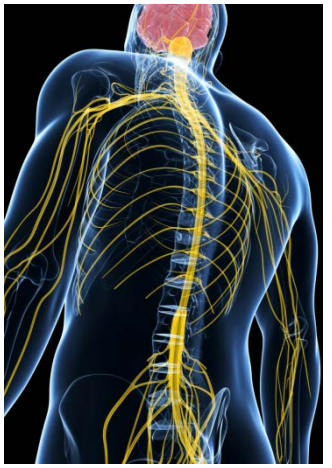
Stimulating Peripheral Activity to Relieve Conditions (SPARC)

OVERVIEW | WORKING GROUP MEMBERS | RESEARCH FUNDING | PUBLICAT

NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund



AUTONOMIC REGULATION OF CARDIAC EXCITABILITY: SCIENTIFIC FOUNDATIONS & HUMAN ARRHYTHMIAS

Kalyanam Shivkumar, MD PhD

Professor of Medicine, Radiology & Bioengineering

UCLA Health System

David Geffen School of Medicine at UCLA & Samueli School of Engineering & Applied Sciences

UCLA Cardiac Arrhythmia Center

UCLA Neurocardiology Research Center of Excellence

Acknowledgements

- ***American Heart Association***
- ***NIH***
- ***NIH-(Bio Engineering Research Partnership)***

American Heart Association

NIH National Institutes of Health
Turning Discovery Into Health

DISCLOSURES: University of California (UCLA campus) has patents developed by my group in the areas of catheter technology, embolism prevention technology, minimally invasive methods for cardiac interventions, cardiac neural diagnostics and therapeutics





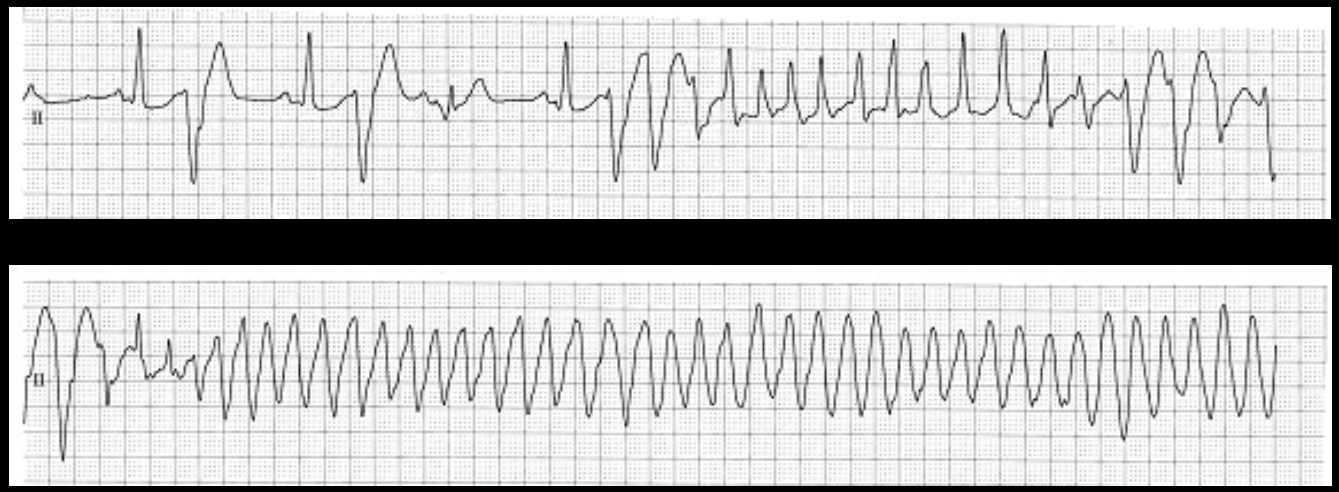







OUR PATIENT TODAY--

- **32 year old male with ‘ARVC’ (previous failed ablation) presents with incessant VT (multiple morphologies)-received 160 shocks-skin burns-intubated sedated-unstable death is imminent**



BEDSIDE TO BENCH…..

AUTONOMIC REGULATION OF THE HEART

- **Physiology and Current Understanding**
- **Neural Response to Cardiac Injury**
- **Neuraxial Therapeutic Strategies**

THE BRAIN-HEART AXIS IN EVOLUTION

Parasympathetic

Sympathetic

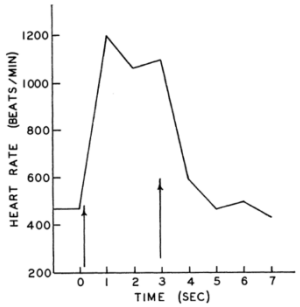
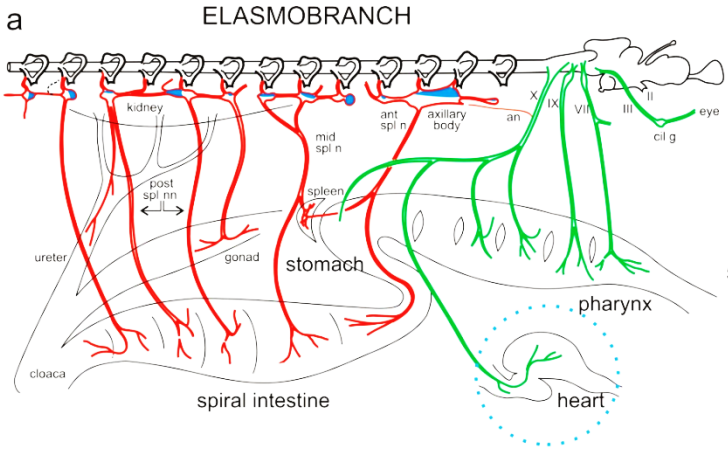
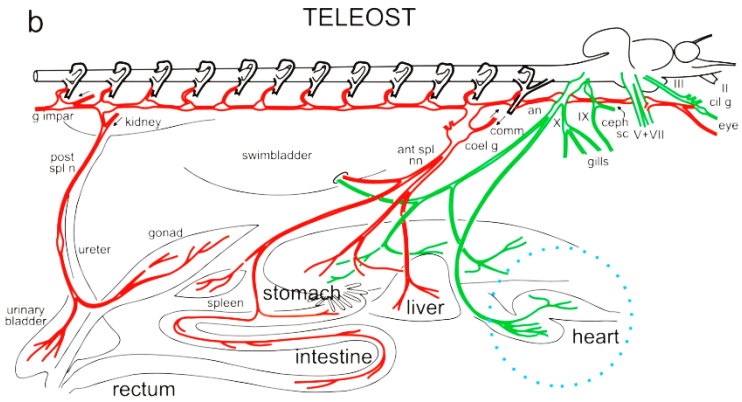
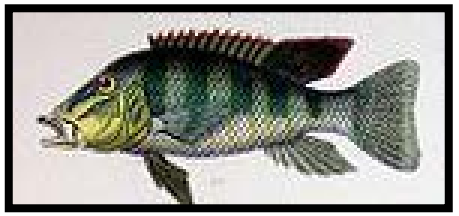


FIG. 1.—Rate of heart beat of *E. fuscus* before, during, and after flight. Arrows mark beginning and end of flight.

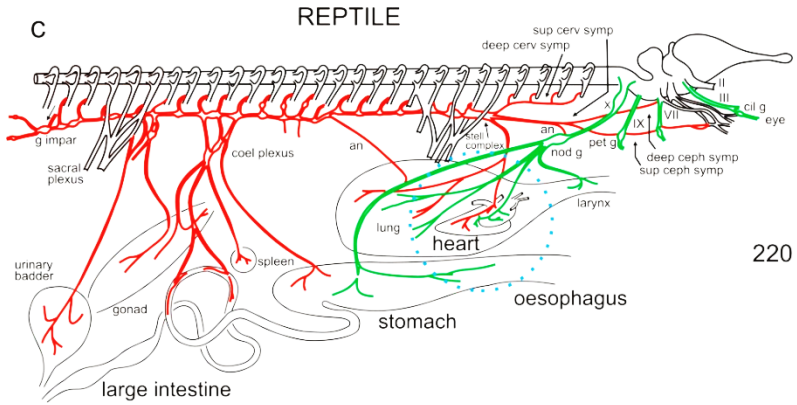


530 mil years





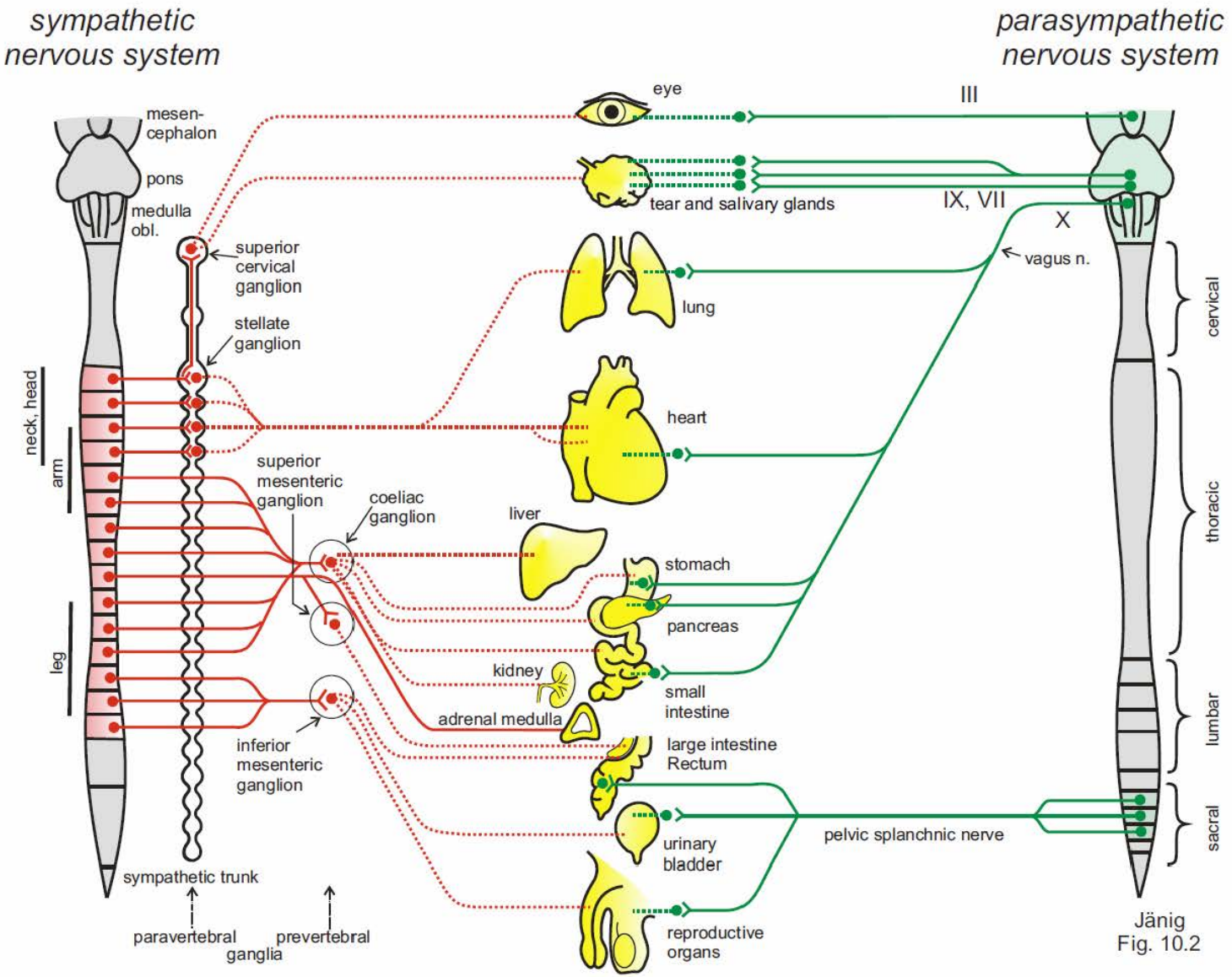
450 mil years



220 mil years

Jänig 2012 Neuroscience
(after Nilsson 1983)

THE AUTONOMIC INNERVATION OF THE VISCERA



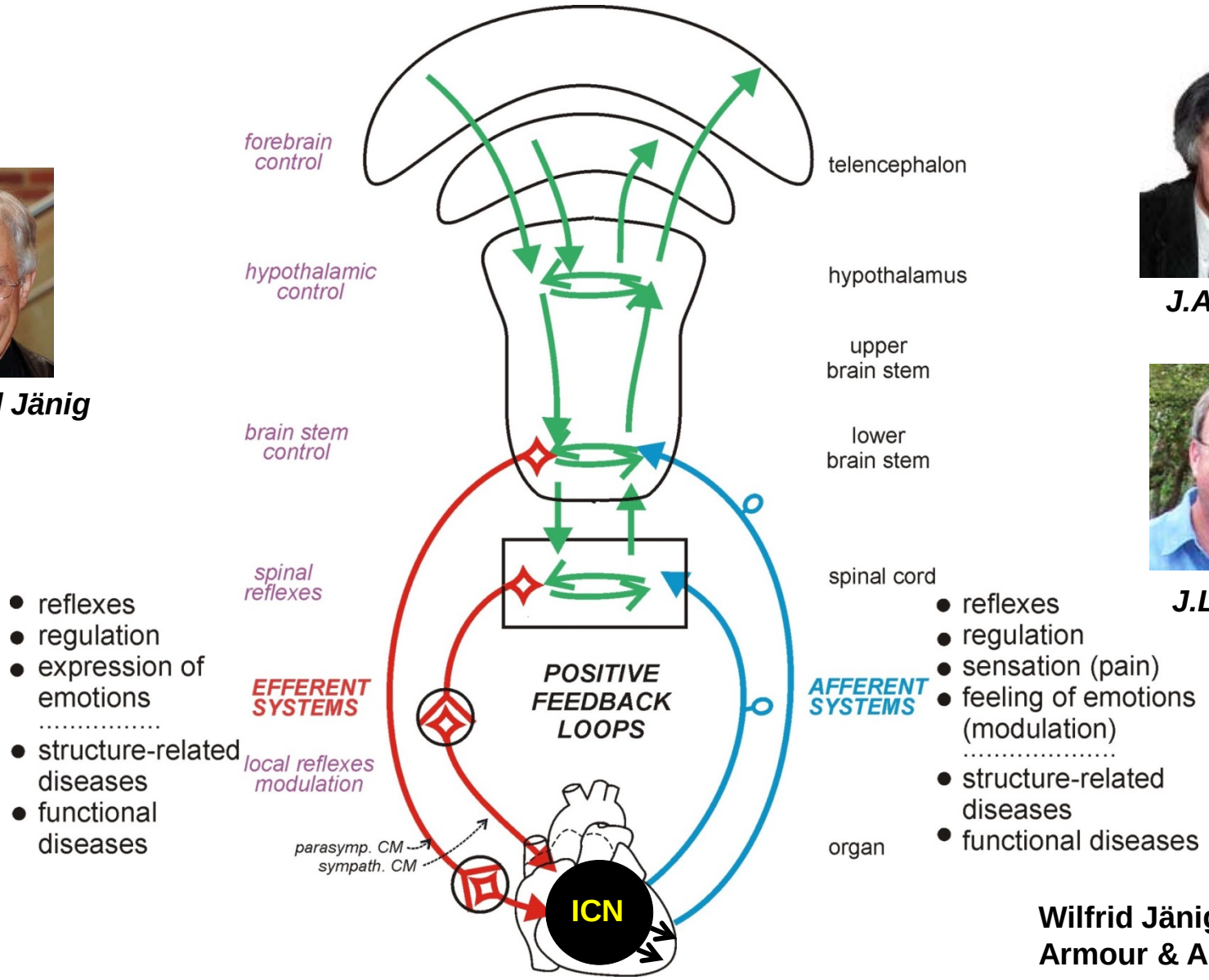
Jänig, W. The autonomic nervous system. In Galizia, G., Lledo, J.-M. (eds.) Neurosciences – From Molecule to Behavior: a University Textbook. Springer-Verlag, Berlin Heidelberg, pp. 179 - 2011 (2013)

CARDIAC NEUROTRANSMISSION

Wilfrid Jänig

J.A. Armour

J.L. Ardell

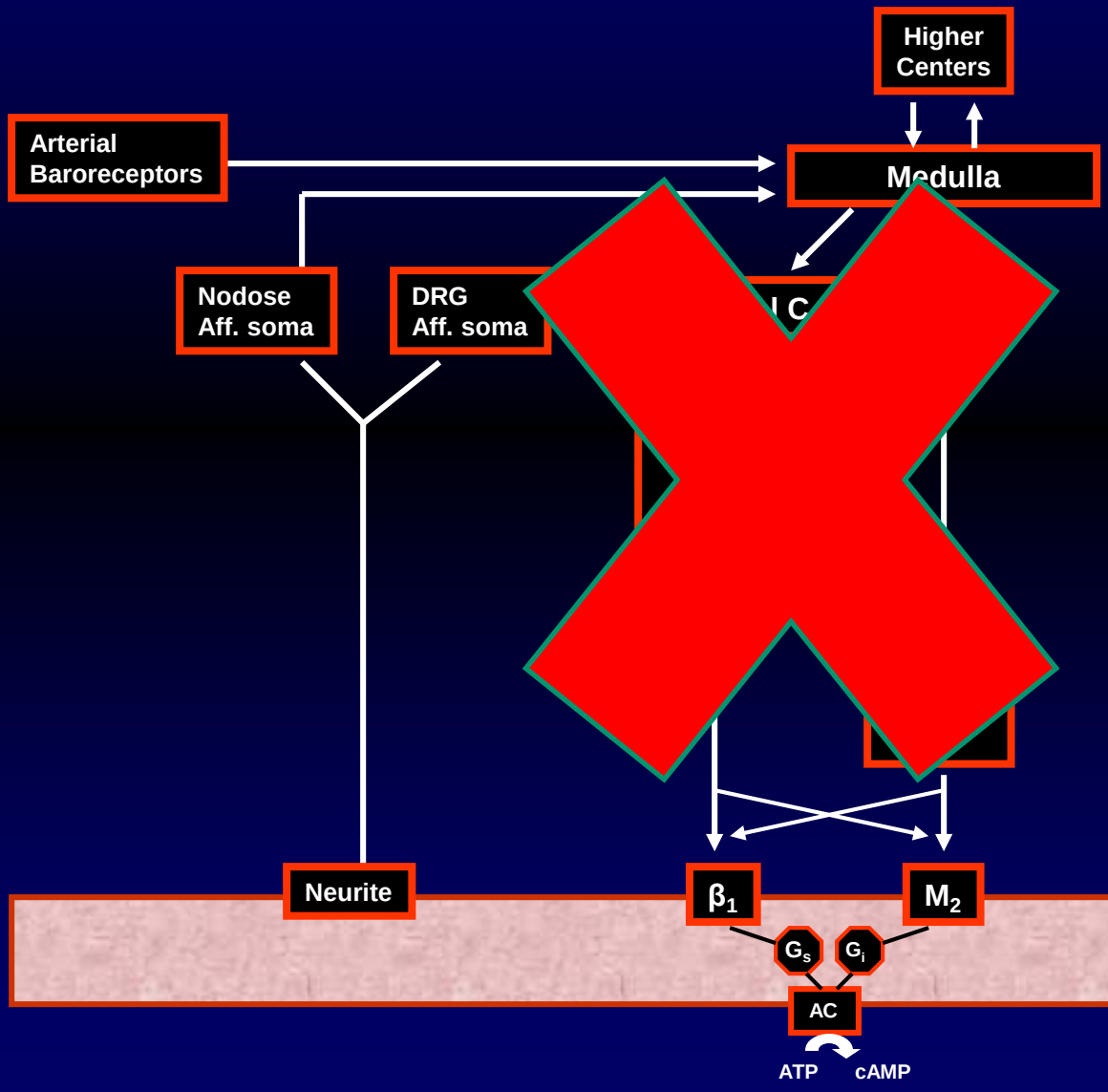


Wilfrid Jänig 2012
Armour & Ardell 2013

The Autonomic Nervous System regulates *all* cardiac physiological functions

- Chronotropy
- Dromotropy (depolarization, repolarization)
- Inotropy
- Lusitropy

Neural Control of the heart: Historical perspective

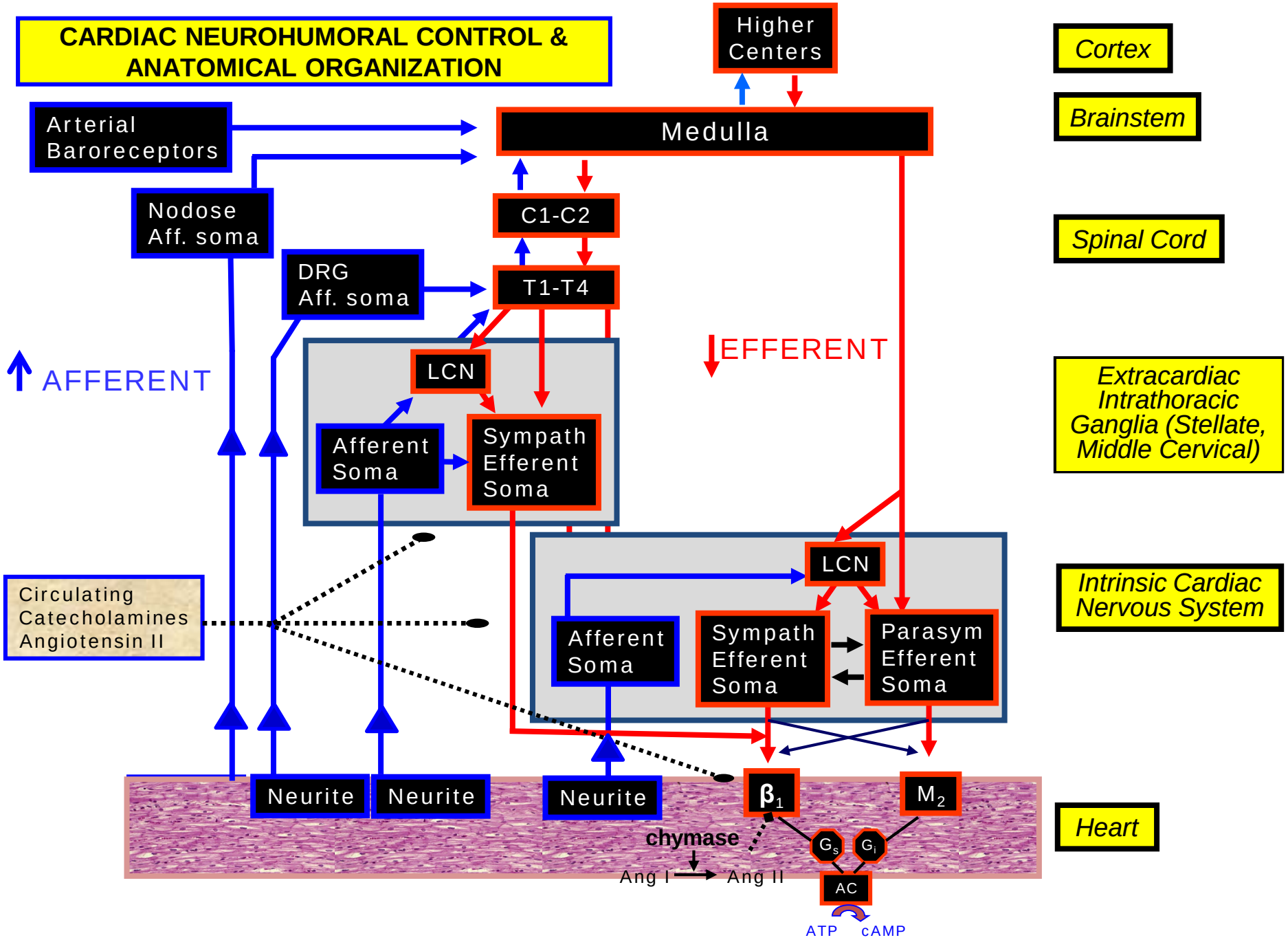


Brainstem

Spinal cord

Intrathoracic Ganglia

Heart



Fukuda K, Kanazawa H, Aizawa Y, Ardell JL & Shivkumar K: Cardiac Innervation and Sudden Cardiac Death
Circulation Research 2015 (in press)

RESEARCH-APPROACHES

EXPERIMENTAL DATA: ANIMAL

EXPERIMENTAL DATA: HUMAN

fMRI

Direct brainstem recordings

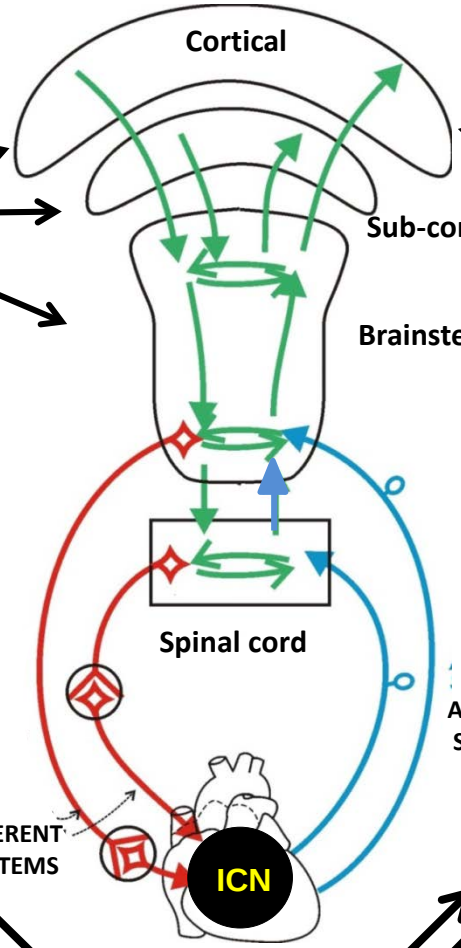
Direct spinal cord recordings

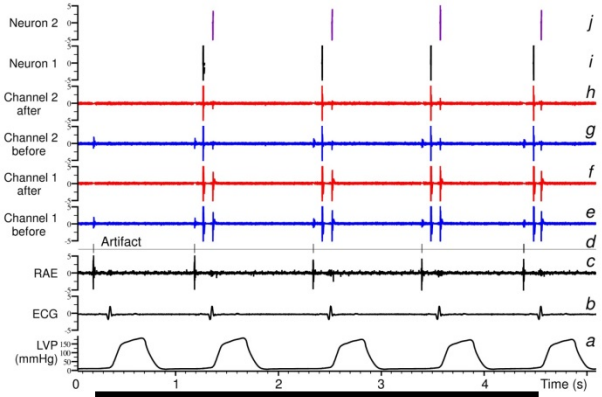
Direct cardiac neural recordings

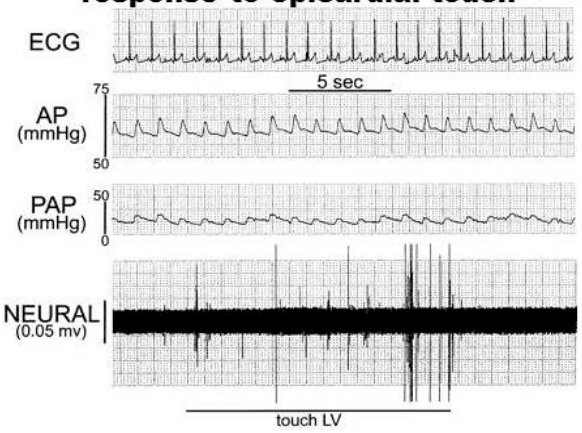
Human functional studies

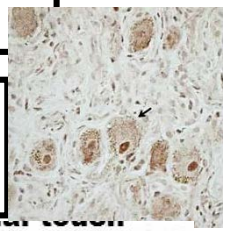
Direct stellate recordings

Direct cardiac neural recordings



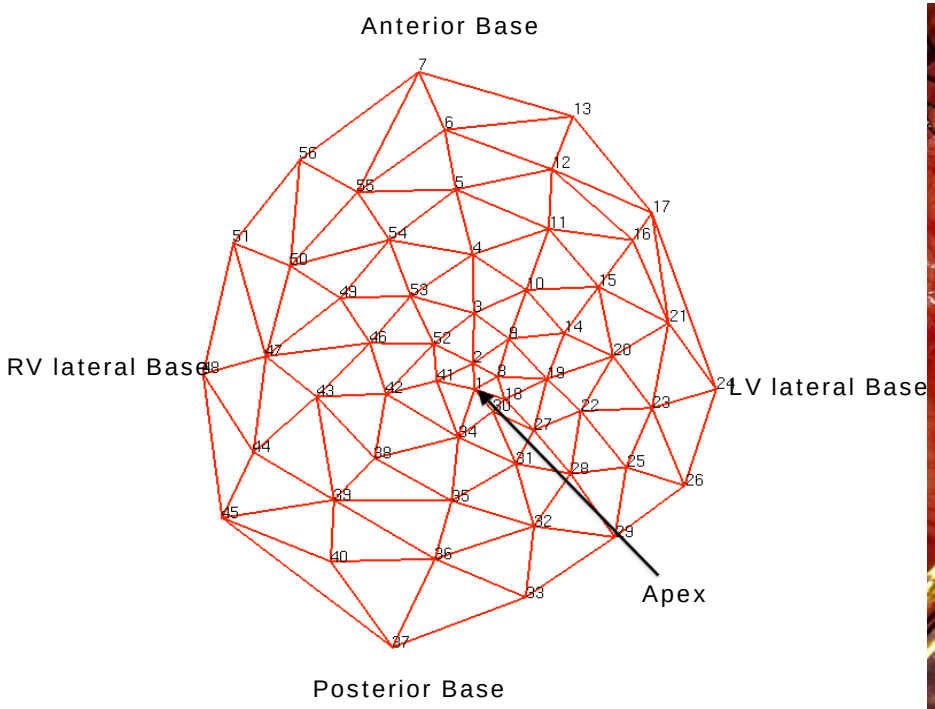


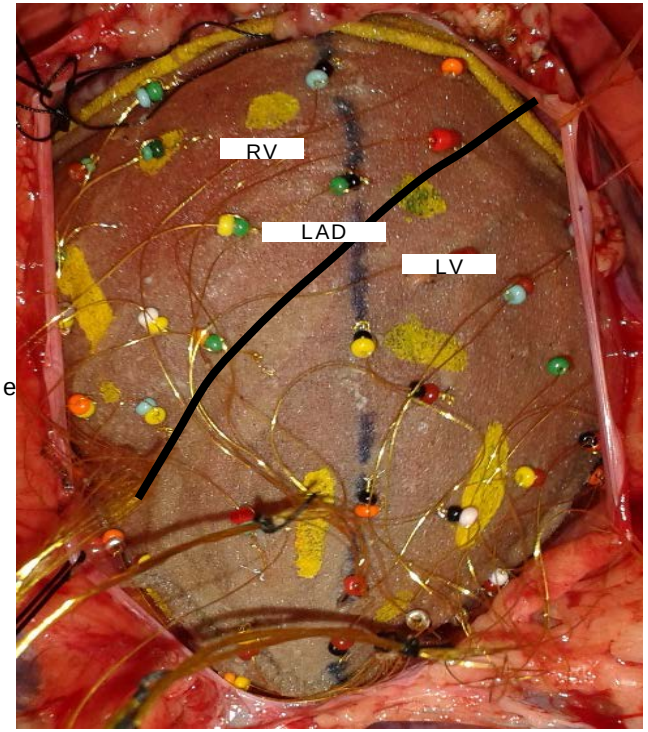


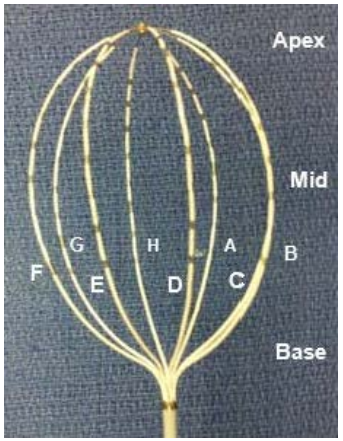


NETWORK MODELING & ANALYTICS

HIGH DENSITY EPICARDIAL AND ENDOCARDIAL MAPPING STUDIES OF AUTONOMIC MODULATION







Ajijola OA, Yagishita D, Patel KJ, Vaseghi M, Zhou W, Yamakawa K, So E, Lux RL, Mahajan A, Shivkumar K. Focal myocardial infarction induces global remodeling of cardiac sympathetic innervation: Neural remodeling in a spatial context. Am J Physiol Heart Circ Physiol. 2013;305:H1031-1040

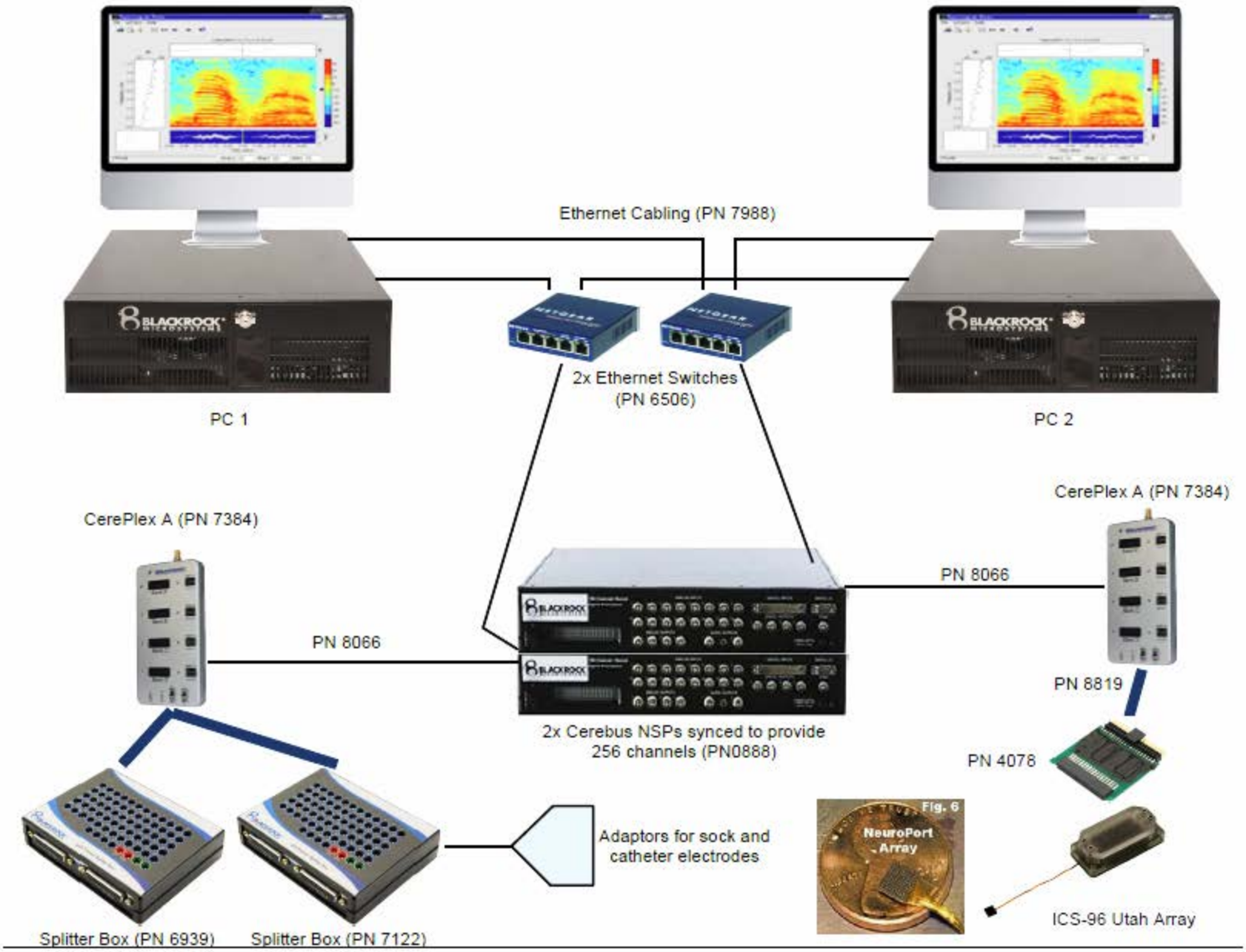
Ajijola OA, Vaseghi M, Zhou W, Yamakawa K, Benharash P, Hadaya J, Lux RL, Mahajan A, Shivkumar K. Functional differences between junctional and extrajunctional adrenergic receptor activation in mammalian ventricle. Am J Physiol Heart Circ Physiol. 2013;304:H579-588

Vaseghi M, Yamakawa K, Sinha A, So EL, Zhou W, Ajijola OA, Lux RL, Laks M, Shivkumar K, Mahajan A. Modulation of regional dispersion of repolarization and t-peak to t-end interval by the right and left stellate ganglia. Am J Physiol Heart Circ Physiol. 2013;305:H1020-1030

Zhou W, Yamakawa K, Benharash P, Ajijola O, Ennis D, Hadaya J, Vaseghi M, Shivkumar K, Mahajan A. Effect of stellate ganglia stimulation on global and regional left ventricular function as assessed by speckle tracking echocardiography. Am J Physiol Heart Circ Physiol. 2013;304:H840-847

Vaseghi M, Zhou W, Shi J, Ajijola OA, Hadaya J, Shivkumar K, Mahajan A. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. Heart Rhythm. 2012;9:1303-1309

CARDIO-NEURAL MAPPING



CARDIAC PARASYMPATHETIC AFFERENT & EFFERENT SYSTEMS

Higher Centers

Cortex

Brainstem

Medulla

Nodose Aff. soma

AFFERENT

Intrinsic Cardiac Nervous System

Parasym Efferent Soma

M_2

Neurite

Heart

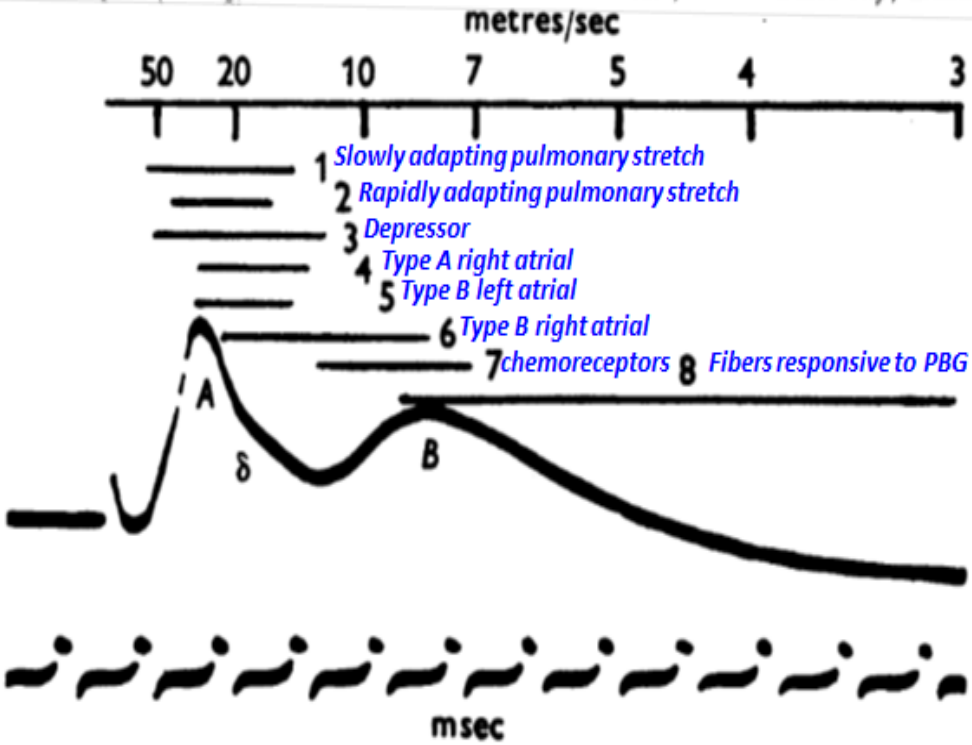
ATP cAMP

Vagal Sensory Receptors and their Reflex Effects

PHYSIOLOGICAL REVIEWS
Vol. 53, No. 1, January 1973
Printed in U.S.A.

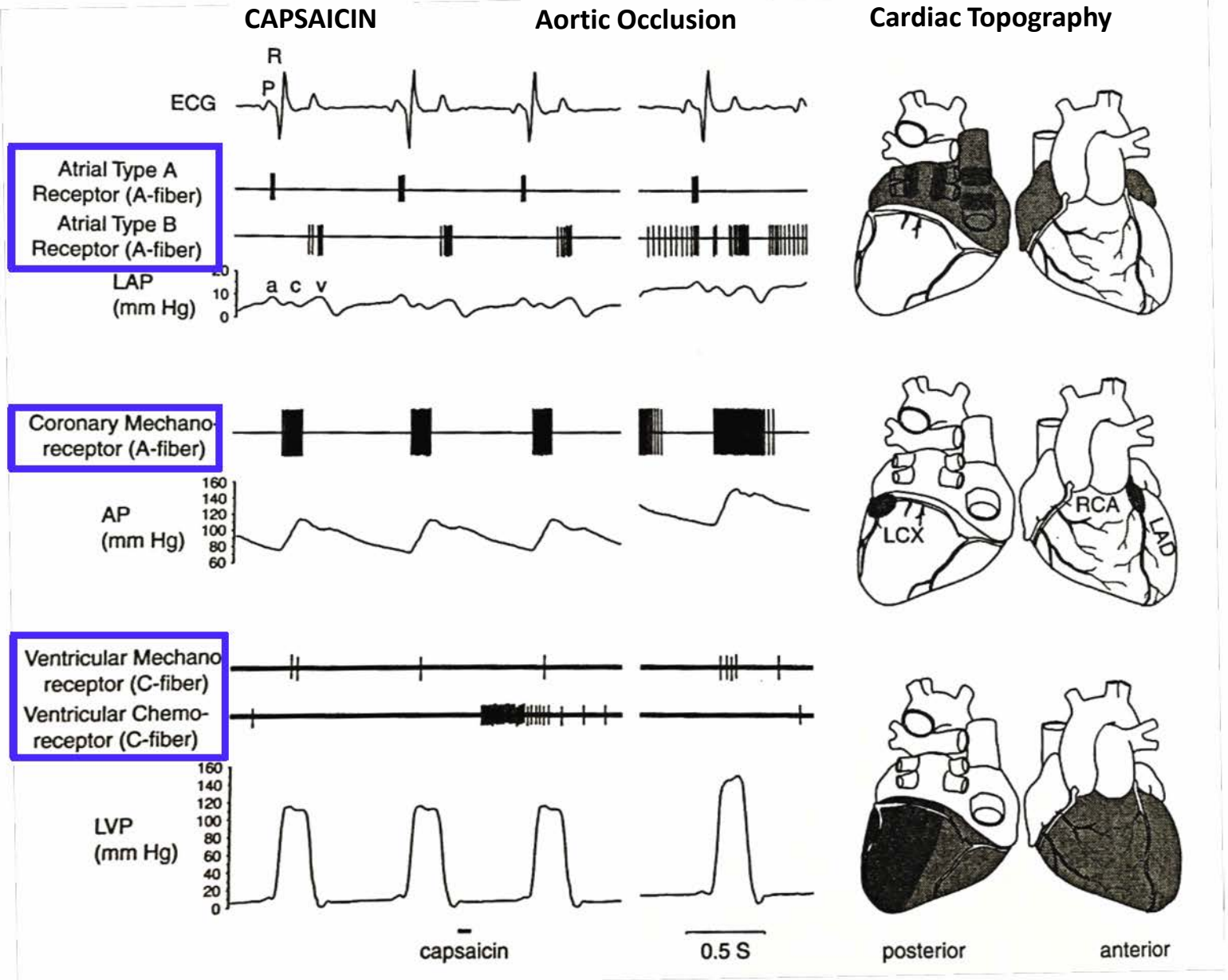
A. S. PAINTAL

Department of Physiology, Vallabhbhai Patel Chest Institute, Delhi University, Delhi, India



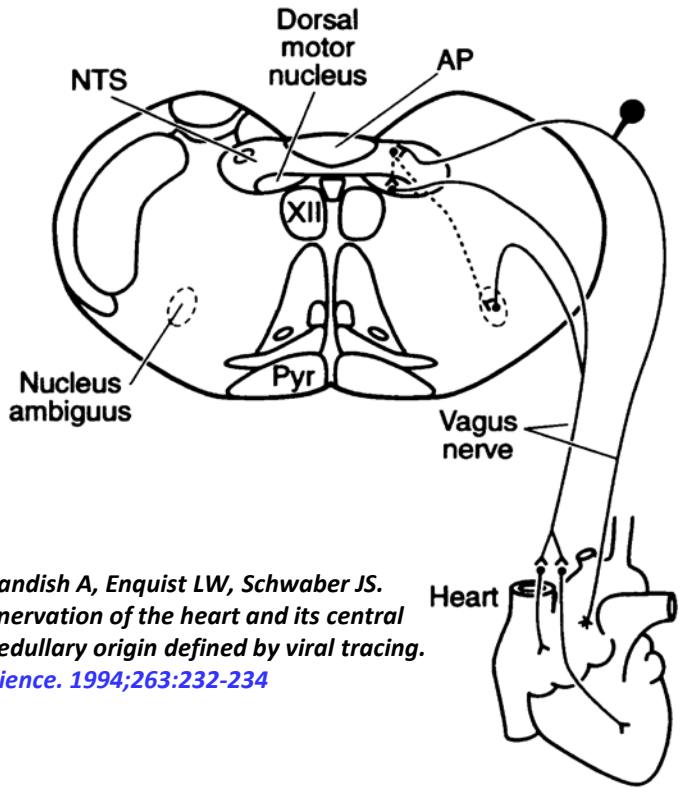
Armour JA, Ardell JL & Shivkumar K: Translational Neurocardiology 2016 (in press)

CARDIAC AFFERENT NEUROTRANSMISSION-VAGAL



Schultz, HD: Cardiac-Vagal Afferent Nerves: in 'Advances in Vagal Afferent Neurobiology' eds Undem BJ, Weinreich D, CRC Press 2005

CARDIAC PARASYMPATHETIC AFFERENT & EFFERENT SYSTEMS



Standish A, Enquist LW, Schwaber JS. Innervation of the heart and its central medullary origin defined by viral tracing. Science. 1994;263:232-234

Higher Centers

Cortex

Medulla

Brainstem

Nodose Aff. soma

EFFERENT

AFFERENT

LCN

Afferent Soma

Sympath Efferent Soma

Parasym Efferent Soma

Intrinsic Cardiac Nervous System

Neurite

β_1

M_2

Neurite

chymase

Ang I → Ang II

G_s

G_i

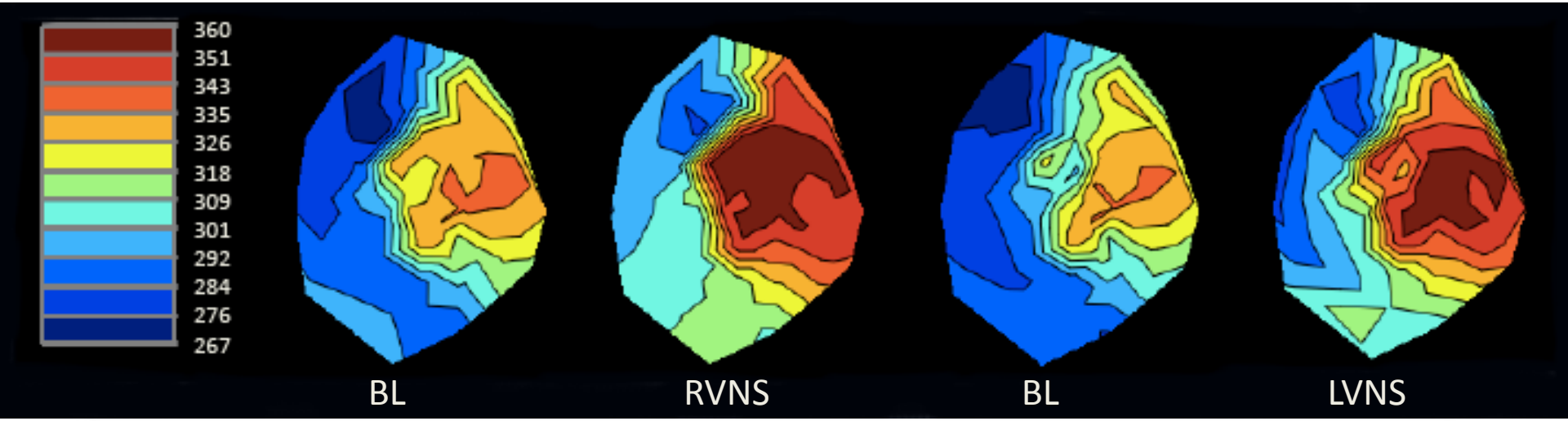
AC

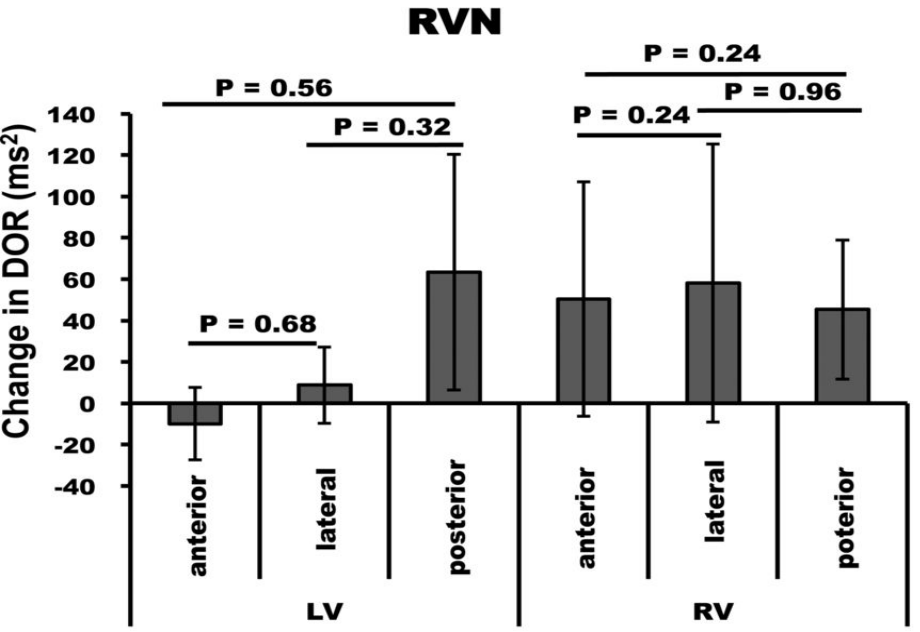
ATP cAMP

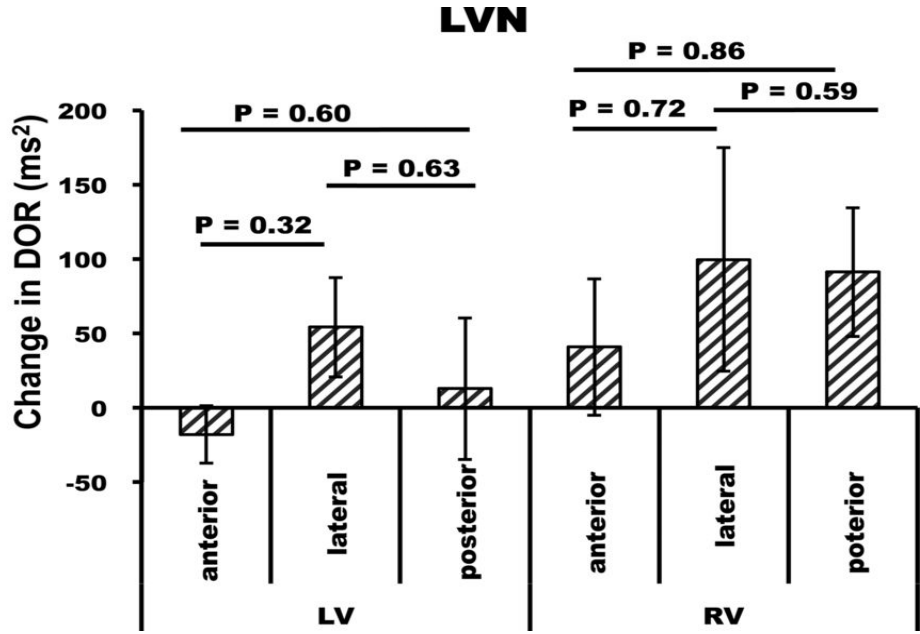
Heart

Armour JA, Ardell JL & Shivkumar K: Translational Neurocardiology 2016 (in press)

VENTRICULAR ELECTROPHYSIOLOGICAL EFFECTS OF VAGAL STIMULATION





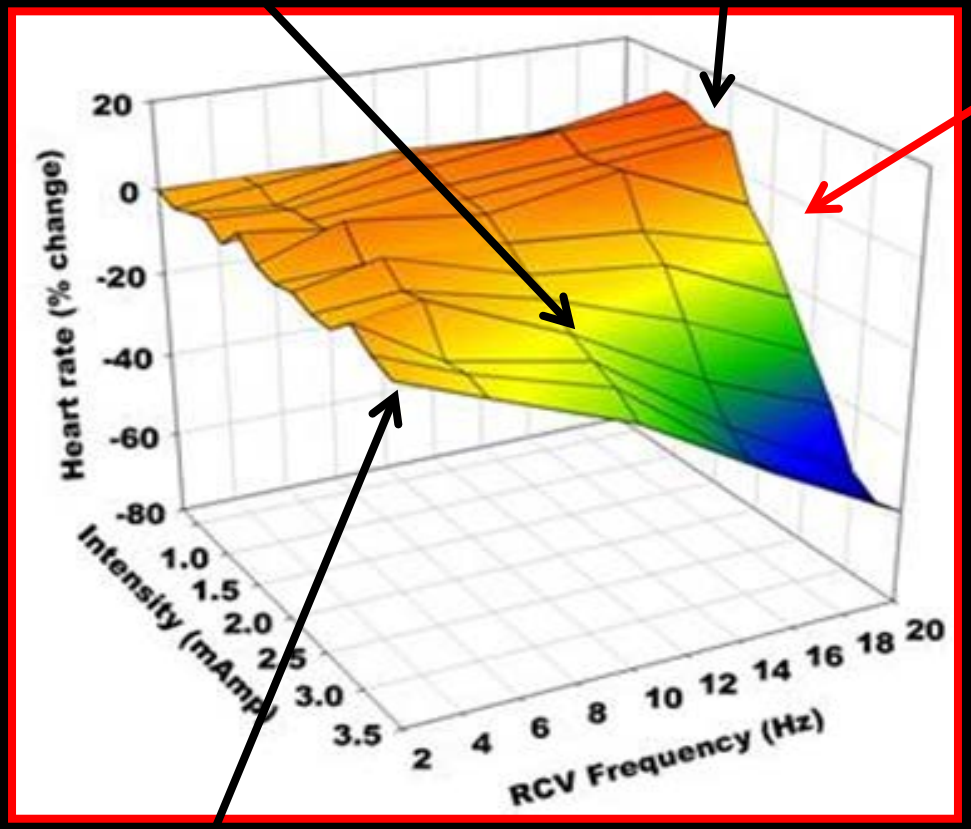


Yamakawa K, So EL, Rajendran PS, Hoang JD, Makkar N, Mahajan A, Shivkumar K, Vaseghi M. Electrophysiological effects of right and left vagal nerve stimulation on the ventricular myocardium. ***Am J Physiol Heart Circ Physiol. 2014;307:H722-731***

NEED FOR A MECHANISTIC UNDERSTANDING OF VAGAL STIMULATION: THE INITIAL HUMAN STUDIES

ANTHEM-HF

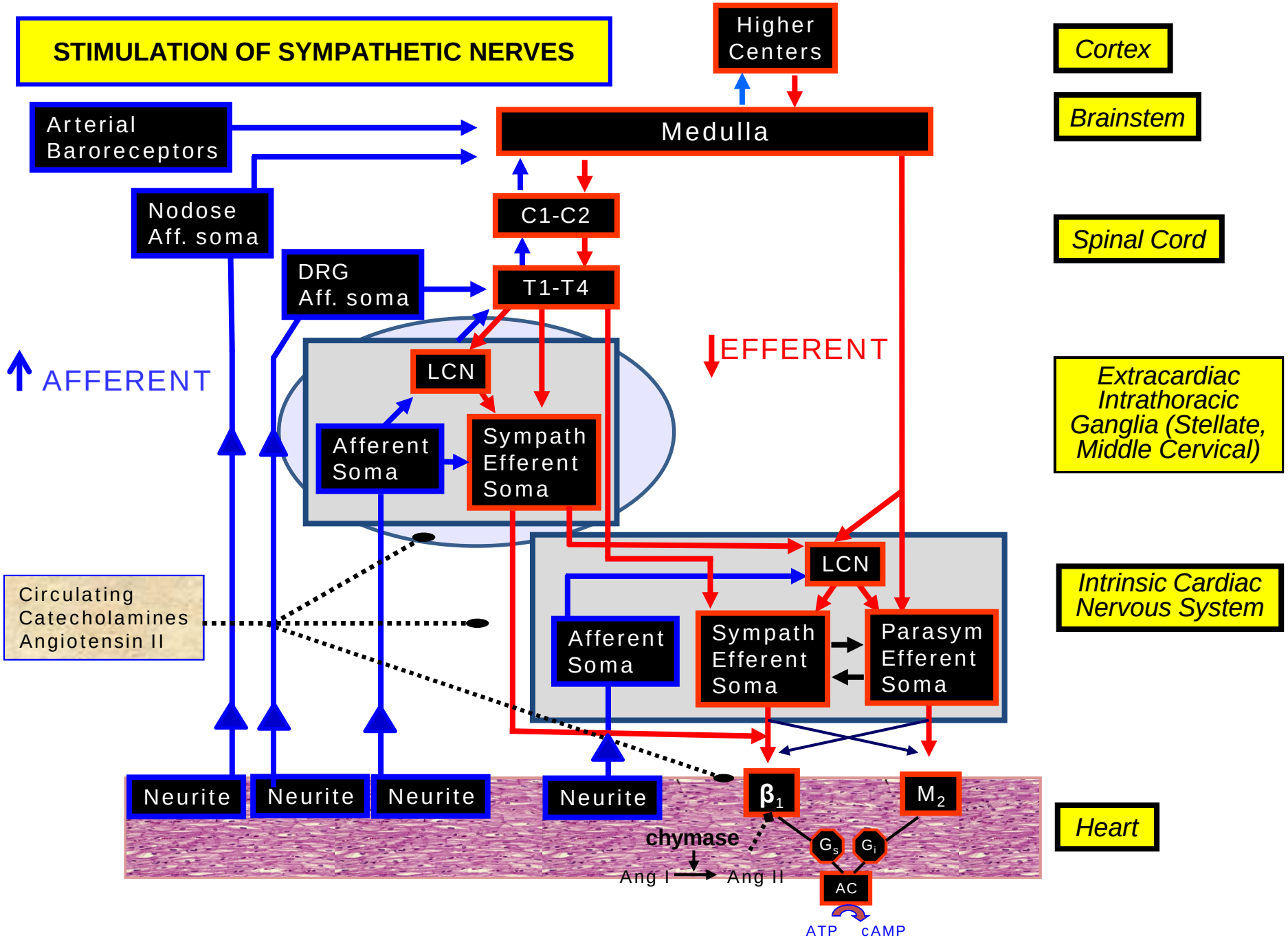
NECTAR-HF



neural fulcrum

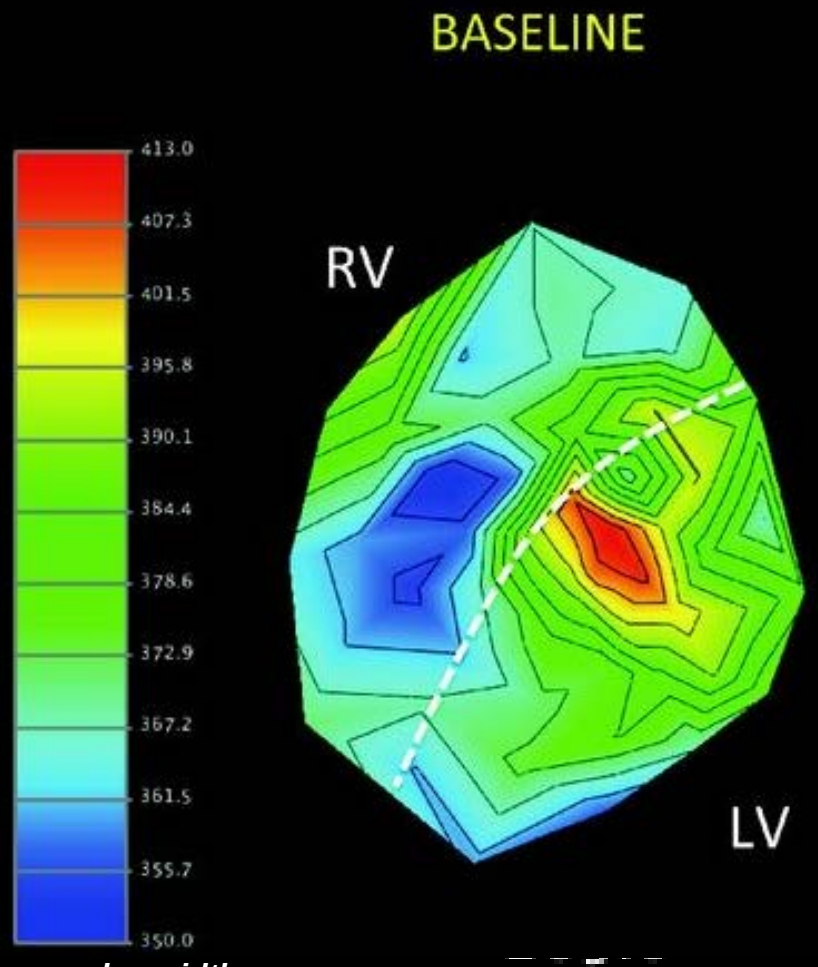
INOVATE-HF

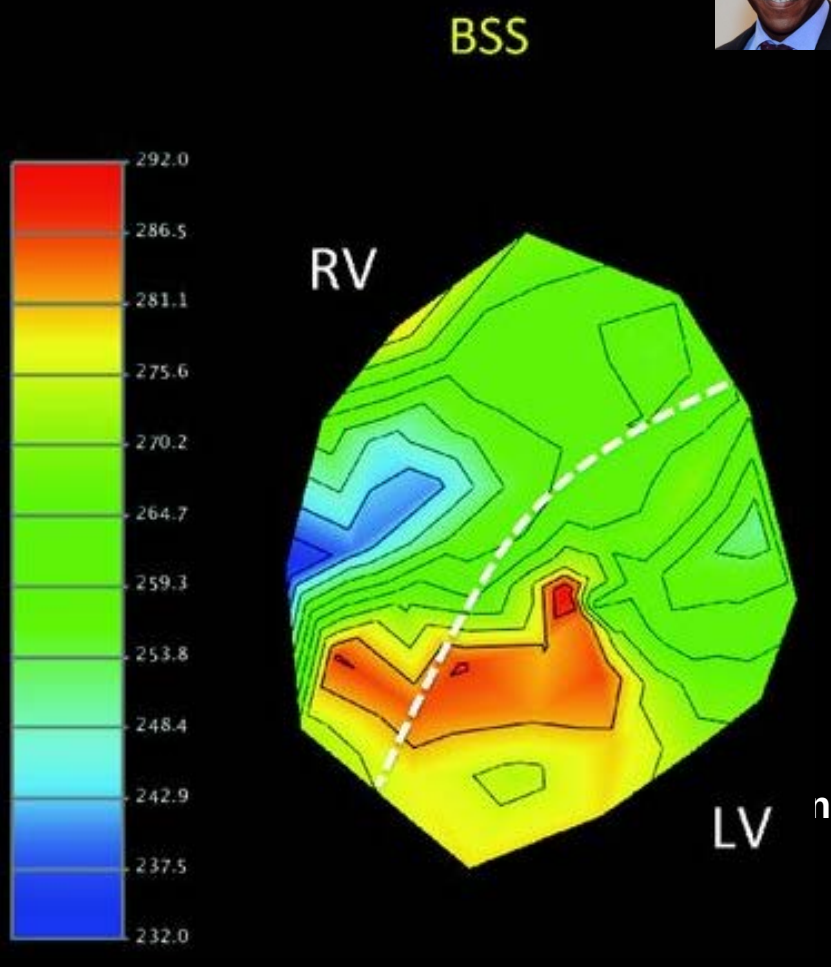
Ardell JL : ART: Vagal Stimulation: in Translational Neurocardiology 2016 eds. Armour, Ardell and Shivkumar (in press)



Fukuda K, Kanazawa H, Aizawa Y, Ardell JL & Shivkumar K: Cardiac Innervation and Sudden Cardiac Death
Circulation Research 2015 (in press)

EFFECT OF SYMPATHETIC EFFERENT NERVE STIMULATION : JUNCTIONAL vs. EXTRA-JUNCTIONAL EFFECTS IN SPATIAL CONTEXT

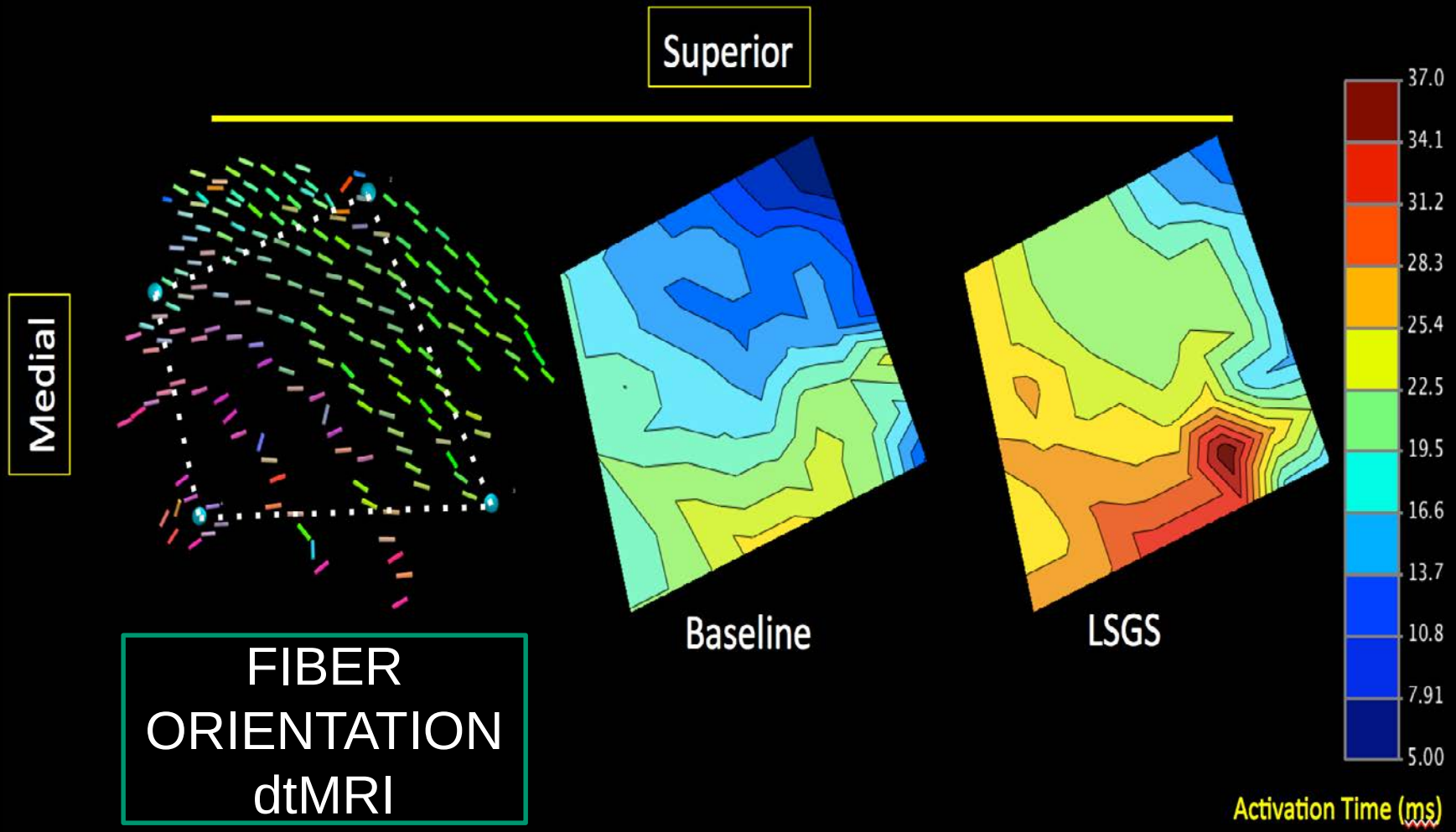




5 ms pulse width
5 ms delay
5 Hz
5 10 Volts

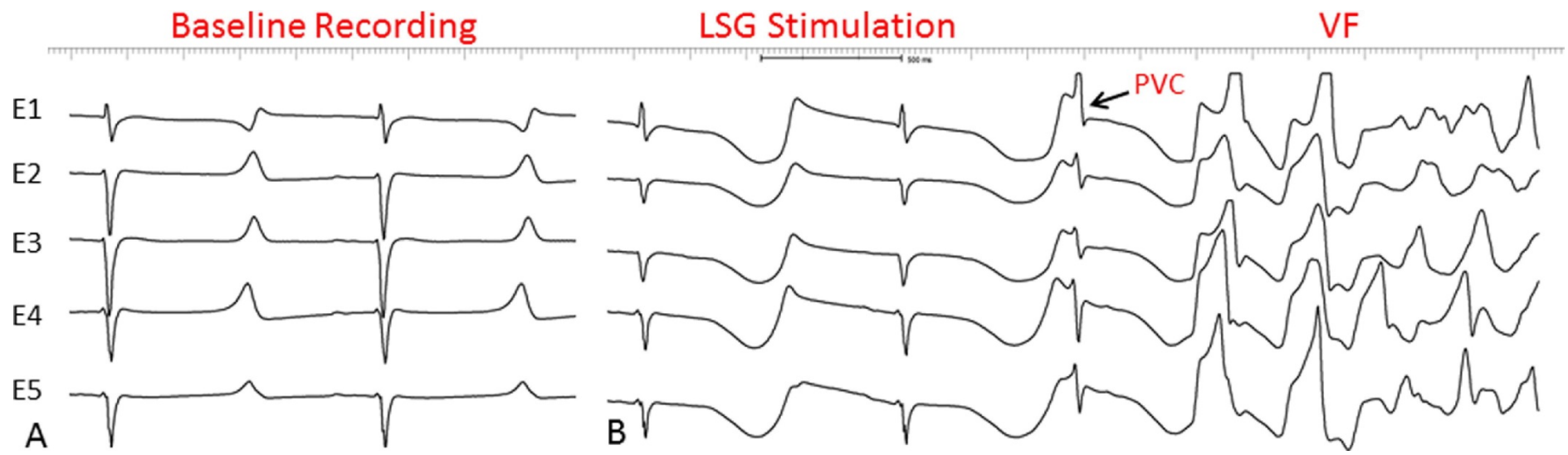
Ajijola OA, Vaseghi M, Zhou W, Yamakawa K, Benharash P, Hadaya J, Lux RL, Mahajan A, Shivkumar K. Functional Differences Between Junctional and Extra Junctional Adrenergic Receptor Activation in Mammalian Ventricle . American Journal of Physiology (Heart & Circulatory Physiol) 2013;304:H579 588

CARDIAC NERVES POWERFULLY CONTROL MUSCLE PROPAGATION



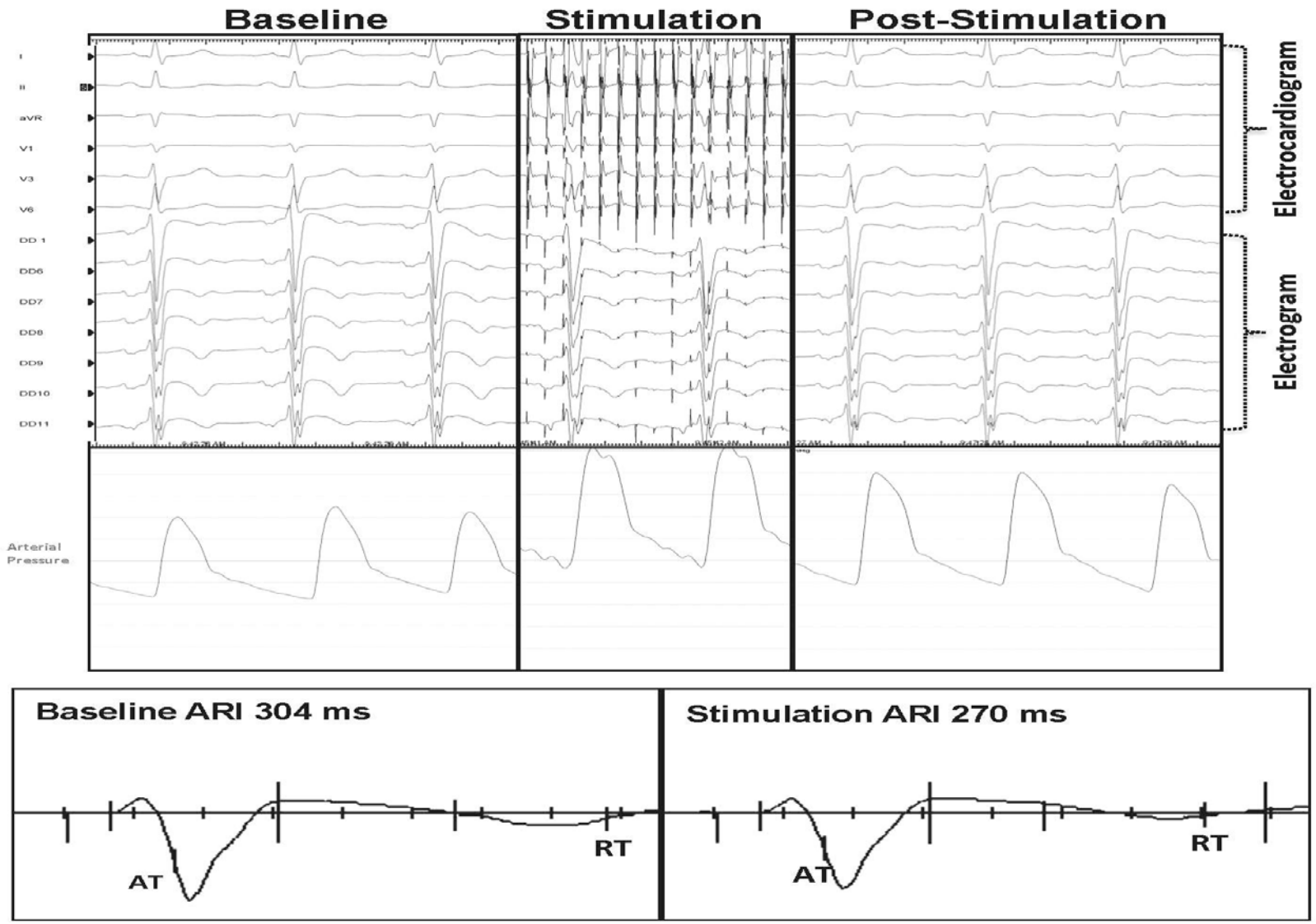
Ajijola OA, Aliotta E, Kwon OJ, Nakamura K, Yamakawa K, So E, Khahera A, Irie T, Ennis D, and Shivkumar . Functional Control of Electrical Propagation in Ventricular Myocardium. 2015 (submitted)

NERVE STIMULATION CAN INDUCE LETHAL ARRHYTHMIAS IN A NORMAL HEART



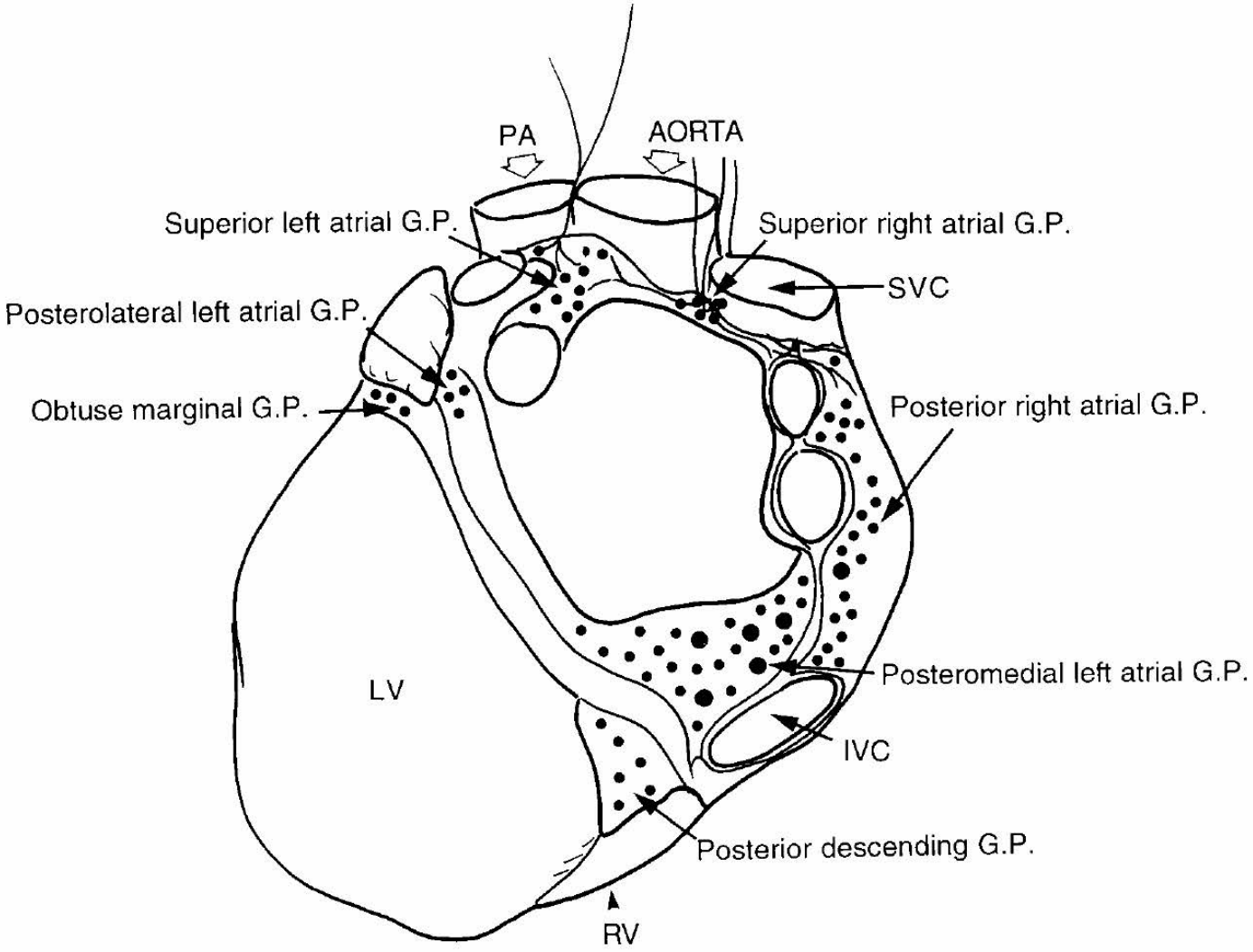
Vaseghi M, Zhou W, Shi J, Ajijola OA, Hadaya J, Shivkumar K, Mahajan A. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. Heart Rhythm. 2012;9:1303-1309

PERCUTANEOUS STIMULATION OF THE STELLATE GANGLION IN HUMANS



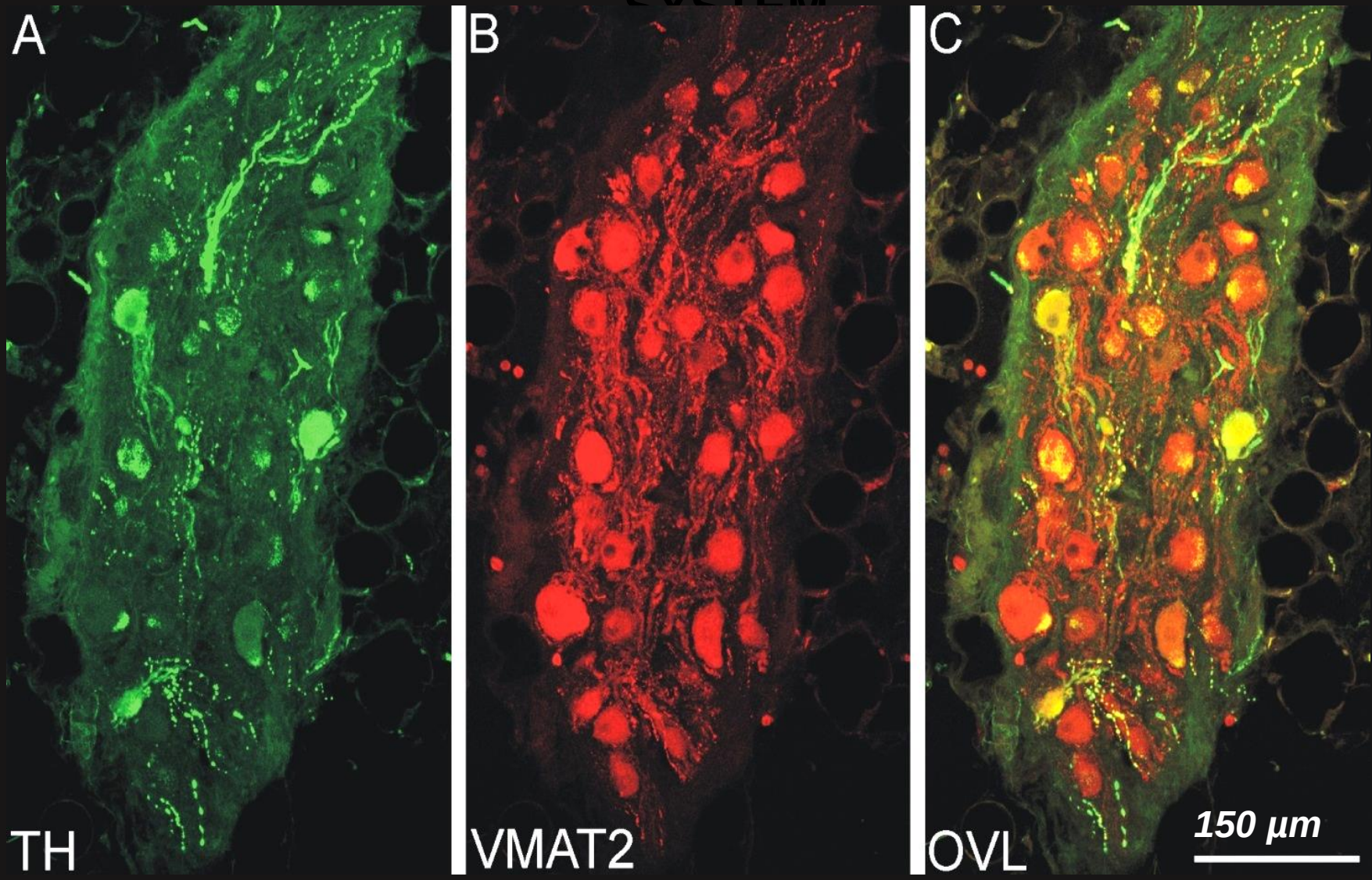
Ajijola OA, Howard-Quijano K, Scovotti J, Vaseghi M, Lee C, Mahajan A & Shivkumar K. Augmentation Of Cardiac Sympathetic Tone By Percutaneous Low Level Stellate Ganglion Stimulation In Humans: A Feasibility Study. ***Physiological Reports 2015*** *(in press)*

Human Cardiac Intrinsic Nervous System



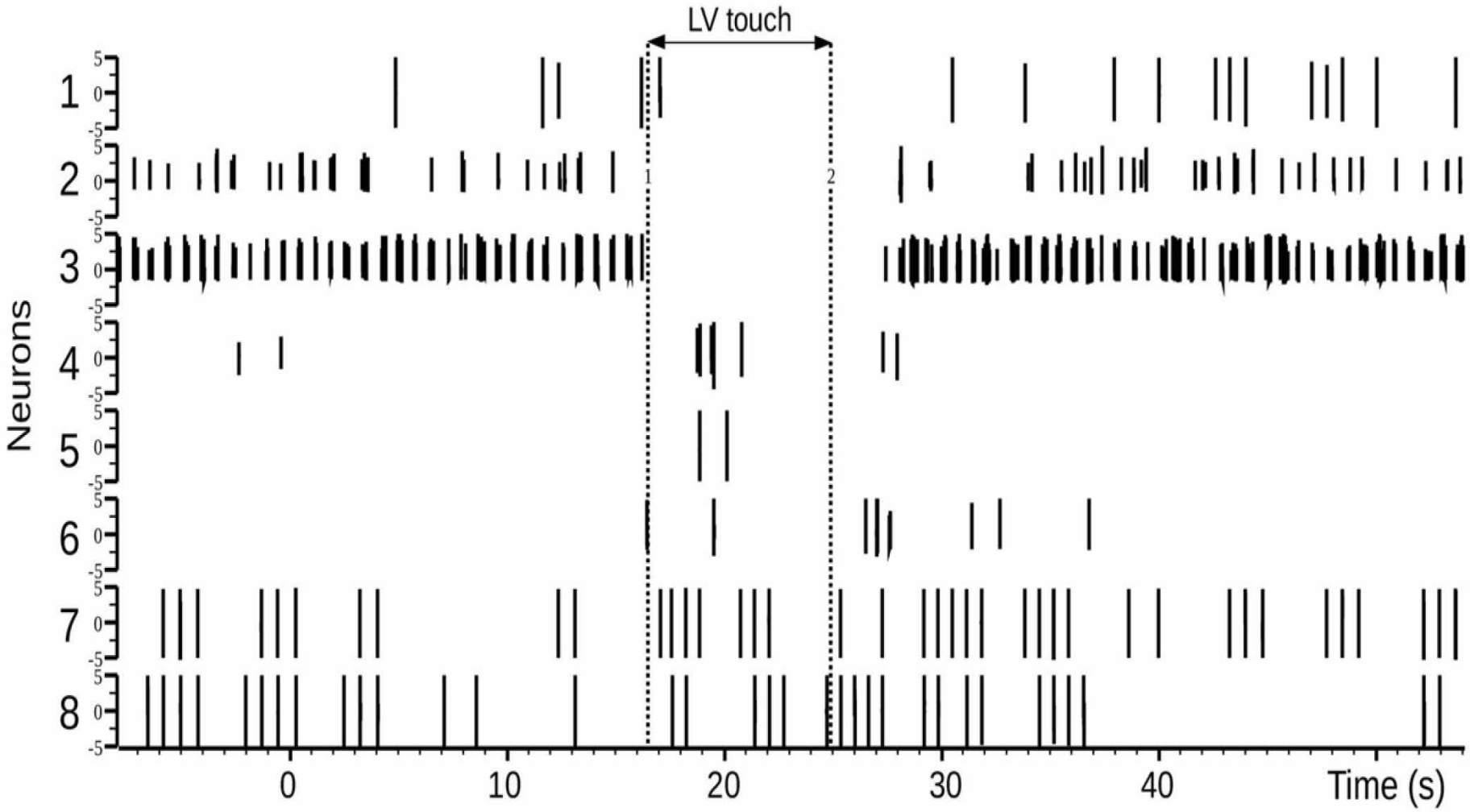
Armour JA, Murphy DA, Yuan BX, MacDonald S, Hopkins D. Gross and Microscopic Anatomy of the Human Intrinsic Cardiac Nervous System. The Anatomical Record 247:289–298 (1997)

HUMAN CARDIAC INTRINSIC NERVOUS SYSTEM



Hoover DB, Isaacs ER, Jacques F et-al. Localization of multiple neurotransmitters in surgically derived specimens of human atrial ganglia. Neuroscience. 2009;164 (3): 1170-9

NETWORK INTERACTIONS WITHIN THE CARDIAC INTRINSIC NERVOUS SYSTEM

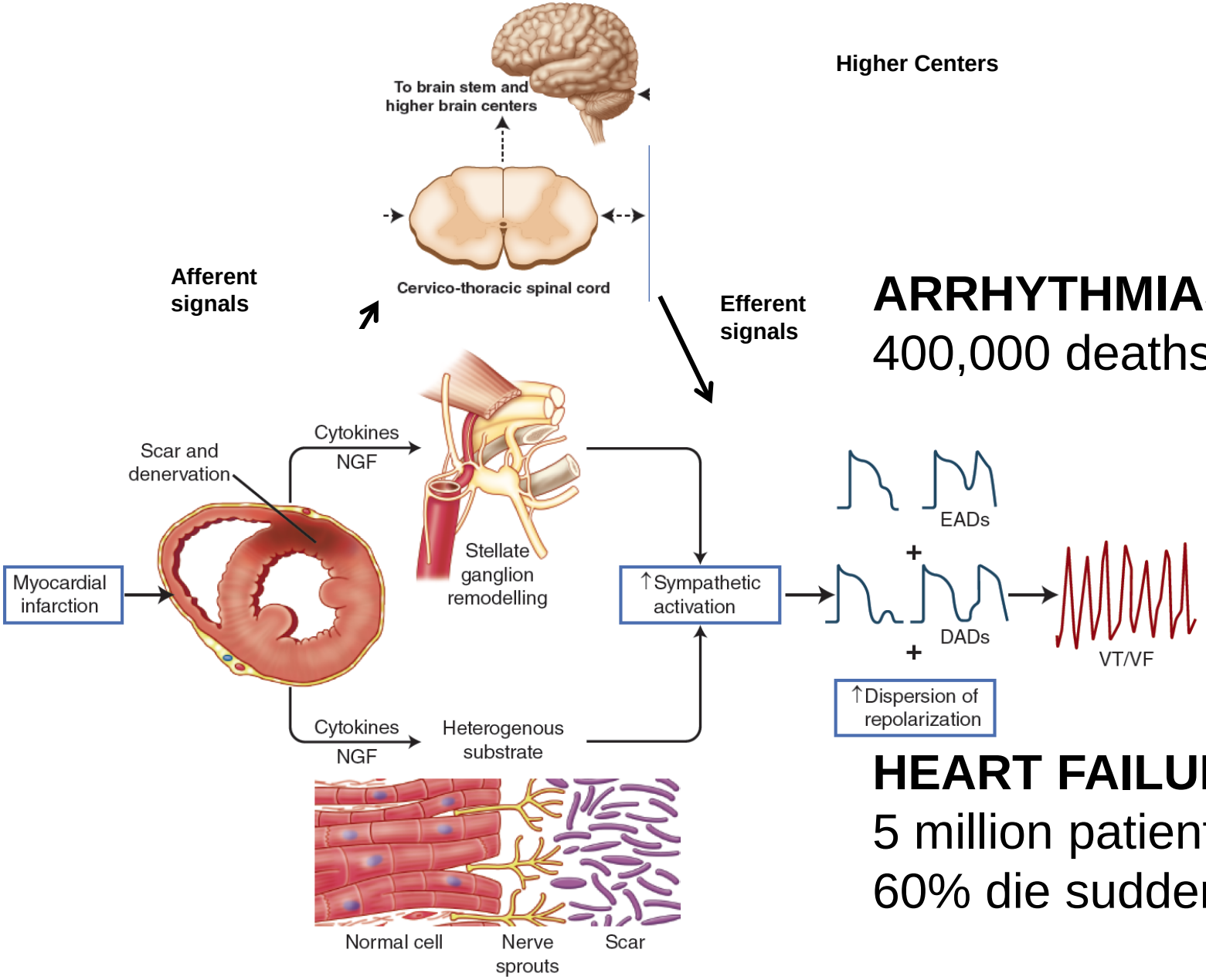


Beaumont E, Salavatian S, Southerland EM, Vinet A, Jacquemet V, Armour JA, Ardell JL: ***Journal of Physiology 2013;591:4515-4533***

AUTONOMIC REGULATION OF THE HEART

- Physiology and Current Understanding
- Neural Response to Cardiac Injury
- Neuraxial Therapeutic Strategies

STRUCTURE -FUNCTION INTERPLAY: SUDDEN DEATH AND HEART FAILURE



ARRHYTHMIAS

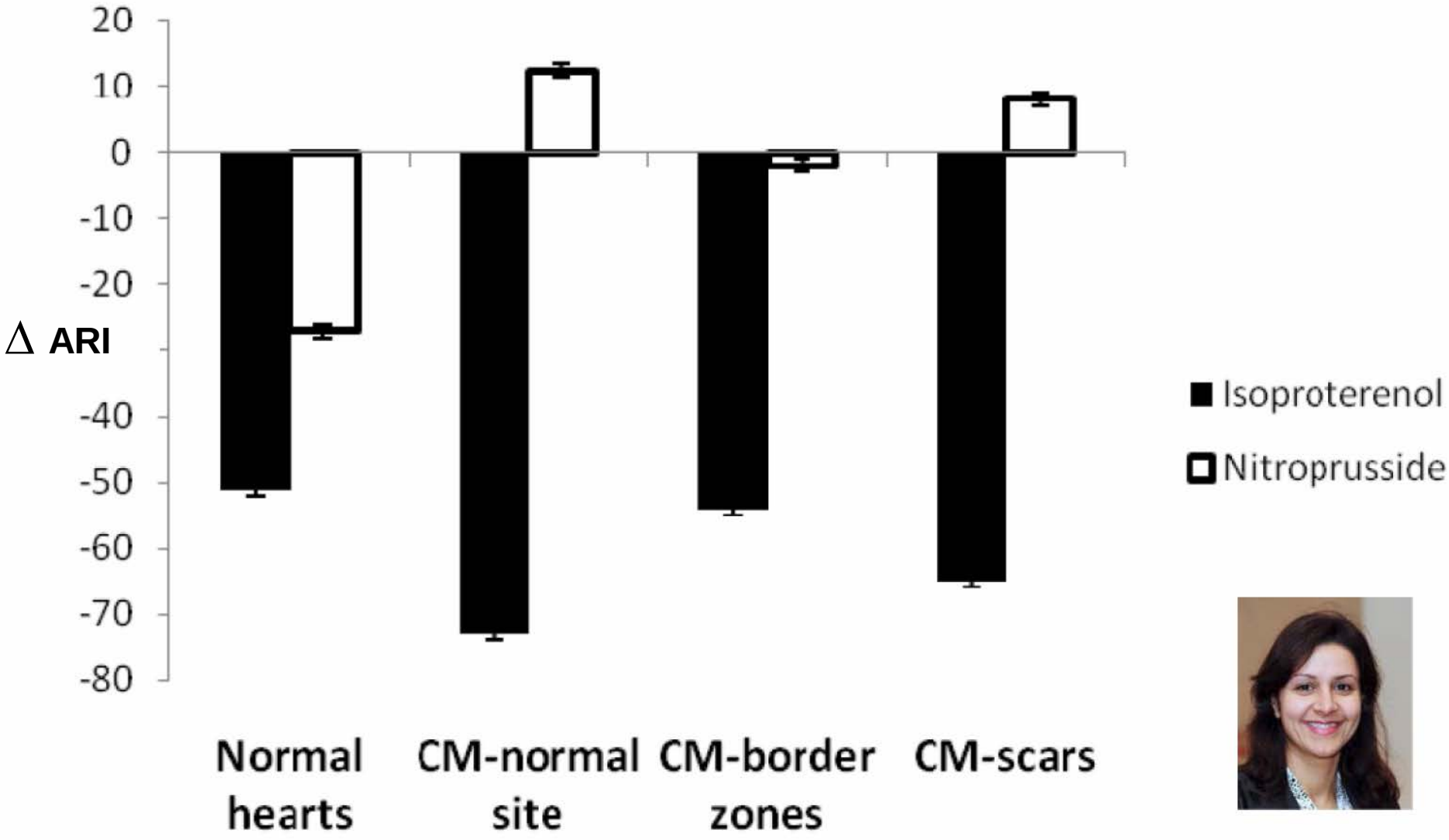
400,000 deaths/yr

HEART FAILURE

5 million patients

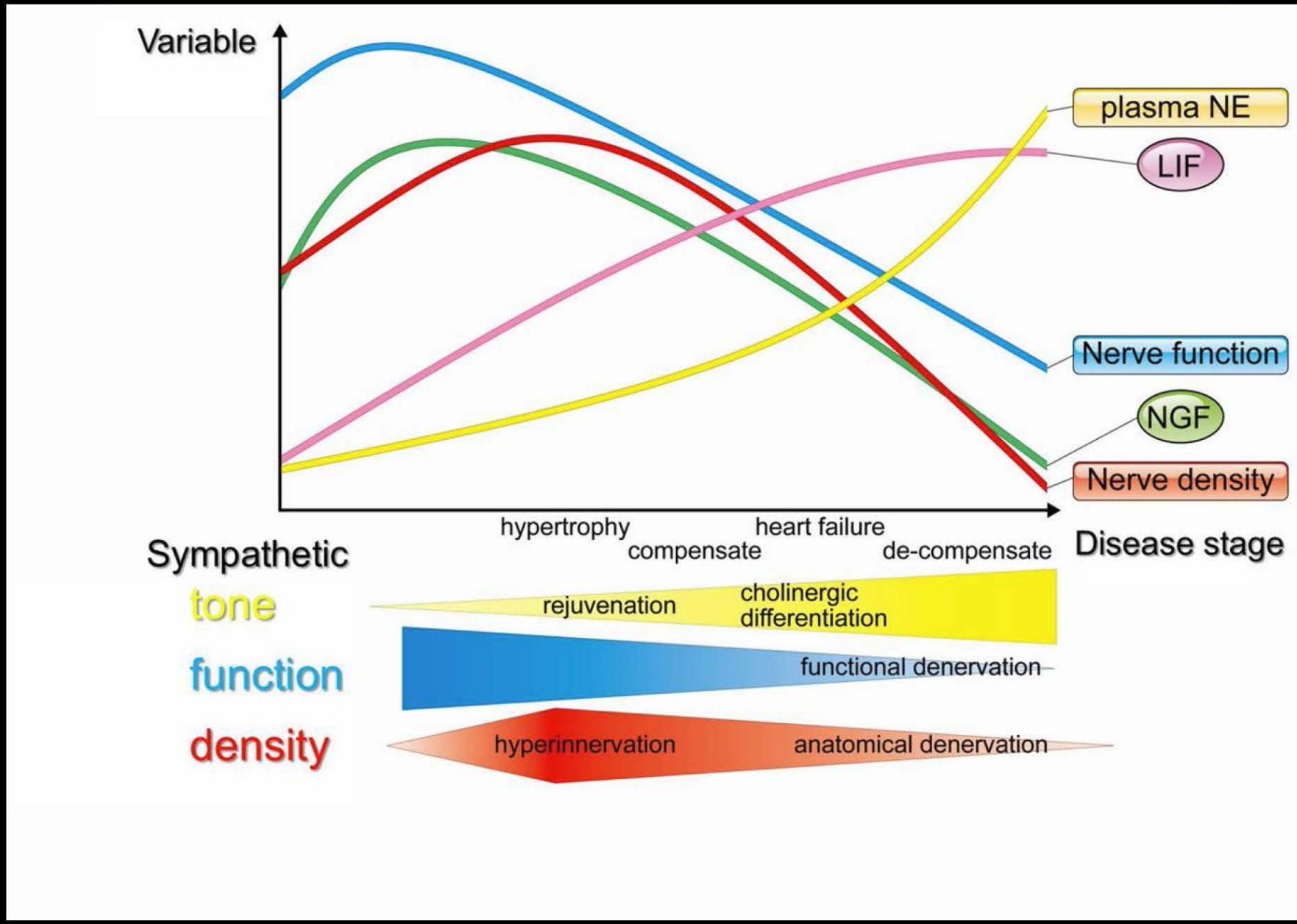
60% die suddenly

HUMAN POST INFARCT HEARTS SHOW HETEROGENEITY IN INNERVATION & REMOTE REGION REMODELING



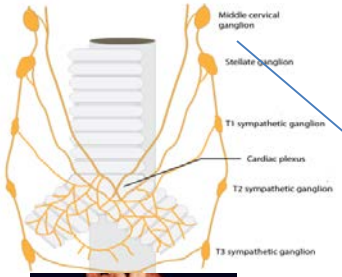
Vaseghi M, Lux R, Mahajan A & Shivkumar K: Heterogeneity in Repolarization Response to Sympathetic Stimulation. Am J Physiol Heart Circ Physiol. 2012;302(9):H1838-1846.

TEMPORAL CHANGES IN CARDIAC INNERVATION WITH DISEASE PROGRESSION

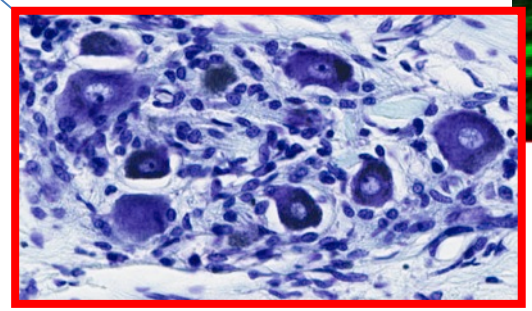


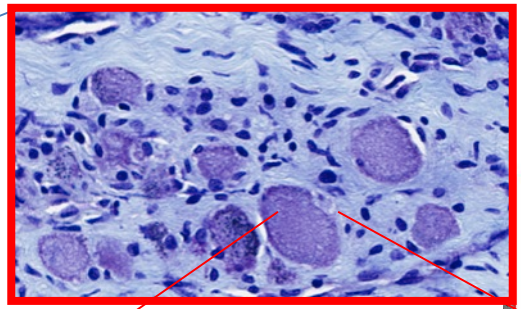
Fukuda K, Kanazawa H, Aizawa Y, Ardell JL & Shivkumar K: Cardiac Innervation and Sudden Cardiac Death Circulation Research 2015 (in press)

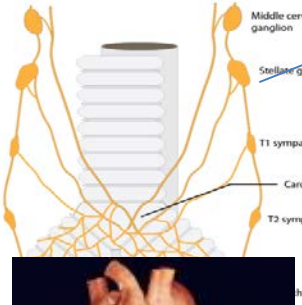
CARDIOMYOPATHY-INDUCED REMODELING OF STELLATE GANGLION NEURONS IN HUMANS

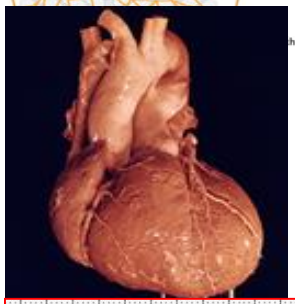


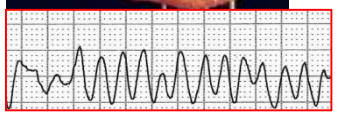
Normal Heart



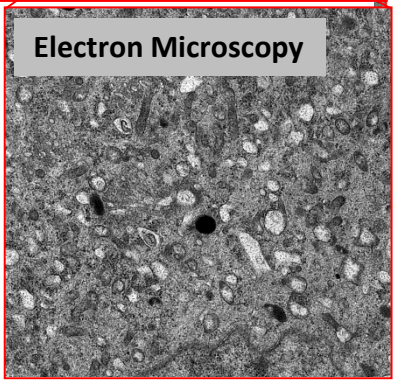




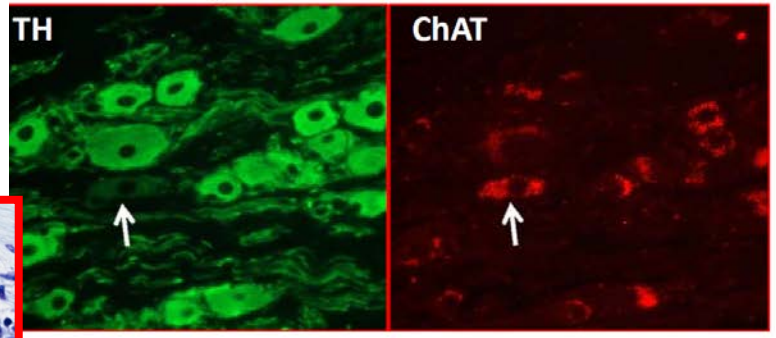




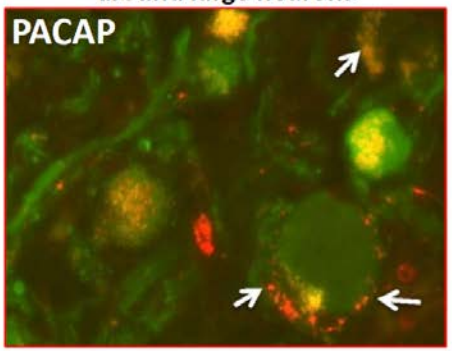
Cardiomyopathic Heart



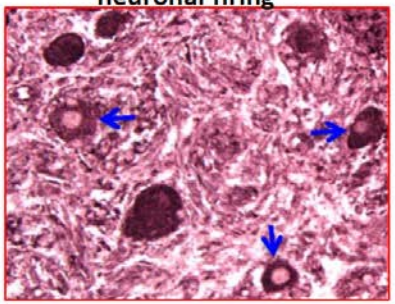
Adrenergic to Cholinergic Transdifferentiation



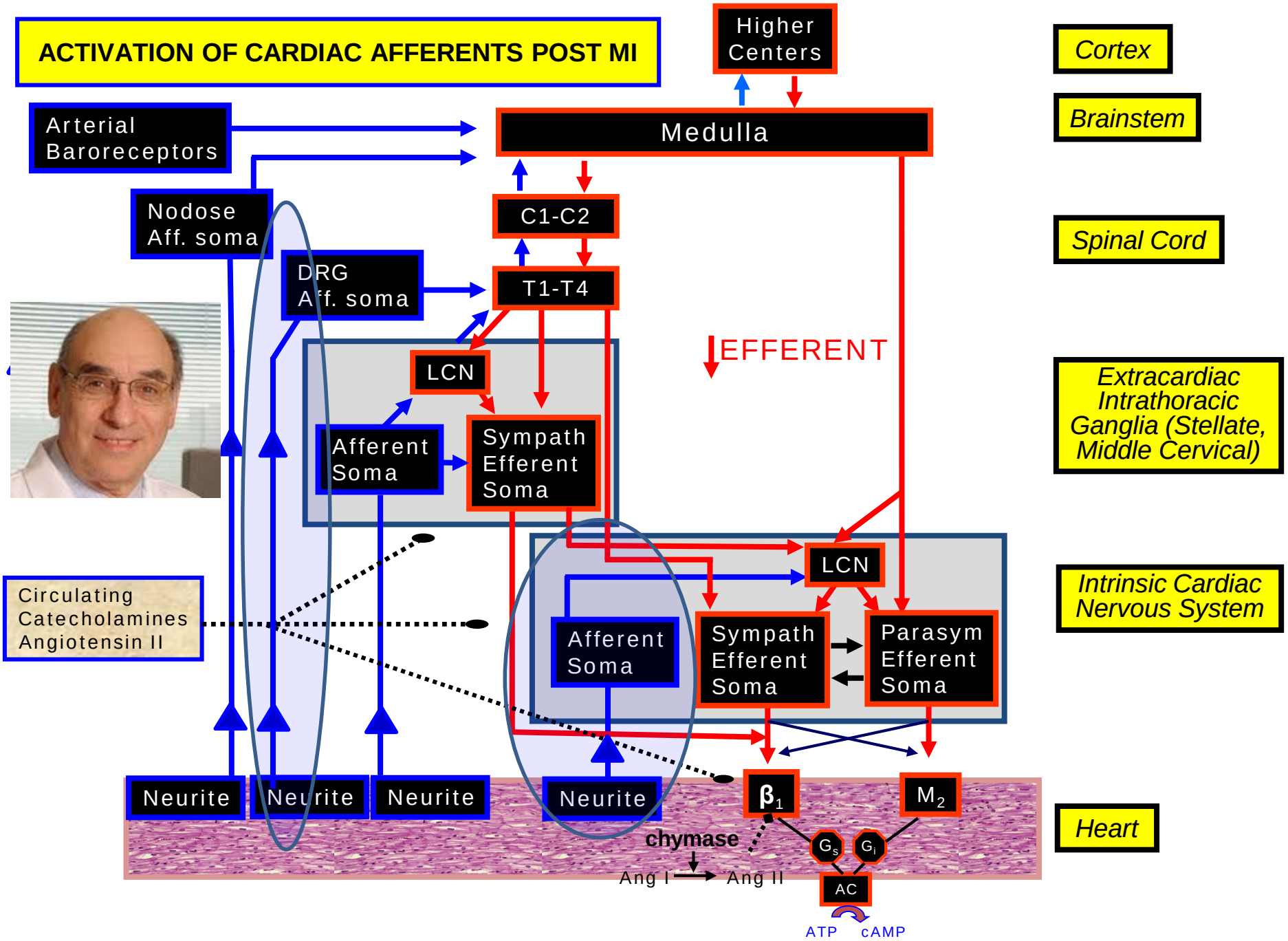
Excitatory synapses densest around large neurons



Heterogeneity in oscillatory neuronal firing

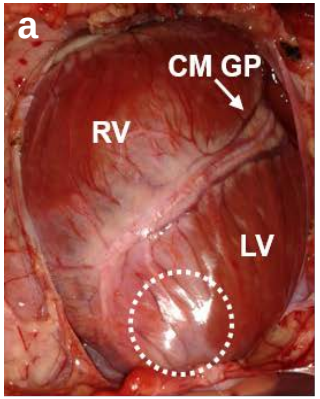


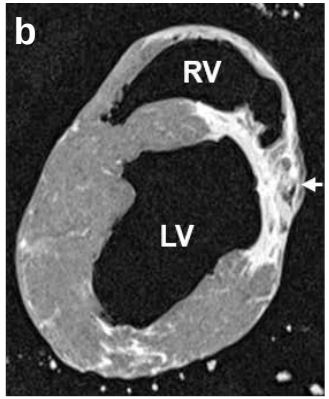
Ajijola OA, Wisco J, Lambert W, Mahajan A, Stark E, Fishbein MC & Shivkumar K: Extra-Cardiac Neural Remodeling in Humans with Cardiomyopathy . Circulation Arrhythmias & Electrophysiology 2012;5:1010-1116).

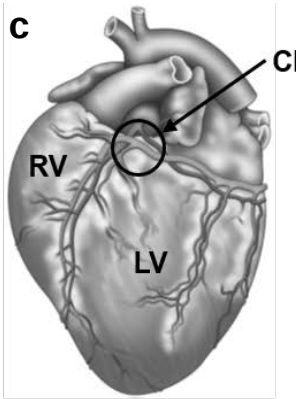


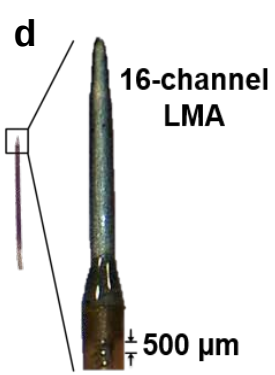
Fukuda K, Kanazawa H, Aizawa Y, Ardell JL & Shivkumar K: Cardiac Innervation and Sudden Cardiac Death
Circulation Research 2015 (in press)

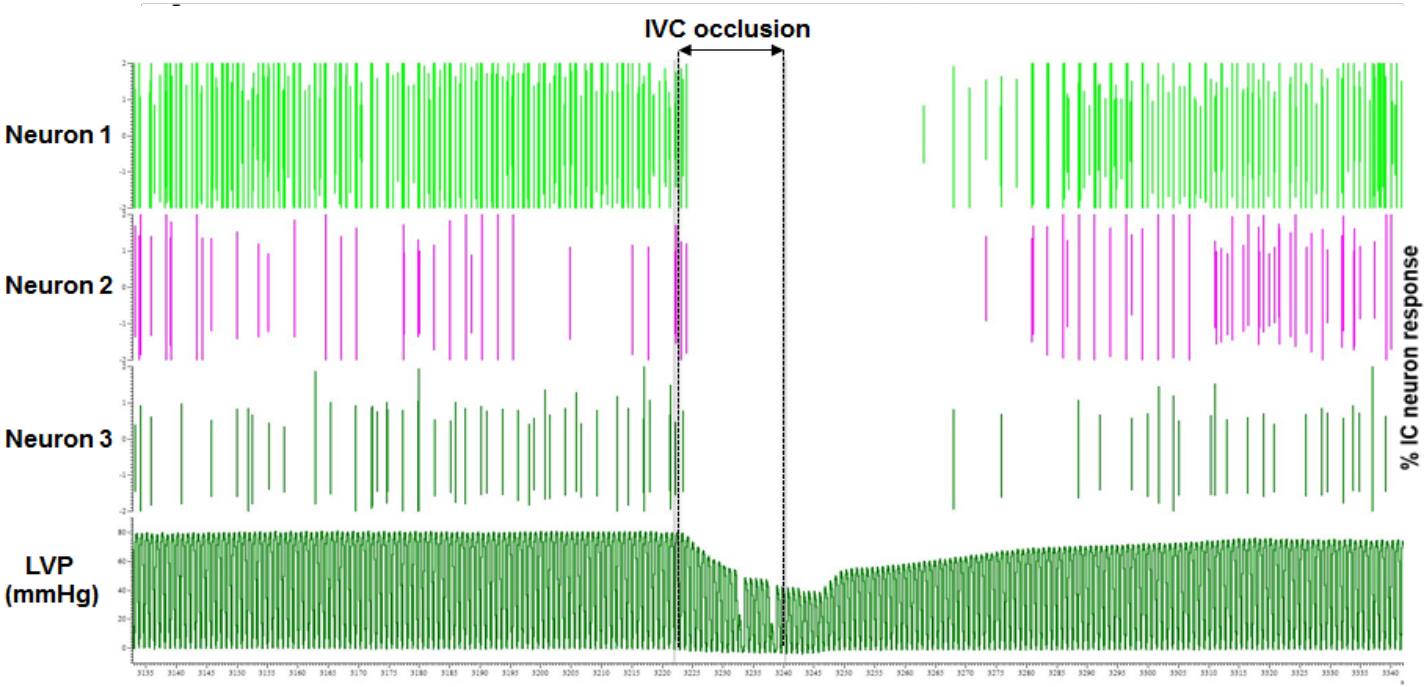
MYOCARDIAL INFARCTION ALTERS CARDIAC AFFERENT NEURONAL SIGNALING:RECORDING FROM INTRINSIC NEURONS ON THE HEART

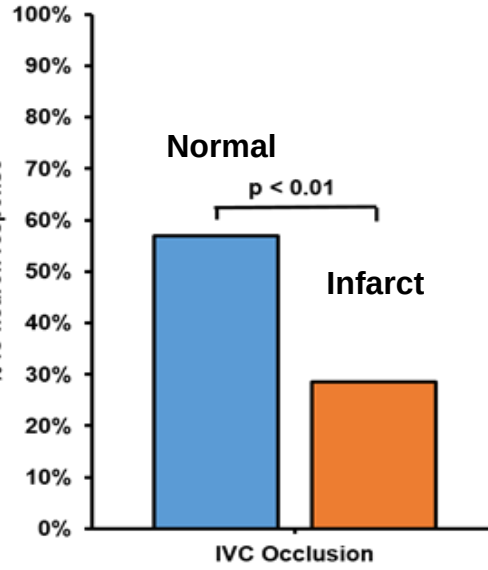












Rajendran P, Vaseghi M, Armour JA, Ardell JL, Shivkumar K: ***Myocardial Infarction Alters Neural Processing Of Afferent Inputs Within The Intrinsic Cardiac Nervous System*** *AHA 2014*

AUTONOMIC REGULATION OF THE HEART

- Physiology and Current Understanding
- Neural Response to Cardiac Injury
- Neuraxial Therapeutic Strategies

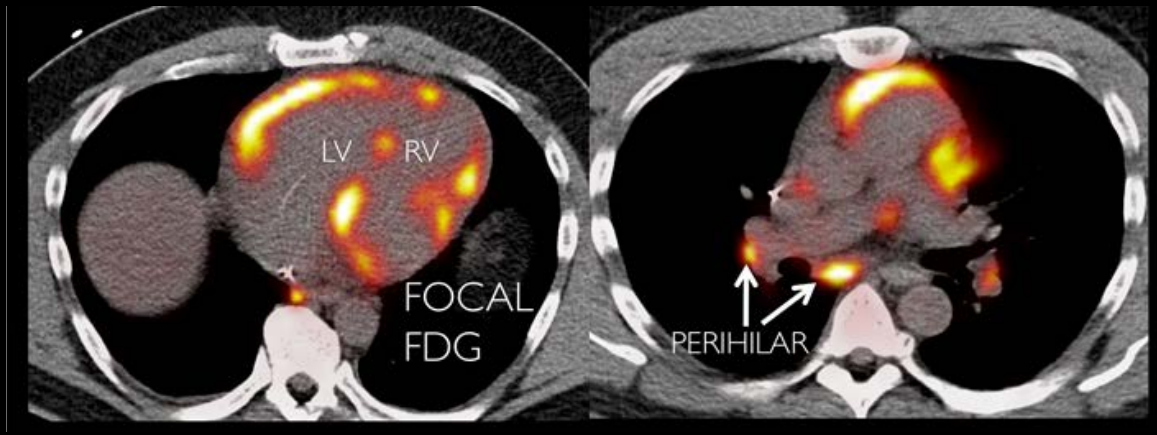
BACK THE PATIENT-CONTINUING CRISIS!

Mahajan A, Moore J, Cesario DA, Shivkumar K. Use of thoracic epidural anesthesia for management of electrical storm: A case report. Heart Rhythm. 2005;2:1359-1362

HOSPITAL COURSE

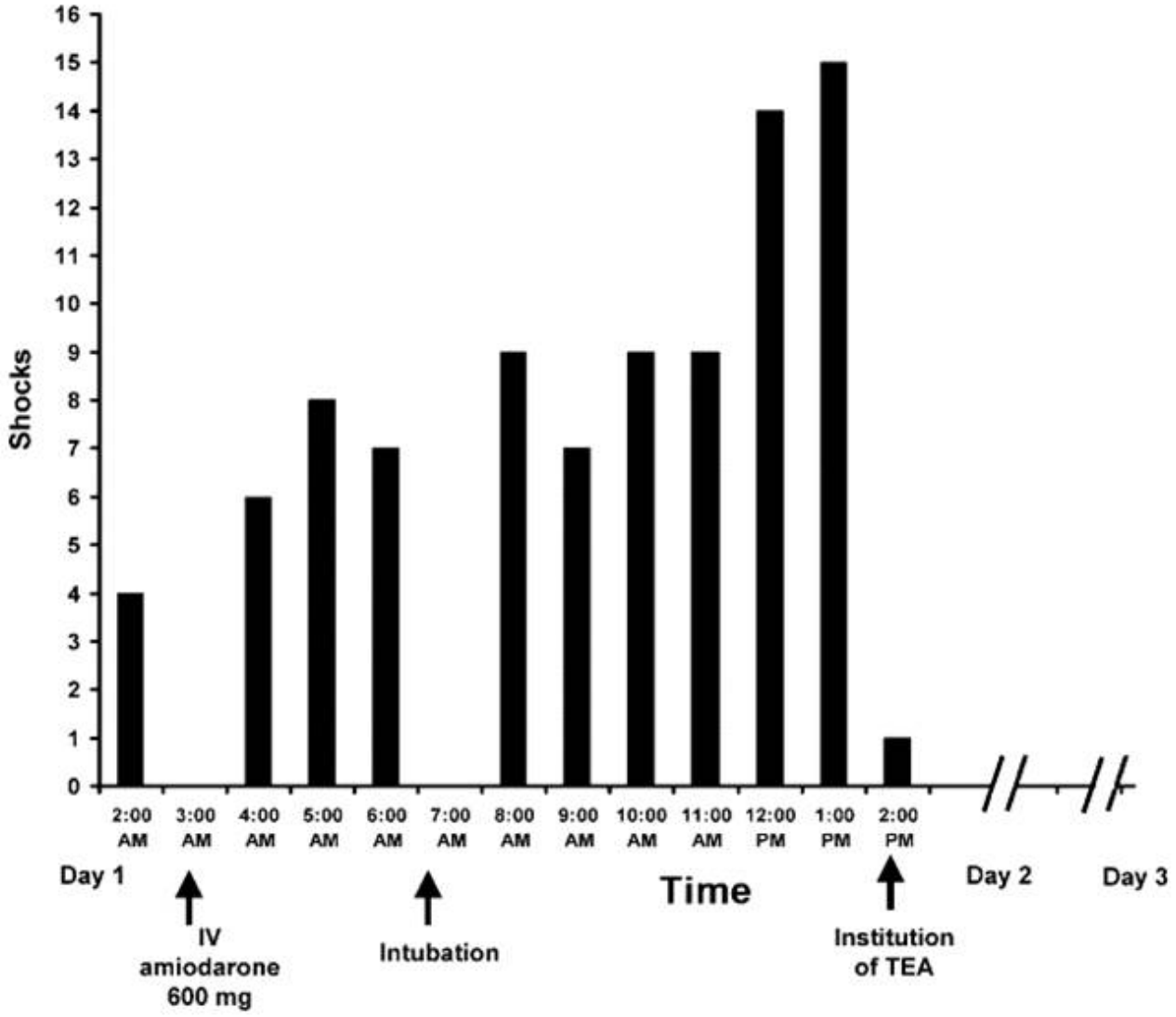
- **32 year old male with ‘ARVC’ (previous failed ablation) presents with incessant VT (multiple morphologies)-received 160 shocks-skin burns-intubated sedated-unstable death is imminent**

- Patient was stabilized with TEA, underwent a PET scan, and biopsy (showed sarcoidosis) and was treated with IV steroids and subsequently underwent catheter ablation and surgical sympathectomy. Stable after 2 years with no further shocks EF improved.



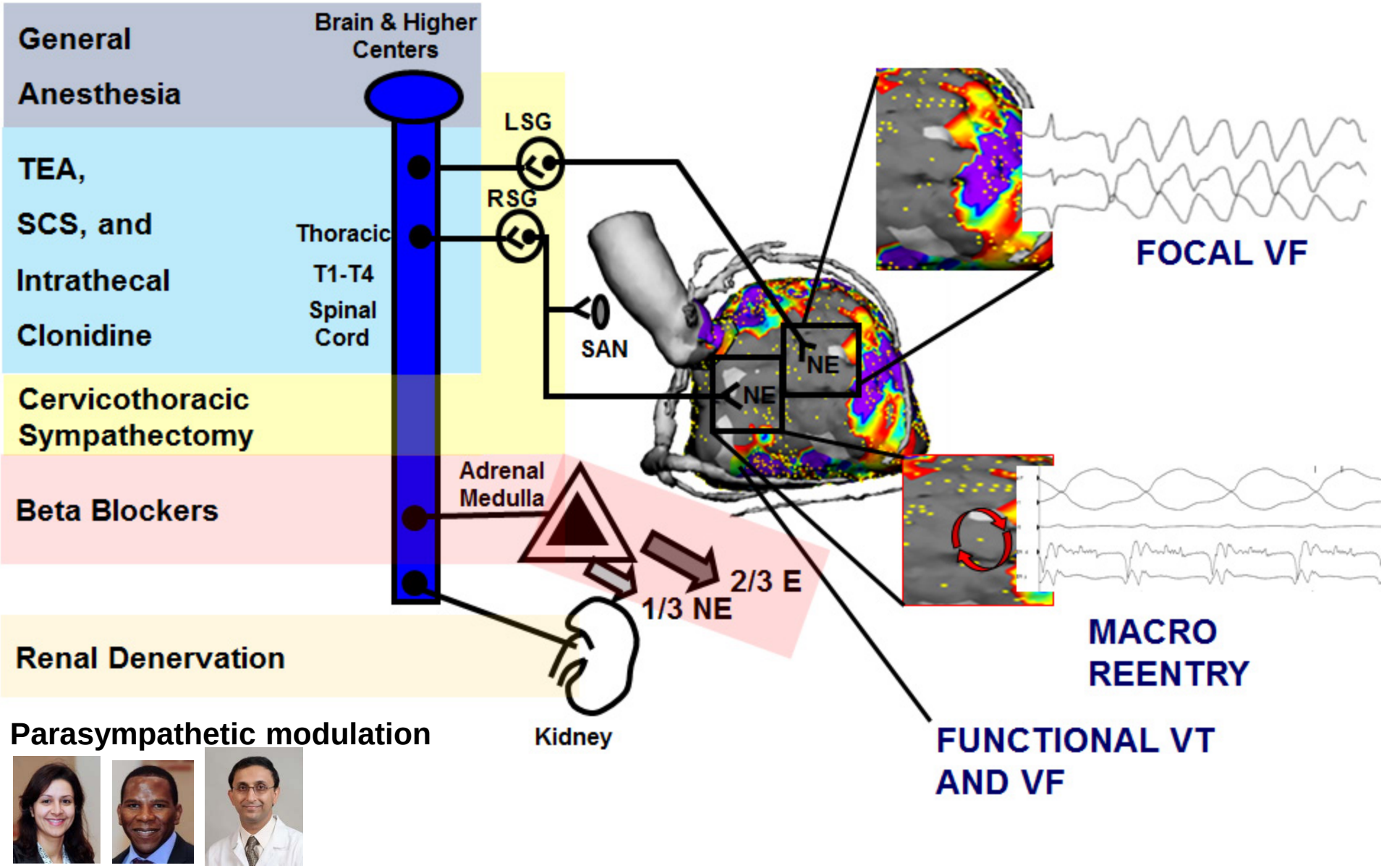
Bauer B, Tung R, Bradfield J, Auerbach M, Schelbert H, Buch E, Vaseghi M, Fujimura O, Mandapati R, Lynch J, Boyle N, Shivkumar K: Ventricular Arrhythmias Due To Isolated Cardiac Sarcoidosis And Arrhythmogenic Inflammatory Cardiomyopathy (AIC) Identified By Abnormal Positron Emission Tomography In Patients With Idiopathic Cardiomyopathy (presented HRS 2014)

VT-VF STORM- CLINICAL COURSE



Mahajan A, Moore J, Cesario DA, Shivkumar K. Use of thoracic epidural anesthesia for management of electrical storm: A case report. Heart Rhythm. 2005;2:1359-1362

NEURAXIAL MODULATION TO TREAT VENTRICULAR ARRHYTHMIAS



Parasympathetic modulation

Vaseghi M, Ajijola OA, Mahajan A, and Shivkumar K: Sympathetic Innervation, Denervation and Cardiac Arrhythmias '*Cardiac Electrophysiology: From Cell to Bedside*' Zipes, D & Jalife, J, 6th ed. Elsevier, 2014

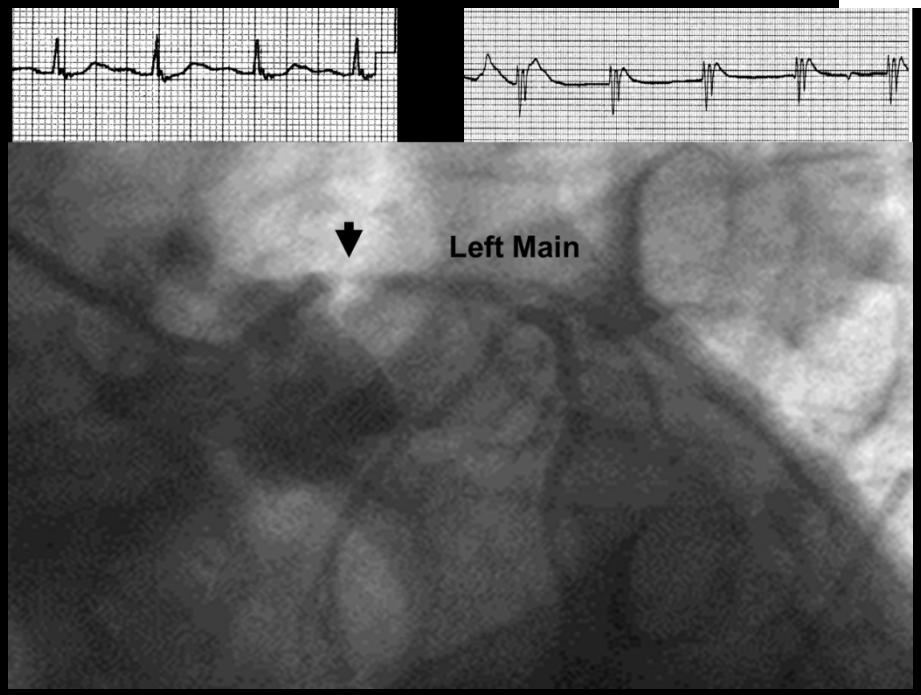
What happens to the transplanted heart?

Mode and mechanisms of death after orthotopic heart transplantation

Marmar Vaseghi, MD,* Nicolas Lellouche, MD,* Harry Ritter, BS,* Gregg C. Fonarow, MD,†
Jignesh K. Patel, MD, PhD,‡ Jaime Moriguchi, MD,‡ Michael C. Fishbein, MD,§
Jon A. Kobashigawa, MD,‡ Kalyanam Shivkumar, MD, PhD*

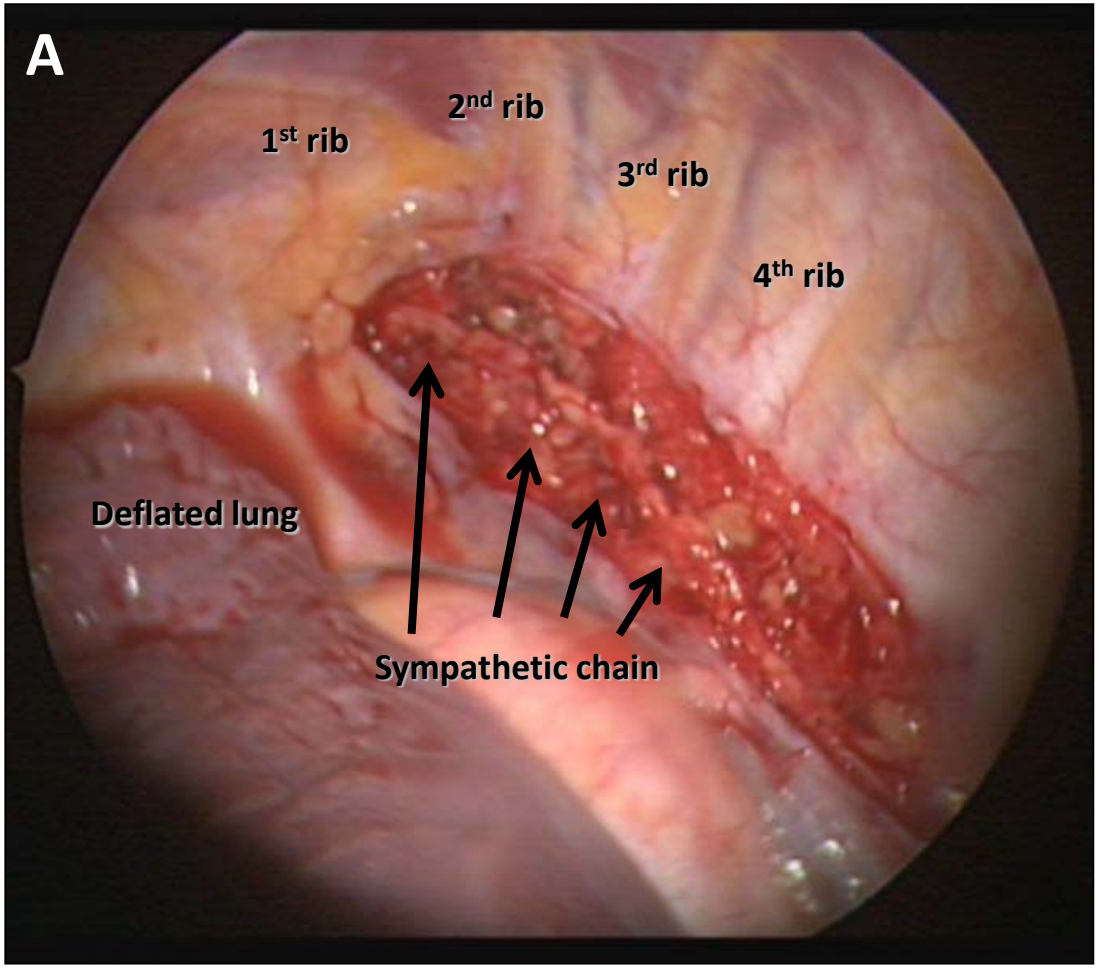
*From the *UCLA Cardiac Arrhythmia Center, †Ahmanson UCLA Cardiomyopathy Center, ‡UCLA Heart Transplantation Program,and §Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California.*

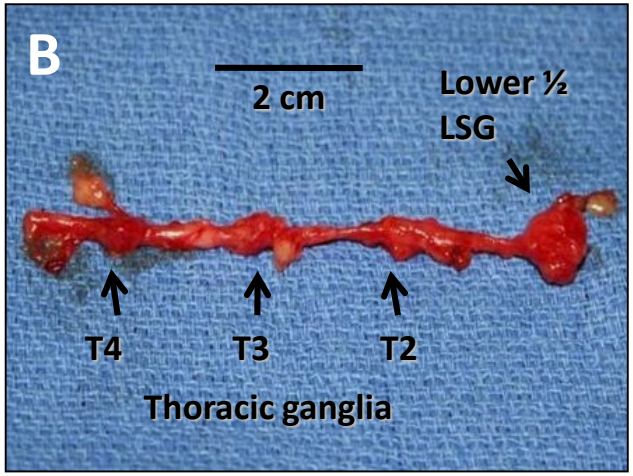
(Heart Rhythm 2009;6:503–509)

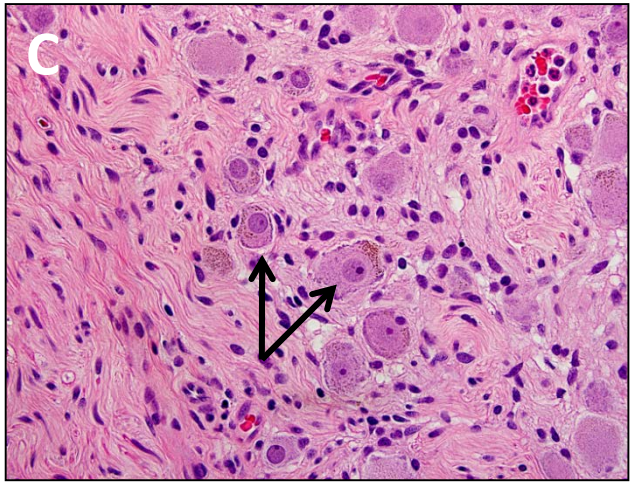


VF IS VERY RARE IN PATIENTS WITH A TRANSPLATED HEART EVEN WITH ACUTE CORONARY OCCLUSION!

Anatomy and histology of left sympathetic chain







Bourke T, Vaseghi M, Michowitz Y, Sankhla V, Shah M, Swapna N, Boyle NG, Mahajan A, Narasimhan C, Lokhandwala Y, Shivkumar K. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. ***Circulation. 2010;121(21):2255-2262***.

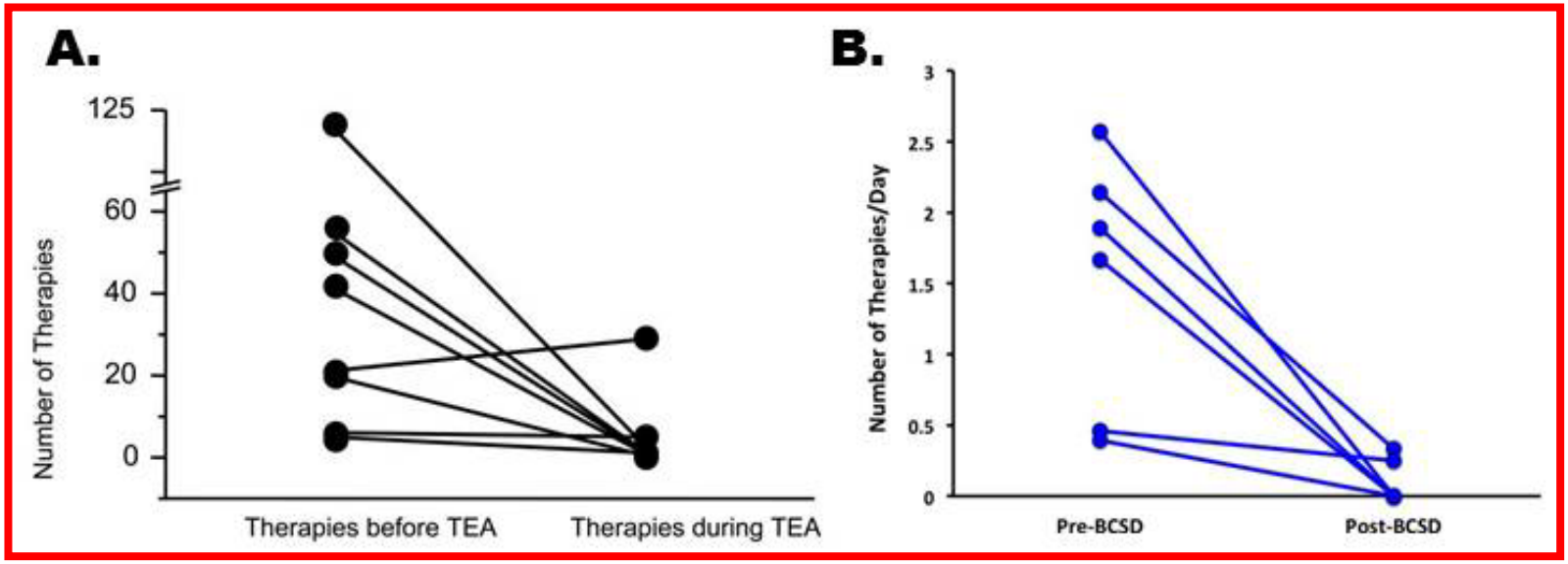
Circulation. 2010;121(21):2255-2262.

Arrhythmia/Electrophysiology

Neuraxial Modulation for Refractory Ventricular Arrhythmias

Value of Thoracic Epidural Anesthesia and Surgical Left Cardiac Sympathetic Denervation

Tara Bourke, MD; Marmar Vaseghi, MD; Yoav Michowitz, MD; Vineet Sankhla, MD; Mandar Shah, MD; Nalla Swapna, MD; Noel G. Boyle, MD, PhD; Aman Mahajan, MD, PhD; Calambur Narasimhan, MD, DM; Yash Lokhandwala, MD, DM; Kalyanam Shivkumar, MD, PhD

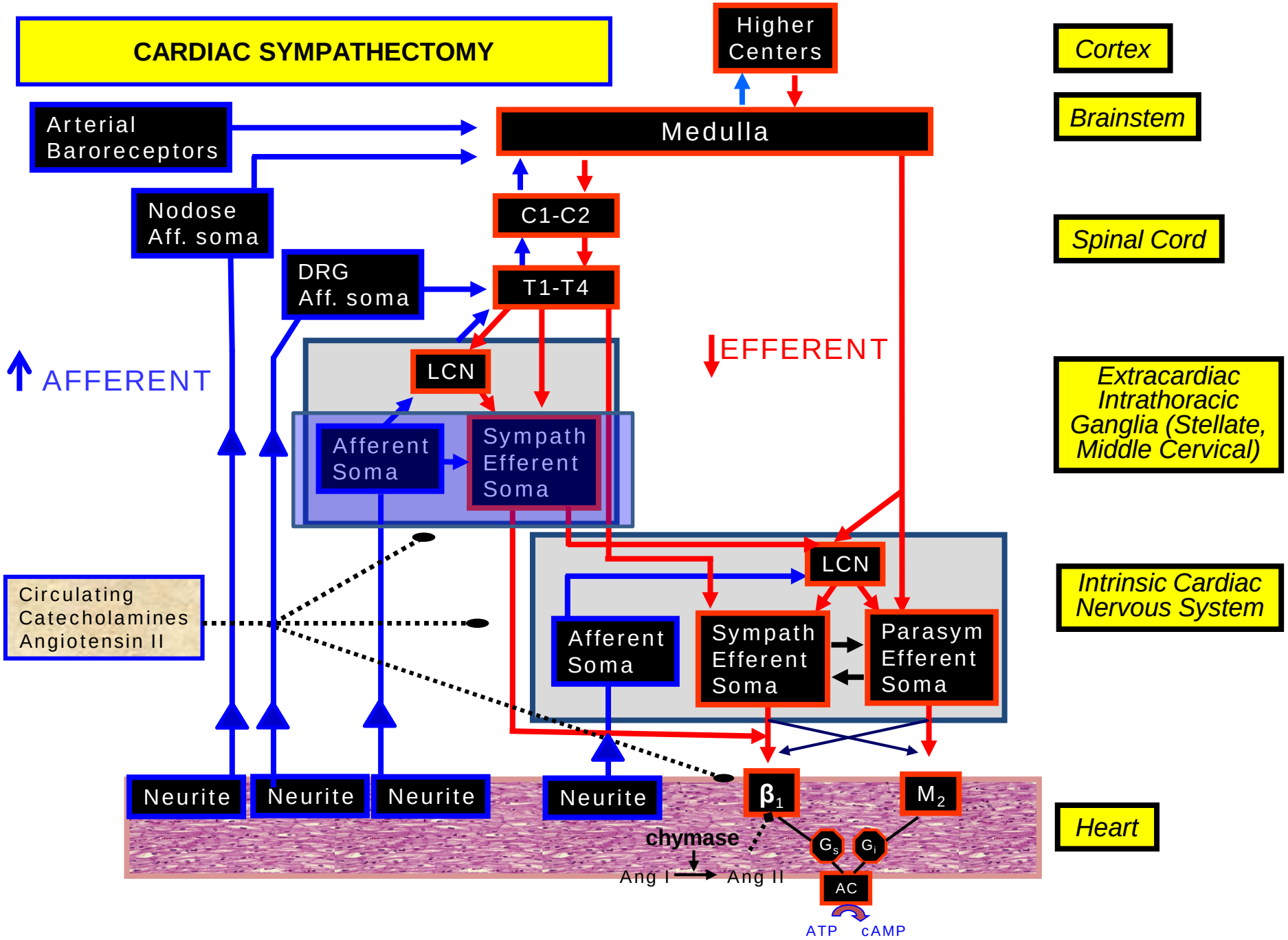


Bourke T, Vaseghi M, Michowitz Y, Sankhla V, Shah M, Swapna N, Boyle NG, Mahajan A, Narasimhan C, Lokhandwala Y, Shivkumar K. Neuraxial modulation for refractory ventricular arrhythmias: value of thoracic epidural anesthesia and surgical left cardiac sympathetic denervation. Circulation. 2010;121(21):2255-2262

Ajijola OA, Lellouche N, Bourke T, Tung R, Ahn S, Mahajan, Shivkumar K: Bilateral Cardiac Sympathetic Denervation For The Management Of Electrical Storm JACC 2012;59(1):91-92

Vaseghi M, Gima J, Kaanan C, Ajijola O, Marmureanu A, Mahajan A, Shivkumar K. Cardiac sympathetic denervation in patients with refractory ventricular arrhythmias or electrical storm: Intermediate and long term follow up. Heart Rhythm. 2014;11:360-366

BUT HOW DOES IT WORK?



Fukuda K, Kanazawa H, Aizawa Y, Ardell JL & Shivkumar K: Cardiac Innervation and Sudden Cardiac Death
Circulation Research 2015 (in press)

CARDIAC SYMPATHECTOMY AND 'INTEROCEPTION'

Synergistic application of cardiac sympathetic decentralization and comprehensive psychiatric treatment in the management of anxiety and electrical storm

Sahib S. Khalsa[1,2], Leila Shahabi[3], Olujimi A. Ajijola[2], Alexander Bystritsky[1], Bruce D. Naliboff[3] and Kalyanam Shivkumar[1,2]*

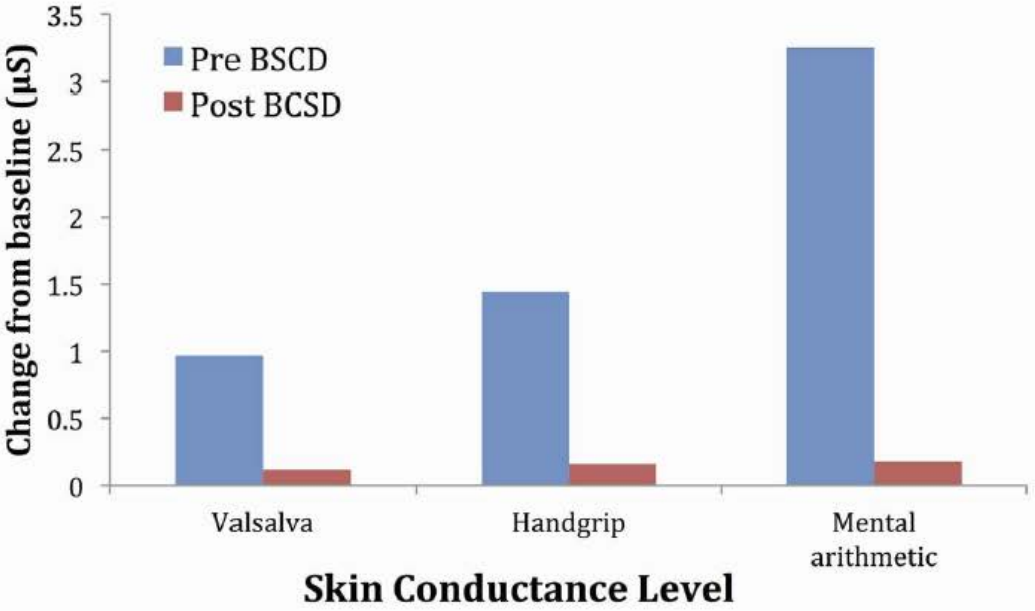
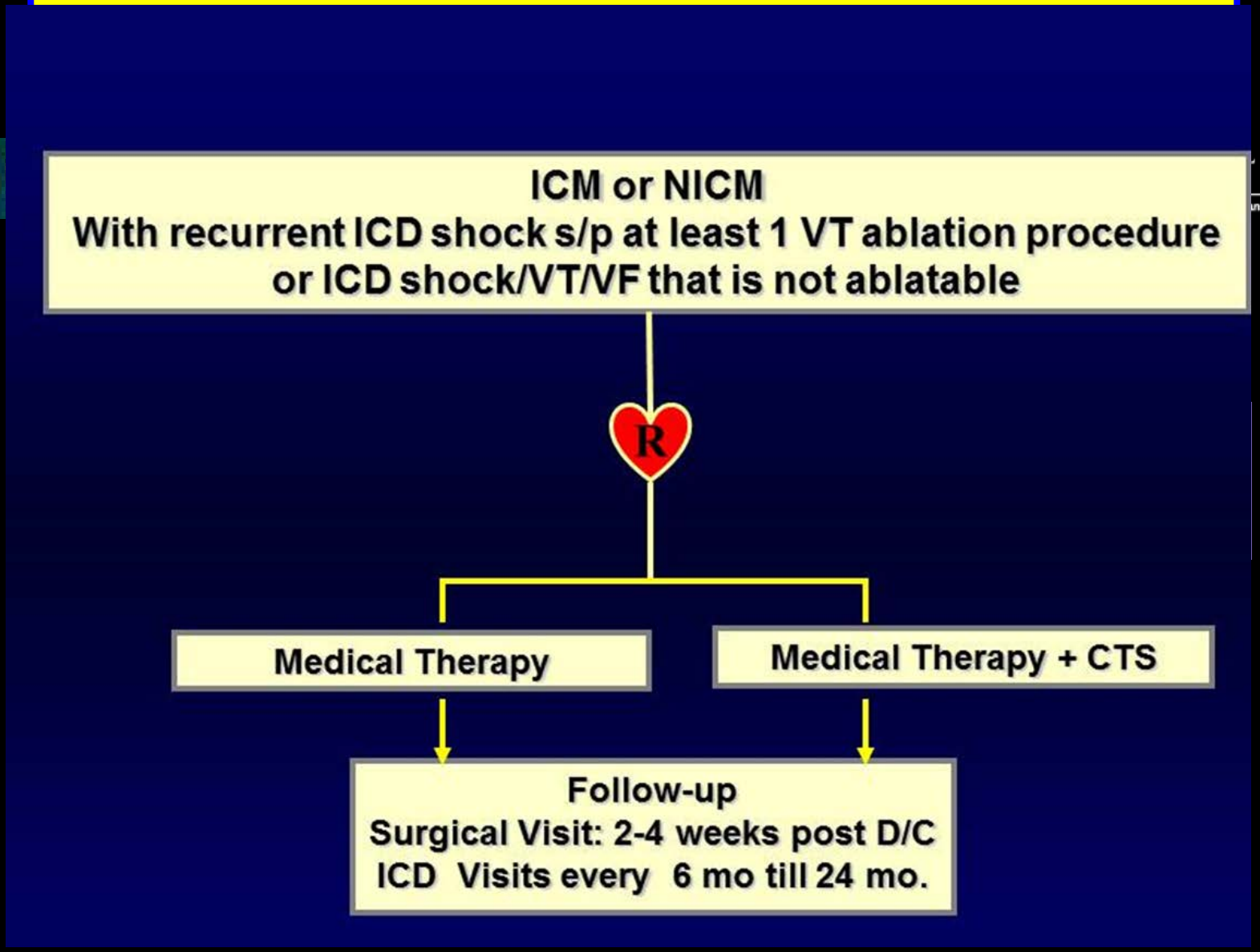


FIGURE 7 | Mean changes in skin conductance level from baseline during autonomic challenge before and after bilateral cardiac sympathetic decentralization (BSCD) in case 2. µS, microsiemens.

PREVENT VT TRIAL

PRophylactic Cervicothoracic Sympathectomy for PrEVENTion of Ventricular Tachyarrhythmias

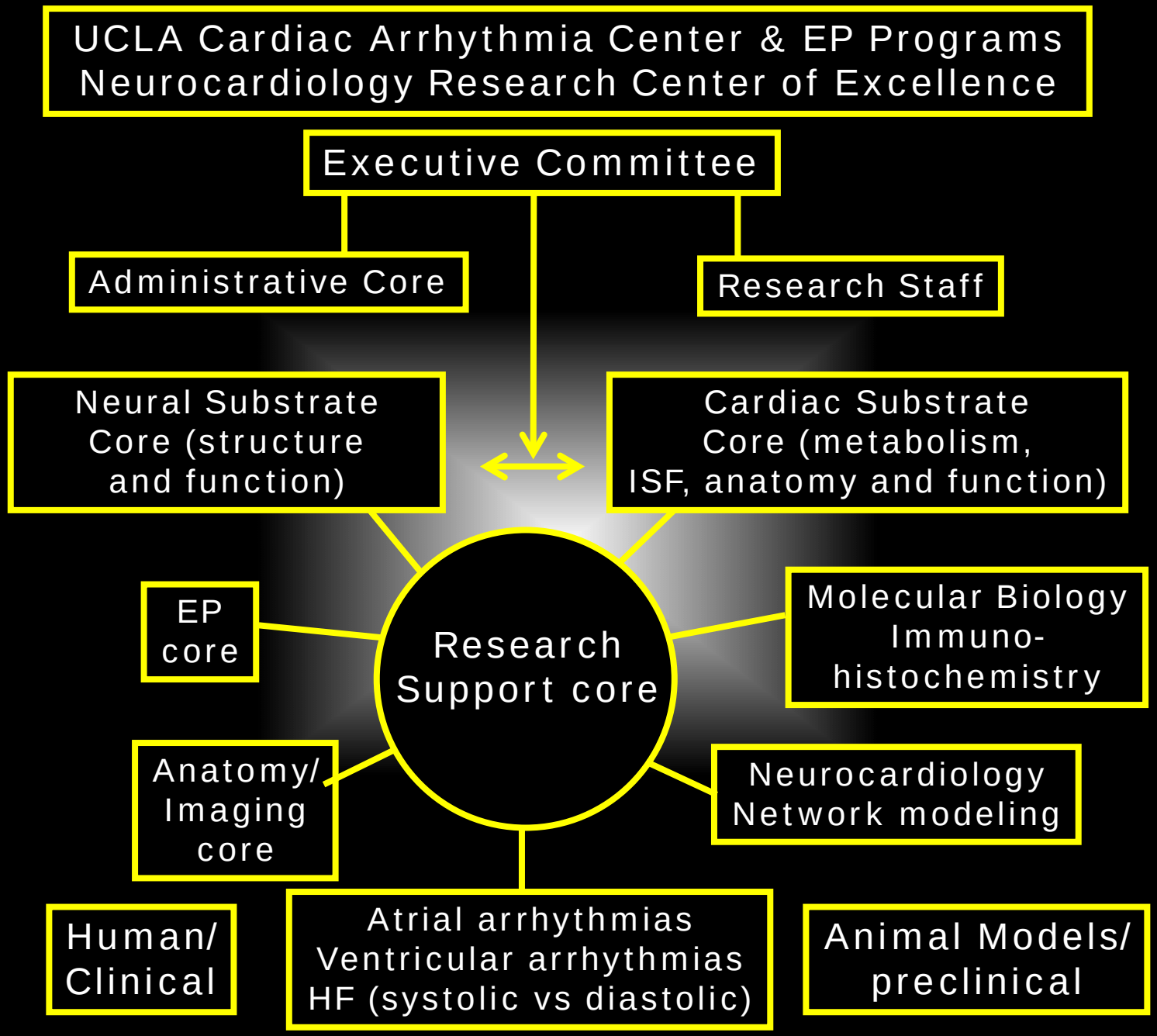


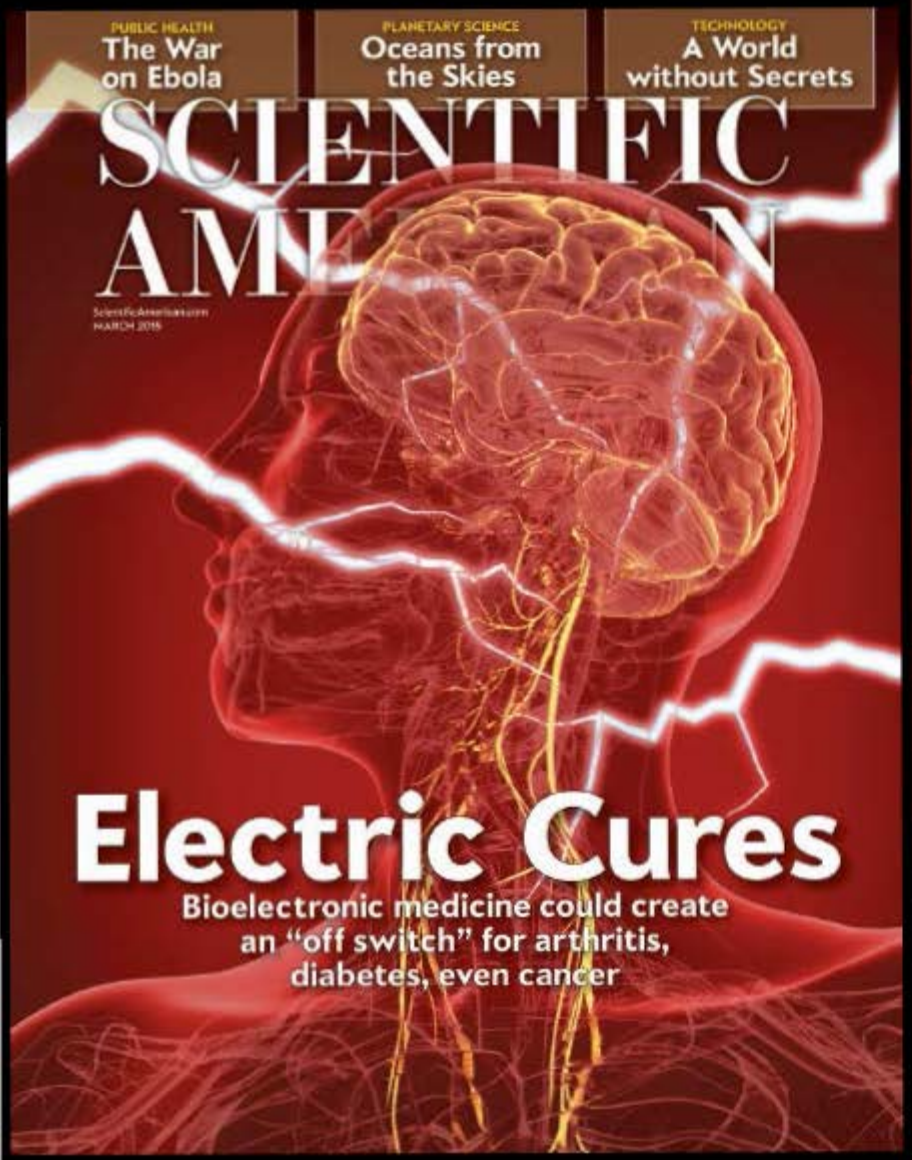
CONCLUSIONS

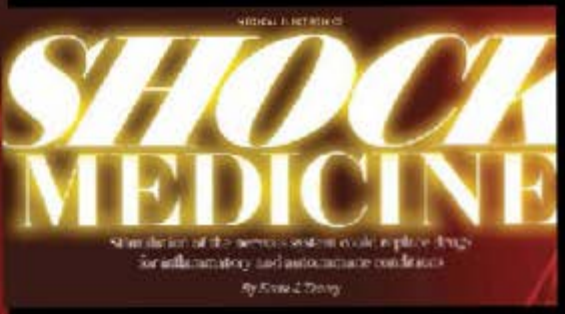
- Multiple levels of the neuraxis are involved in cardiac regulation. The heart also has an important regulatory neural network in place
- Neural remodeling occurs in the heart and extra-cardiac structures following cardiac injury and modulates cardiac arrhythmias
- Neuromodulation therapies show great therapeutic promise and need in-depth mechanistic understanding
- Cardiac sympathectomy is showing efficacy in humans effective and needs intense study to develop it

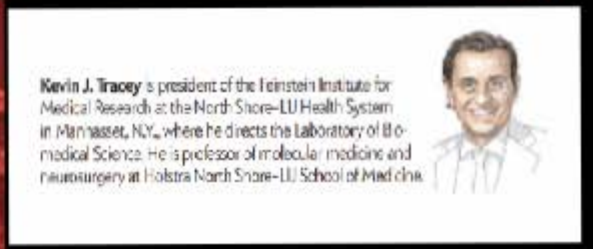
CONCLUSIONS-II-NEEDS

- A neurovisceral map of the heart
- Better electrode technology for recording and stimulation
- Integrative physiology studies in small and large animal models to guide therapies.
- Mechanistic studies in humans


UCLA Cardiac Arrhythmia Center & EP Programs
Neurocardiology Research Center of Excellence
Executive Committee
Administrative Core
Research Staff
Neural Substrate Core (structure and function)
Cardiac Substrate Core (metabolism, ISF, anatomy and function)
EP core
Research Support core
Molecular Biology Immuno-histochemistry
Anatomy/ Imaging core
Neurocardiology Network modeling
Human/ Clinical
Atrial arrhythmias
Ventricular arrhythmias
HF (systolic vs diastolic)
Animal Models/ preclinical


PUBLIC HEALTH
The War on Ebola
PLANETARY SCIENCE
Oceans from the Skies
TECHNOLOGY
A World without Secrets
SCIENTIFIC AMERICAN
ScientificAmerican.com
MARCH 2015
Electric Cures
Bioelectronic medicine could create an "off switch" for arthritis, diabetes, even cancer


SHOCK MEDICINE


Kevin J. Tracey is president of the Feinstein Institute for Medical Research at the North Shore-LIJ Health System in Manhasset, N.Y., where he directs the Laboratory of Biomedical Science. He is professor of molecular medicine and neurosurgery at Hofstra North Shore-LIJ School of Medicine.

Autonomic Control (the higher centers)

Bodh Gaya, India

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Marmar Vaseghi MD MS, *Dir*

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