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)*

**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

Jänig 2012 Neuroscience
(after Nilsson 1983)
THE AUTONOMIC INNERVATION OF THE VISCERA

CARDIAC NEUROTRANSMISSION

- reflexes
- regulation
- expression of emotions
- structure-related diseases
- functional diseases

- telencephalon
- hypothalamus
- upper brain stem
- lower brain stem
- spinal cord

- positive feedback loops
- efferent systems
- afferent systems
- local reflexes modulation
- parasymp. CM
- sympath. CM

- 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
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

- fMRI
- Direct brainstem recordings
- Direct spinal cord recordings
- Direct cardiac neural recordings

EXPERIMENTAL DATA: HUMAN

- Human functional studies
- Direct stellate recordings
- Direct cardiac neural recordings

NETWORK MODELING & ANALYTICS

Afferent Systems

Cortical

Sub-cortical

Brainstem

Spinal cord

Effector Systems

Human functional studies

Response to epiduralal touch


CARDIO-NEURAL MAPPING

- 2x Ethernet Switches (PN 6506)
- Ethernet Cabling (PN 7988)
- 2x Cerebus NSPs synced to provide 256 channels (PN 0888)
- Adaptors for sock and catheter electrodes
- Splitter Box (PN 6839)
- Splitter Box (PN 7122)
- CerePlex A (PN 7384)
- ICS-96 Utah Array
- NeuroPort Array

SoBiter Box C PN 6939
S[Biter Box < PN 7122

PC 1

PC 2
Vagal Sensory Receptors and their Reflex Effects

A. S. PAINTAL

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

Physiological Reviews
Vol. 53, No. 1, January 1973
Printed in U.S.A.

Cardiac parasympathetic afferent & efferent systems

Higher centers

Medulla

Cortex

Brainstem

Nodose aff. soma

Intrinsic cardiac nervous system

Heart

Cardiac parasympathetic afferent & efferent systems


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

ANTHEM-HF

NECTAR-HF

INOVATE-HF

STIMULATION OF SYMPATHETIC NERVES

Arterial Baroreceptors

Nodose Aff. soma

DRG Aff. soma

C1-C2

T1-T4

LCN

AFFERENT

Sympath Efferent Soma

Parasym Efferent Soma

LCN

Afferent Soma

Sympath Efferent Soma

AFFERENT

Circulating Catecholamines
Angiotensin II

Neurite

Neurite

Neurite

Neurite

Heart

Cortex

Brainstem

Spinal Cord

Extracardiac Intrathoracic Ganglia (Stellate, Middle Cervical)

Intrinsic Cardiac Nervous System

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

Baseline

Bilateral Stellate Ganglion Stimulation


5 ms pulse width
5 ms delay
5 Hz
5 10 Volts
CARDIAC NERVES POWERFULLY CONTROL MUSCLE PROPAGATION

NERVE STIMULATION CAN INDUCE LETHAL ARRHYTHMIAS IN A NORMAL HEART

PERCUTANEOUS STIMULATION OF THE STELLATE GANGLION IN HUMANS

Human Cardiac Intrinsic Nervous System

NETWORK INTERACTIONS WITHIN THE CARDIAC INTRINSIC NERVOUS SYSTEM

• Physiology and Current Understanding

• **Neural Response to Cardiac Injury**

• Neuraxial Therapeutic Strategies
STRUCTURE - FUNCTION INTERPLAY: SUDDEN DEATH AND HEART FAILURE

Higher Centers

ARRHYTHMIAS
400,000 deaths/yr

HEART FAILURE
5 million patients
60% die suddenly

Afferent signals
Myocardial infarction
Cytokines
NGF
Scar and denervation

Cervico-thoracic spinal cord
To brain stem and higher brain centers

Efferent signals
EADs
DADs
VT/VF

Stellate ganglion remodelling
Heterogenous substrate

↑Sympathetic activation
↑Dispersion of repolarization

Normal cell
Nerve sprouts
Scar
HUMAN POST INFARCT HEARTS SHOW HETEROGENEITY IN INNERVATION & REMOTE REGION REMODELING

△ARI

Isoproterenol
Nitroprusside

Normal hearts CM-normal site CM-border zones CM-scars

TEMPORAL CHANGES IN CARDIAC INNERVATION WITH DISEASE PROGRESSION

Variable

Sympathetic function density

Disease stage

hypertrophy compensate heart failure de-compensate

Sympathetic tone function density

rejuvenation cholinergic differentiation functional denervation

hyperinnervation anatomical denervation

CARDIOMYOPATHY-INDUCED REMODELING OF STELLATE GANGLION NEURONS IN HUMANS

ACTIVATION OF CARDIAC AFFERENTS POST MI

- Arterial Baroreceptors
- Nodose Aff. soma
- DRG Aff. soma
- Circulating Catecholamines Angiotensin II
- Neurite

Higher Centers

Medulla

C1-C2

T1-T4

LCN

Anterograde Neurites

Efferent Soma

Sympath Soma

Parasym Soma

β

M

Intrinsic Cardiac Nervous System

Cortex

Brainstem

Spinal Cord

Extracardiac Intrathoracic Ganglia (Stellate, Middle Cervical)

Heart

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

AUTONOMIC REGULATION OF THE HEART

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

Thoracic Epidural Delivery of 0.25% Bupivacaine at T1-T2 Interspace: Fluroscopic view of contrast injected via epidural catheter.

VT-VF STORM - CLINICAL COURSE

Parasympathetic modulation

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) © 2009 Heart Rhythm Society. All rights reserved.

VF IS VERY RARE IN PATIENTS WITH A TRANSPLANTED HEART EVEN WITH ACUTE CORONARY OCCLUSION!
Anatomy and histology of left sympathetic chain

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


BUT HOW DOES IT WORK?
Circulating Catecholamines Angiotensin II

Neurite Neurite Neurite Neurite

Arterial Baroreceptors

Nodose Aff. soma

DRG Aff. soma

C1-C2

T1-T4

Medulla

Sympath Soma

Efferent Soma

AFFERENT

EFFERENT

Higher Centers

Cortex

Brainstem

Spinal Cord

Extracardiac Intrathoracic Ganglia (Stellate, Middle Cervical)

Intrinsic Cardiac Nervous System

Heart

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

Sahib S. Khalsa¹,²*, Leila Shahabi³, Olujimi A. Ajijola², Alexander Bystritsky¹, Bruce D. Naliboff³ and Kalyanam Shivkumar¹,²

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

ICM or NICM
With recurrent ICD shock s/p at least 1 VT ablation procedure or ICD shock/VT/VF that is not ablatable

Medical Therapy

Medical Therapy + CTS

Follow-up
Surgical Visit: 2-4 weeks post D/C
ICD Visits every 6 mo till 24 mo.
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.
• 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
Electric Cures

Bioelectronic medicine could create an “off switch” for arthritis, diabetes, even cancer
Autonomic Control (the higher centers)

Bodh Gaya, India
Cardiomyopathy & Transplantation:
- Gregg C. Fonarow MD
- Tamara Horwich MD
- Daniel Cruz MD
- Arnold Baas MD
- Mario Deng MD
- Ali Nsair MD

ACHD:
- Ravi Mandapati MD
- Jamil Aboulhosn MD
- Pamela Miner RN NP

Cardiac Surgery:
- Hillel Laks MD
- Murray Kwon MD
- Richard Shemin MD
- Peyman Benharash MD
- Curtis Hunter MD

Echocardiography:
- Barbara Natterson MD
- Aman Mahajan MD PhD

Cardiac Anesthesia:
- Komal Patel MD
- J. Schwarzenberger MD
- Jonathan Ho MD
- Jason Chua MD
- Ryan Crowley MD
- Ali Salehi MD

Specialized Program for AF:
- Eric F. Buch MD, MS, Dir

Specialized Program for VT:
- Roderick H. Tung MD, Dir

Implanted Devices Clinic:
- Osamu Fujimura MD, Dir

Cardiac EP, UCLA Olive View:
- Jason S. Bradfield MD, Dir

Clinical & Translational Research:
- Marmar Vaseghi MD MS, Dir

West Los Angeles-VAMC:
- Zenaida Feliciana MD, Dir
- Malcolm Bersohn MD
- Janet Han MD

Electrophysiology Faculty:
- Olujimi A. Ajijola MD PhD
- Carlos Macias MD
- Ravi Mandapati MD

EP Fellows/trainees:
- Tahmeed Contractor MD
- Jorge Romero MD
- Yuliya Krokhaleva MD
- Keijiro Nakamura MD PhD
- Tadanobu Irie MD PhD
- Una Buckley MD
- David Hamon MD
- Pradeep Rajendran BS (MSTP/PhD)
- Ray Chui BS (MCIP/PhD)

Neurocardiology Research Center of Excellence:
- Jeffrey L. Ardell PhD, Dir
- J. Andrew Armour MD PhD
- John Tompkins PhD
- Eileen So BS

EP Nurse Practitioners:
- Shelly Cote RN MN NP
- Jean Gima RN MN NP
- Geraldine Pavez RN MN NP

Research Administration:
- Julie M. Sorg RN MSN

Healthy Hearts Program:
- Sahib Khalsa MD PhD

Radiology:
- J. Paul Finn MD PhD
- Stephen J. Kee MD
- John Moriarty MD
- Stefan Ruehm MD

Administrative:
- Susana Morales
- Carmen Mora BS
- Tamika L. Jefferson
- Julie Ramirez BS

Health System:
- Laura Brandsen Yost MSHA
- Erick Ascencio CVT

Coach John R. Wooden
1910-2010