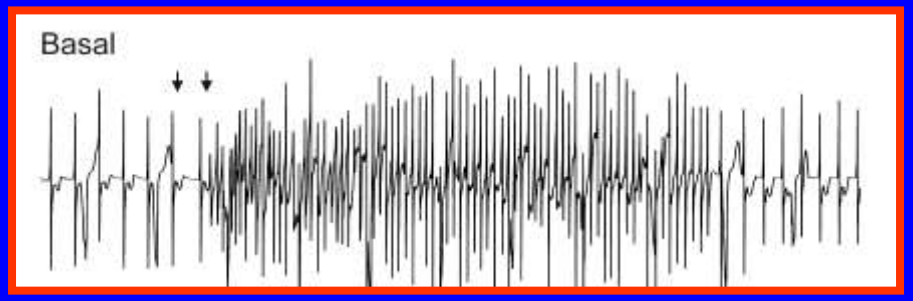


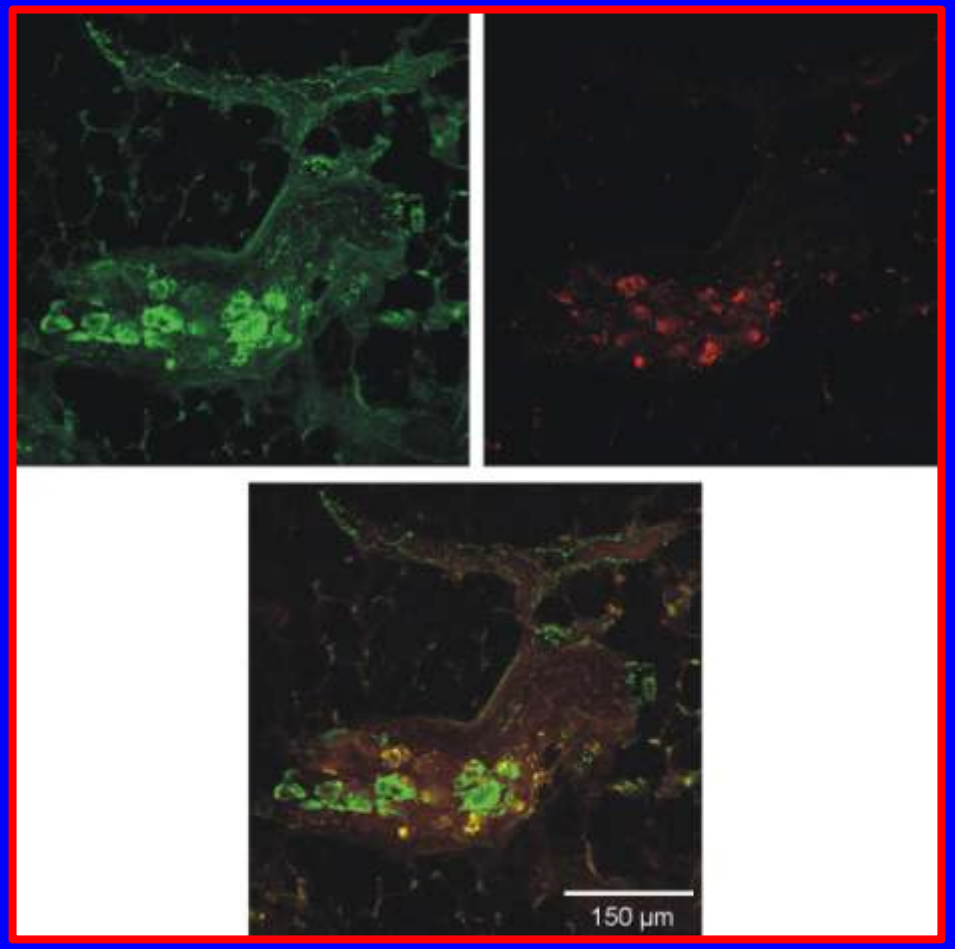
Armour et al, Autonomic Neurosci, 118, 2005

Extrinsic autonomic inputs to the heart directly innervate only a subset of intrinsic cardiac neurons

Stimulation and injection site



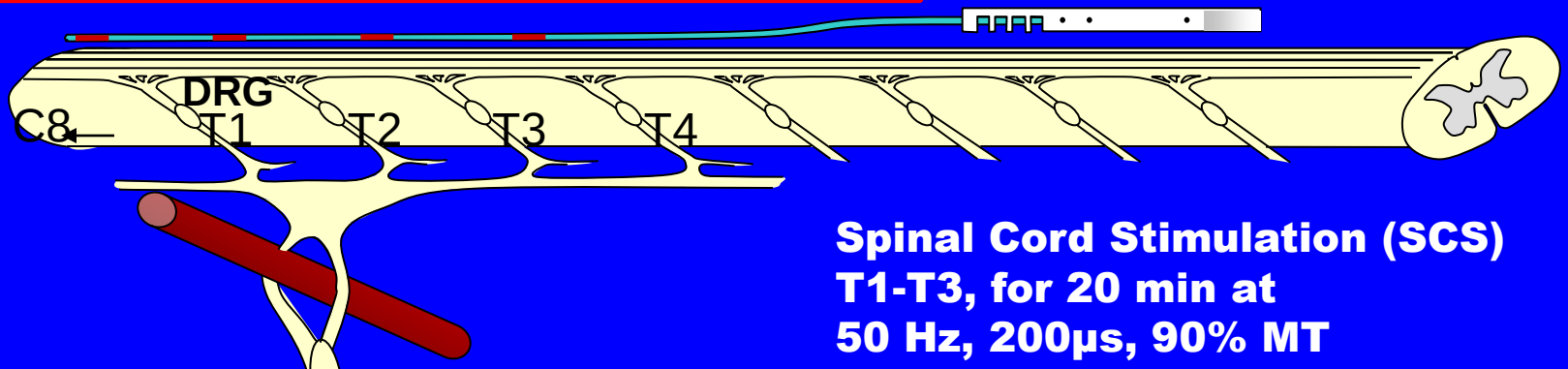




Green: PGP 9.5, Red: DiI, Yellow: overlay

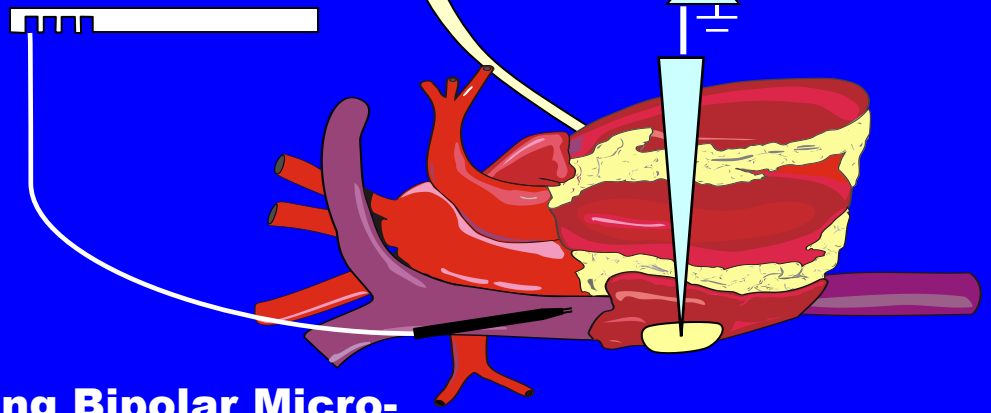
Mediastinal nerve stimulation induces prompt activation of neurons within the intrinsic cardiac ganglia

Grass S88 Stimulator



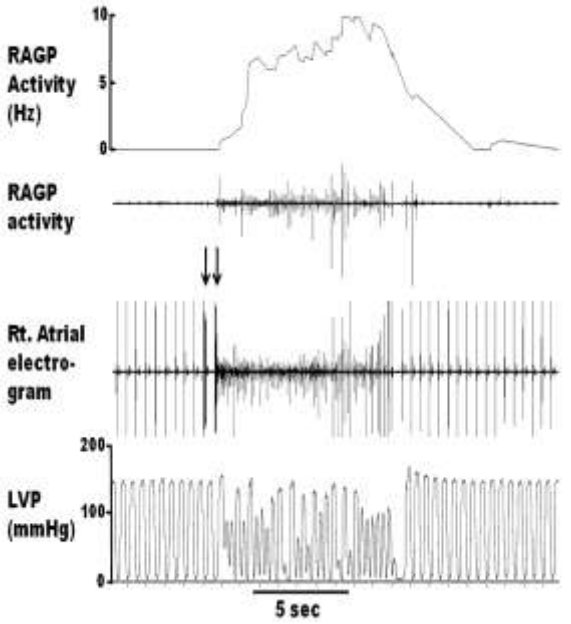
Spinal Cord Stimulation (SCS)
T1-T3, for 20 min at
50 Hz, 200μs, 90% MT

Grass S88 Stimulator



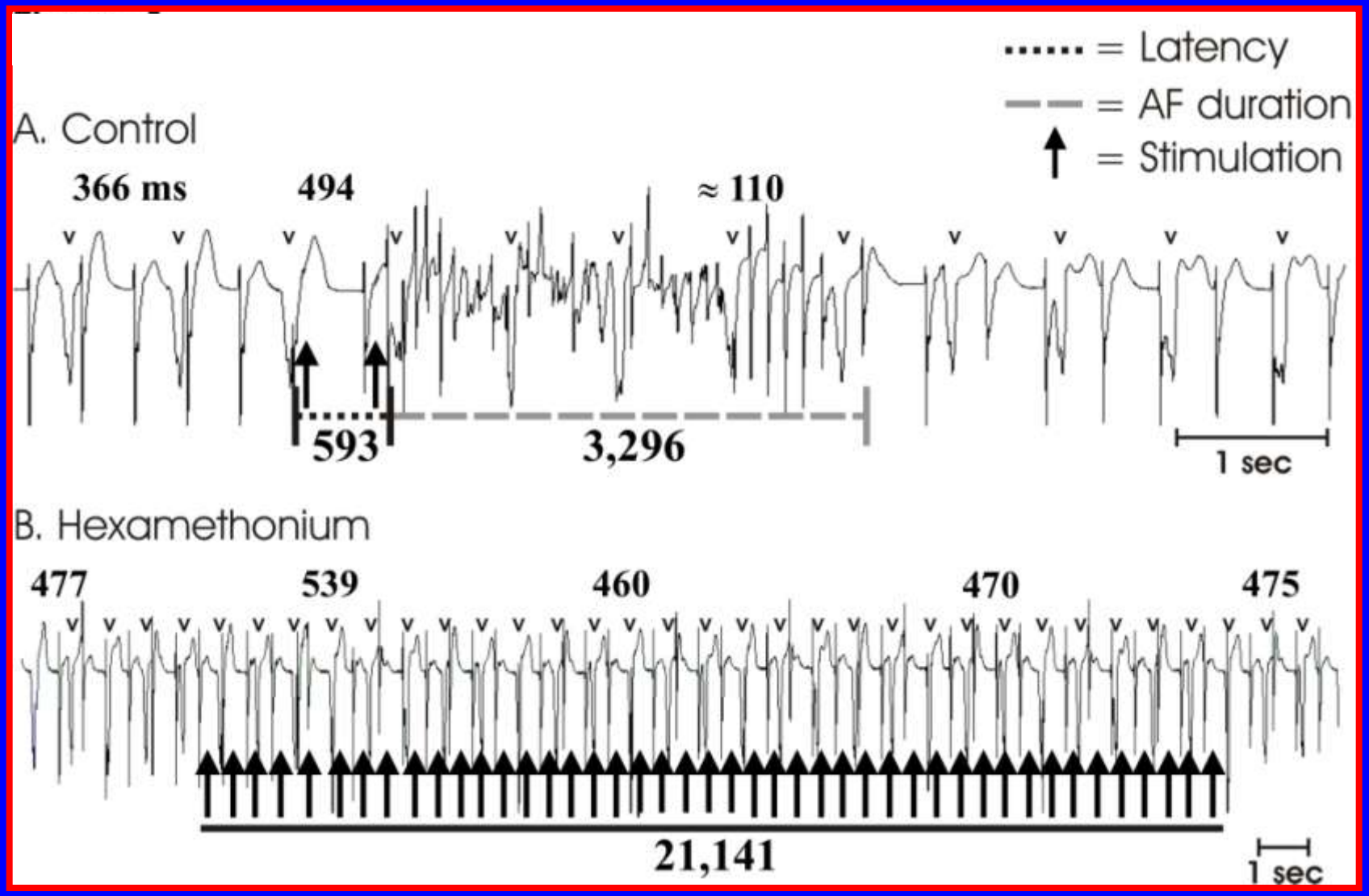
Roving Bipolar Micro-stimulus Probe

Computer



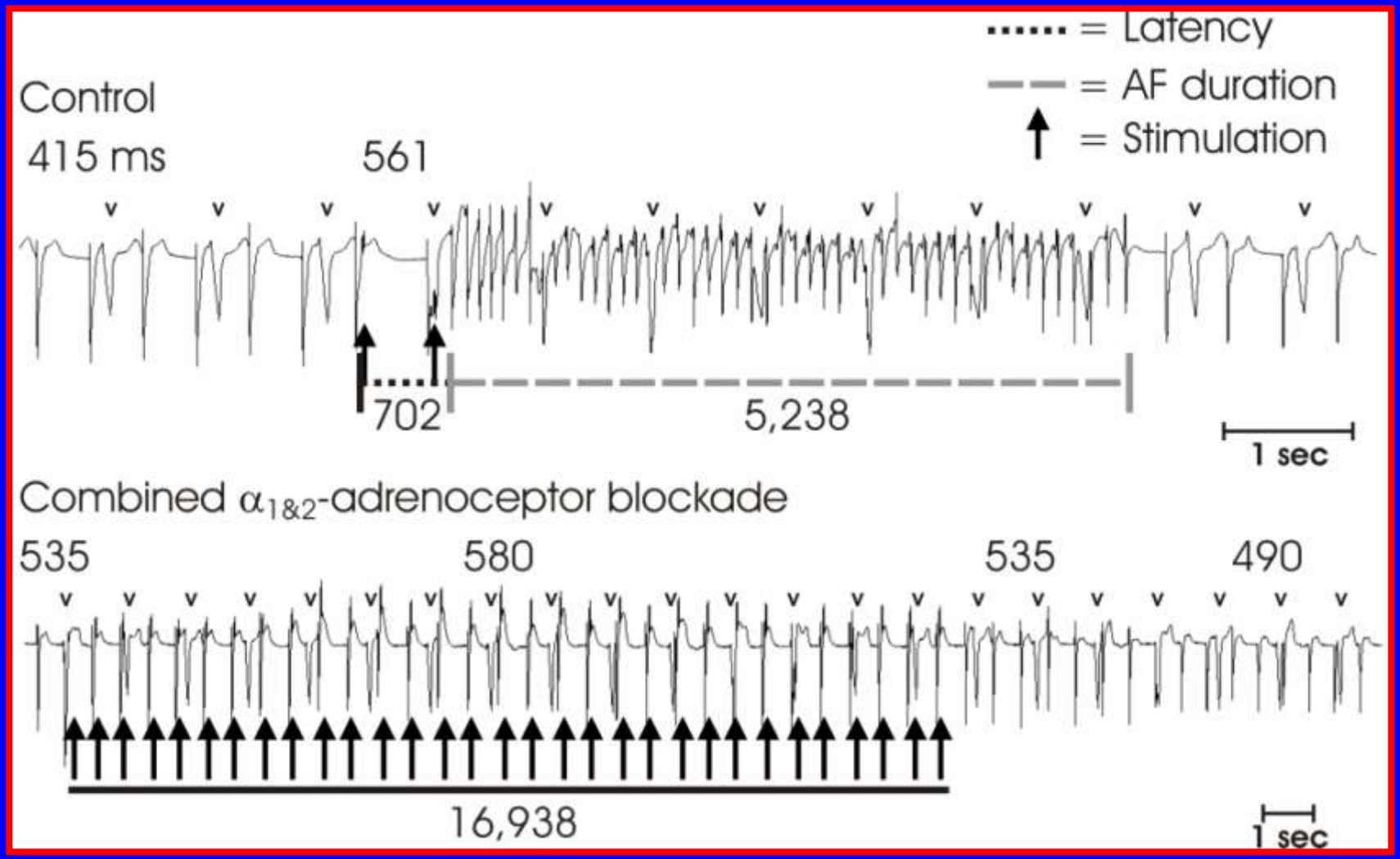
Neurally-induced arrhythmias can be modified pharmacologically

Hexamethonium exerts a global suppression of ICN activity

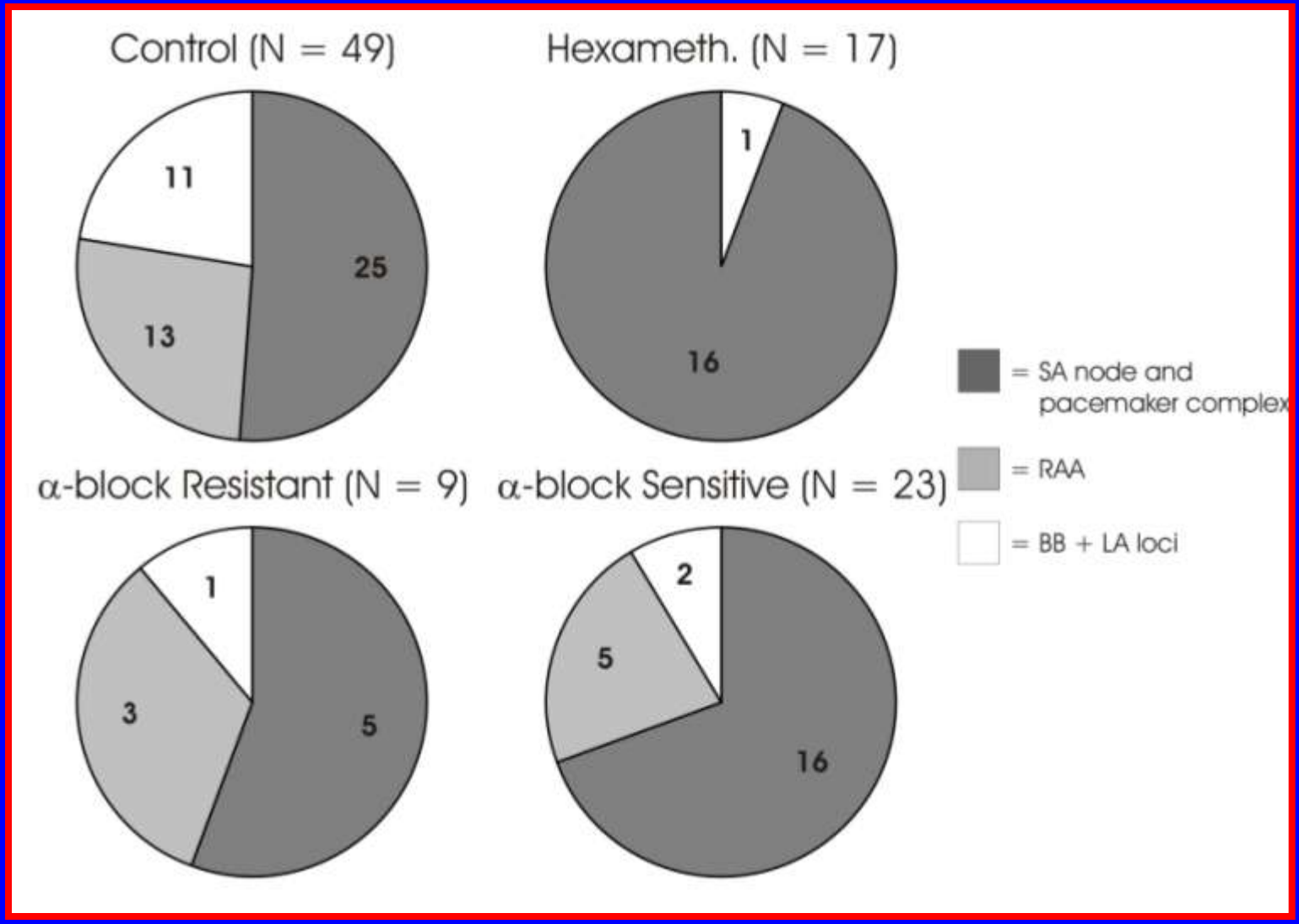


Neurally-induced arrhythmias can be modified pharmacologically

α-adrenoceptor blockade targets local circuit neurons involved in arrhythmia generation

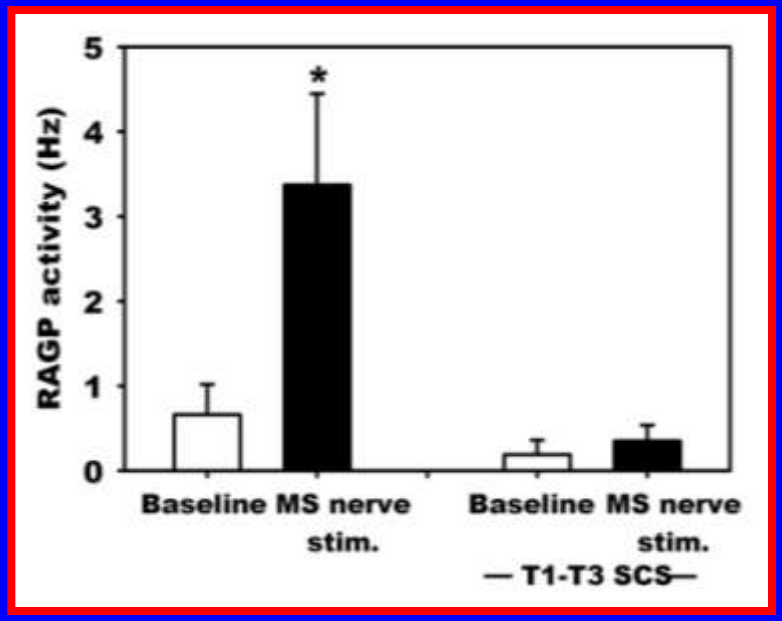


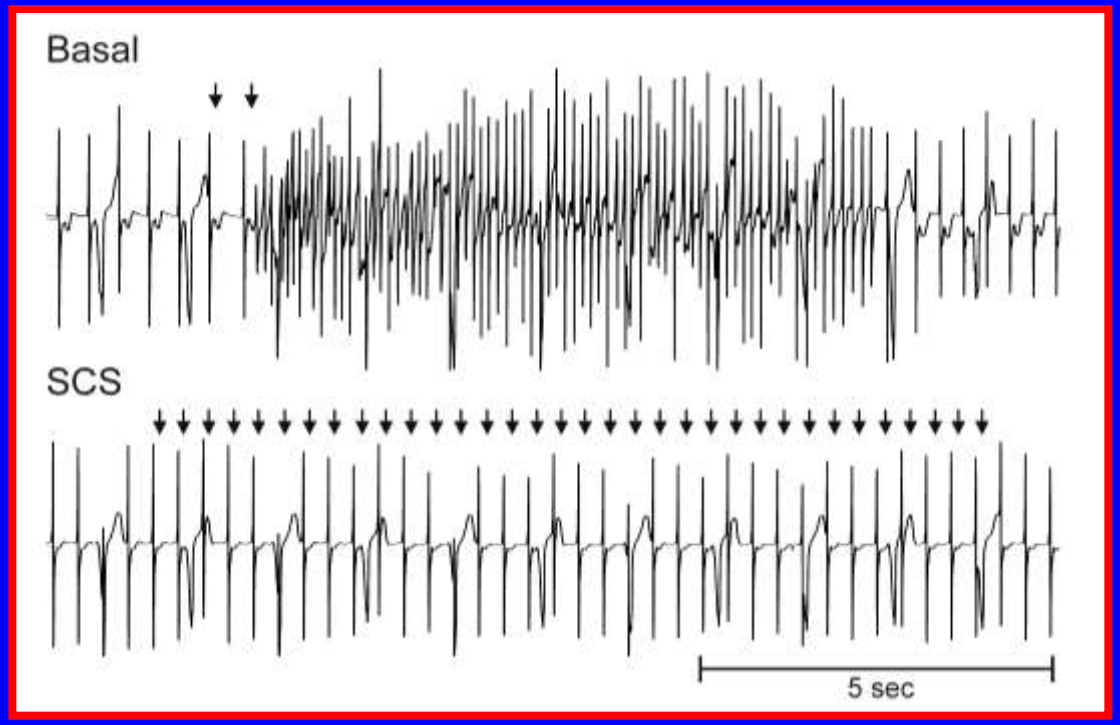
Pharmacological stabilization of intrinsic cardiac neurons reduces pacemaker dispersion to neurally-induced tachydysrhythmias



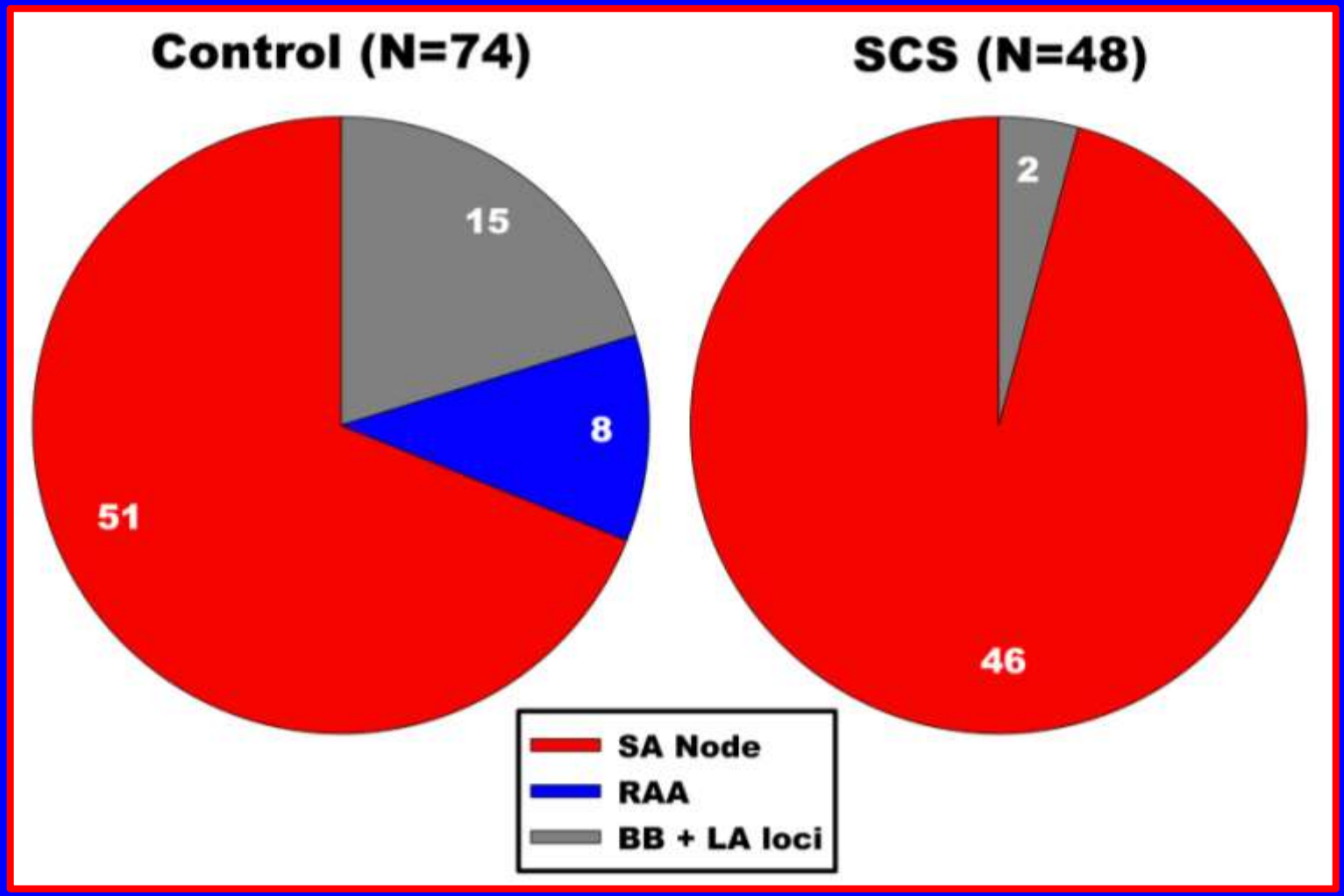
SCS neuromodulation reduces the neurally-induced potential for atrial fibrillation.

The likely target for this neuromodulation is the local circuit neurons of the intrinsic cardiac nervous system.





SCS-induced stabilization of intrinsic cardiac neurons reduces pacemaker dispersion to neurally-induced tachydysrhythmias



Conclusions

1. Mediastinal nerve stimulation induces heterogeneous activation of the intrinsic cardiac nervous system, thereby increasing the cardiac arrhythmogenic substrate.

2. SCS stabilizes the arrhythmogenic substrate created by mediastinal nerve stimulation by suppressing select elements of the intrinsic cardiac nervous system.

3. SCS-mediated stabilization of ICN function is reflected in maintenance of primary pacemaker function with the SA nodal complex, even during periods of excessive nerve inputs to the cardiac nervous system.

Overall conclusions and take home points

Most intrinsic cardiac neurons generate concurrent stochastic activity that is predicated primarily upon local network processing of cardiac chemotransduction.

These intrinsic cardiac nerve networks exhibit short-term control over regional cardiac function.

Over longer time scales, interdependent neural coordination of cardiac function is mediated via interganglionic interconnections and descending inputs.

Overall conclusions and take home points

Asymmetric activation of the cardiac nervous system contributes to adverse effects on cardiac function impacting electrical stability, myocyte viability and contractile synchrony.

Activation of subpopulations of neurons within the T1-T3 spinal segments of the spinal cord stabilizes, via activated descending projections, information processing within intrathoracic extracardiac and intrinsic cardiac ganglia (likely by targeting contained local circuit neurons).

Such stabilization of information processing with intrathoracic ganglia is fundamental to the cardioprotection afforded by spinal cord stimulation.

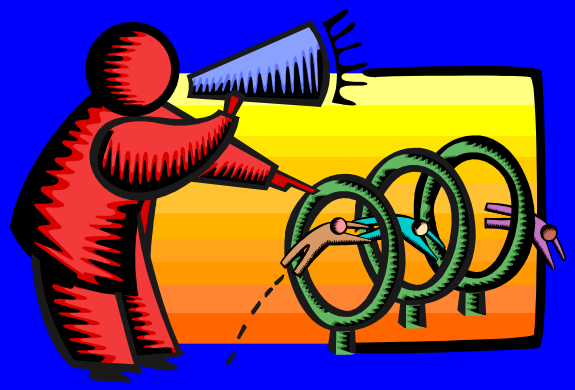
Acknowledgements

Canada
J. Andrew Armour
Rene Cardinal

Netherlands
Mike J.L. DeJongste

IWGN

Sweden
Bengt Linderoth



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Jeffrey L. Ardell
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Donald B. Hoover
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Marie Southerland