60th International Conference of the Israel Heart Society
April 22, 2013

"New Observations on the Role of the Autonomic Nervous System in Arrhythmias"

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Krannert Institute of Cardiology
Editor-in-Chief Heart*Rhythm*

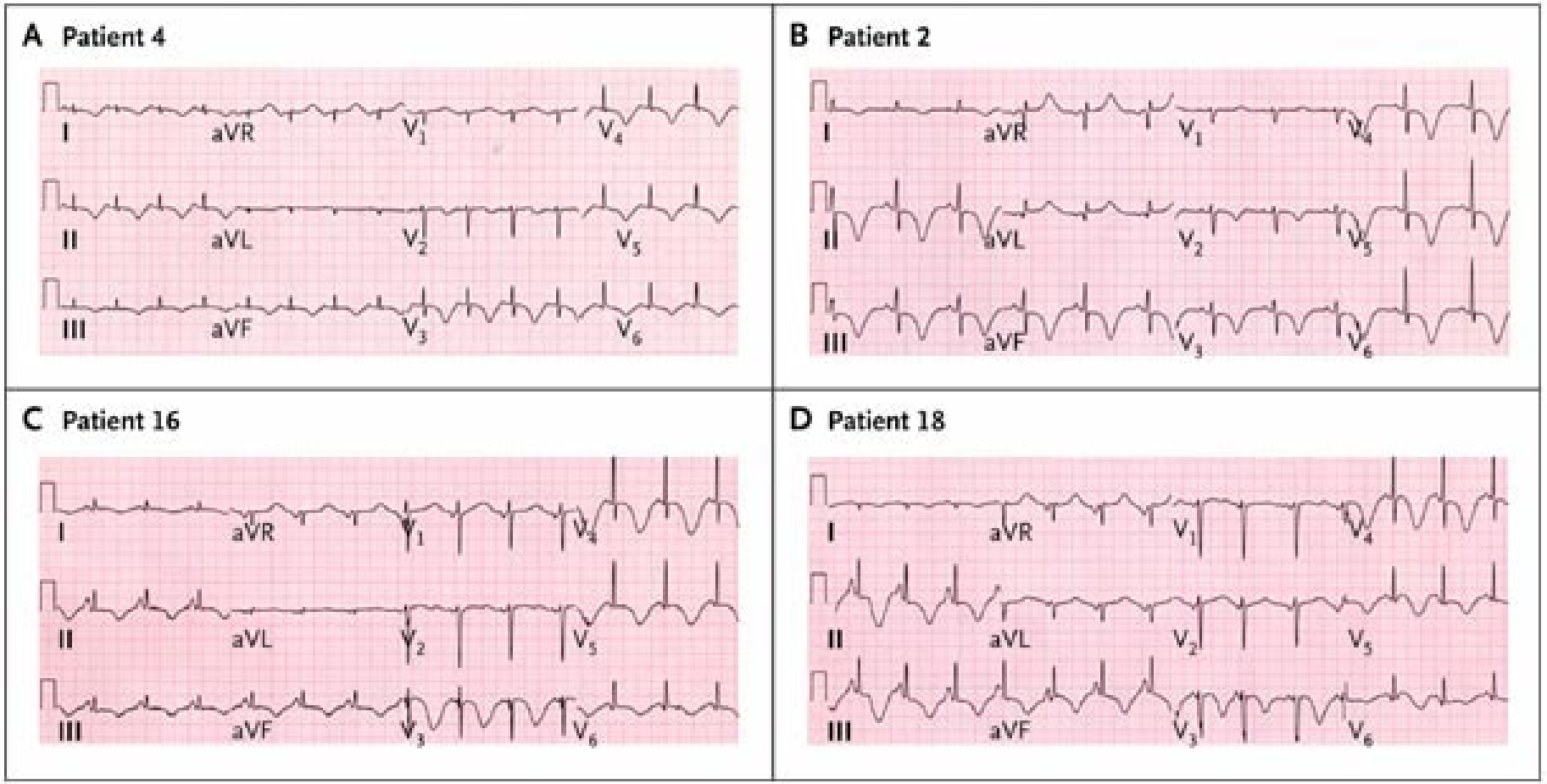
Conflicts of Interest:
Co-PI on DEFEAT HF
No consultant or stock conflicts

ESTABLISHED CLINICAL SITUATIONS

- 6 am to 12 noon increase in sudden cardiac arrest, stroke, and myocardial infarction (PERHAPS related to increased catecholamine secretion upon arising,
- BUT clock-dependent oscillator, krüppel-like factor 15 (Klf15) transcriptionally controls rhythmic expression of Kv channel-interacting protein 2 (KChIP2), a critical subunit required for generating the transient outward potassium current-(Jeyaraj et al. Nature 483:96, 2012)
- Increased sudden death in winter months: adults and infants, dogs with MI, Los Angeles or Canada, or Ausralia (June – August) Is there a seasonal oscillator also? BP, QT (males), and lipids all increase in winter months: SHORT DAYS?
- Increased sudden death after stress such as natural disasters or personal loss

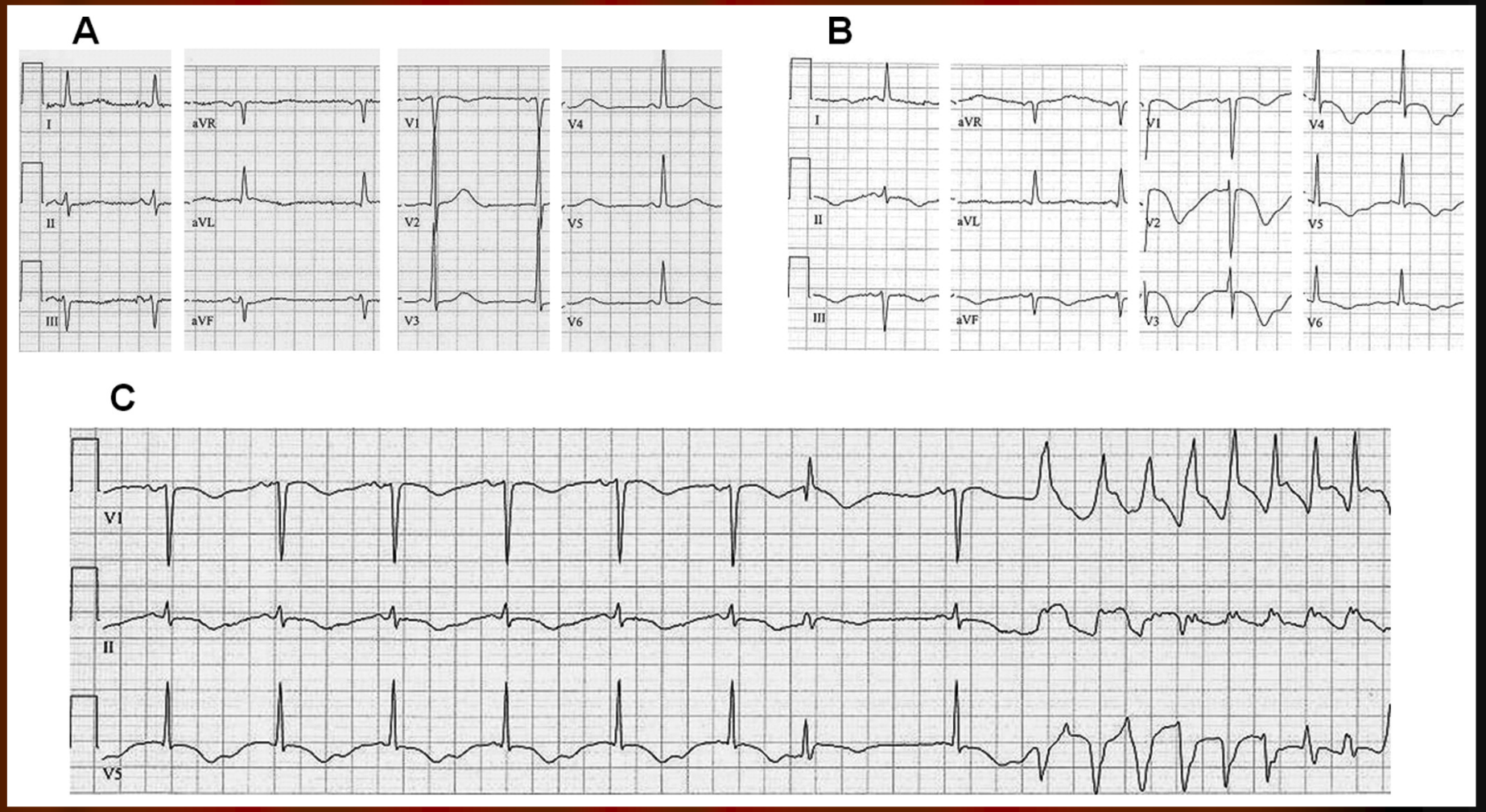
STRESS INDUCED CARDIOMYOPATHY (Takotsubo)

Typical Electrocardiograms Obtained 24 to 48 Hours after Presentation in Four Patients with



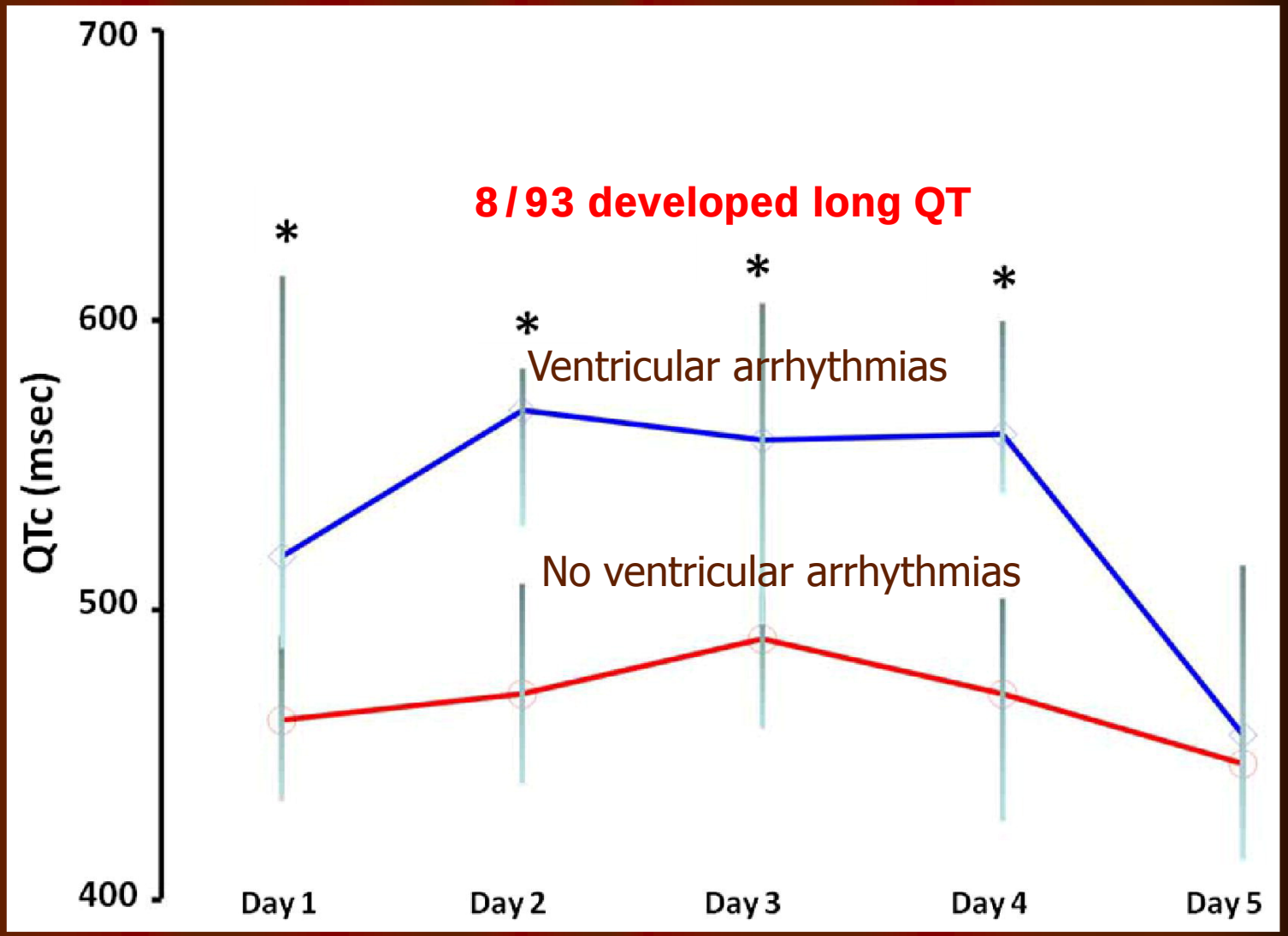
Wittstein et al: Neurohumoral features of myocardial stunning due to sudden emotional stress.N Engl J Med. 2005 Feb 10;352(6):539-48

Acquired long QT from stress cardiomyopathy



Source: Heart Rhythm (DOI:10.1016/j.hrthm.2010.12.012)

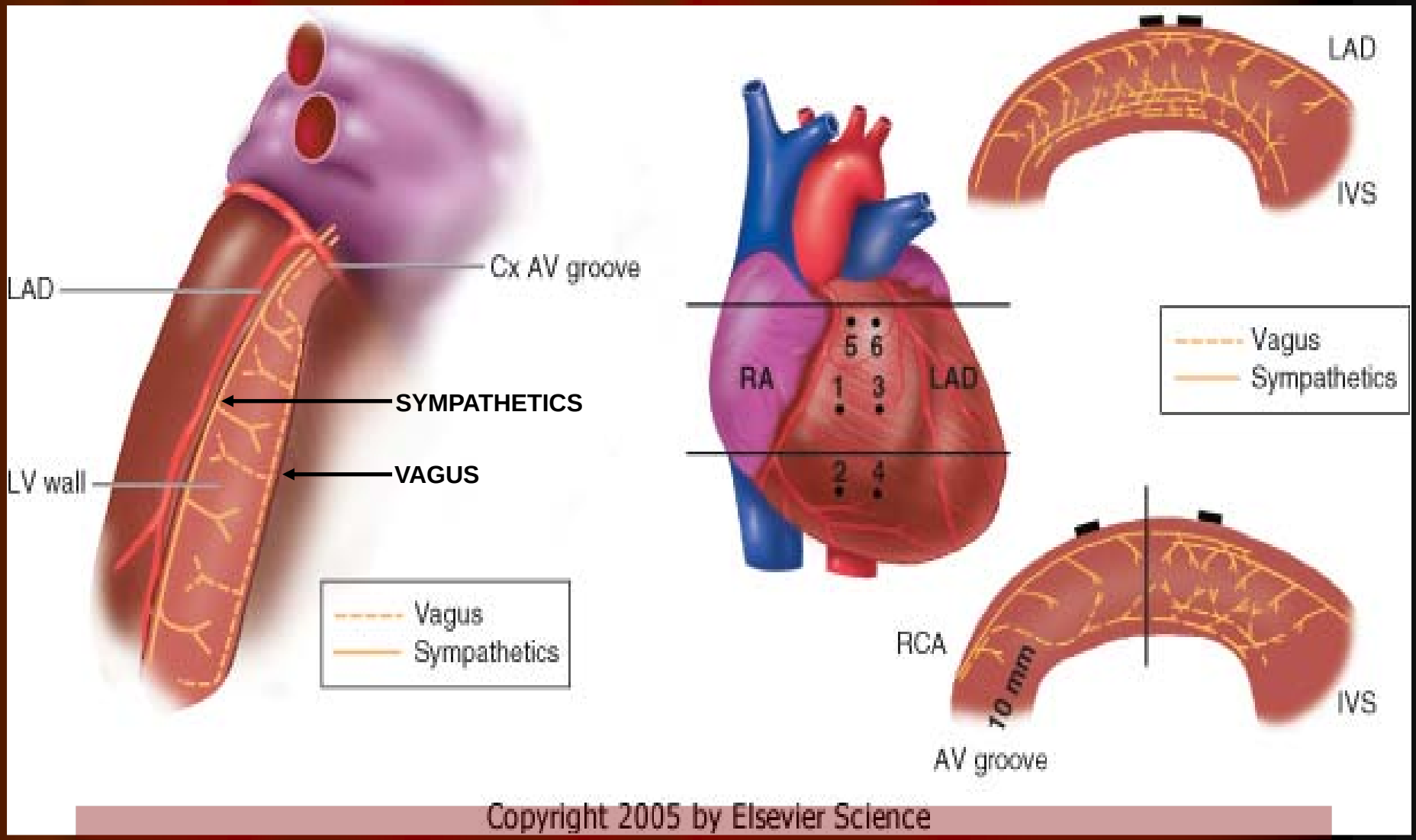
Acquired long QT from stress cardiomyopathy



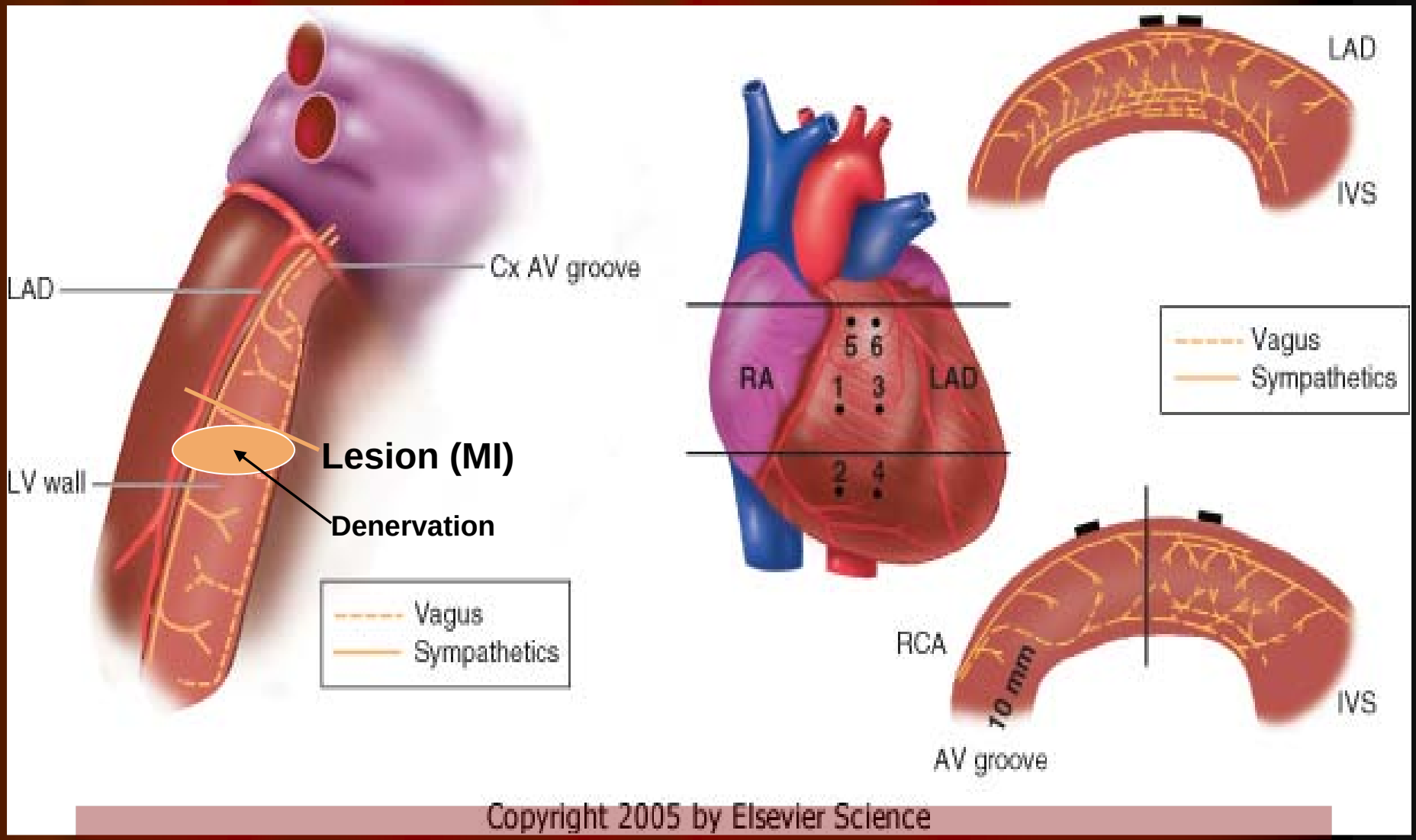
What are potential mechanisms by which ANS can trigger death? There may be multiple, but let us consider two:

- Autonomic heterogeneity
- Sympathetic discharge

AUTONOMIC INNERVATION OF THE VENTRICLES



AUTONOMIC INNERVATION OF THE VENTRICLES



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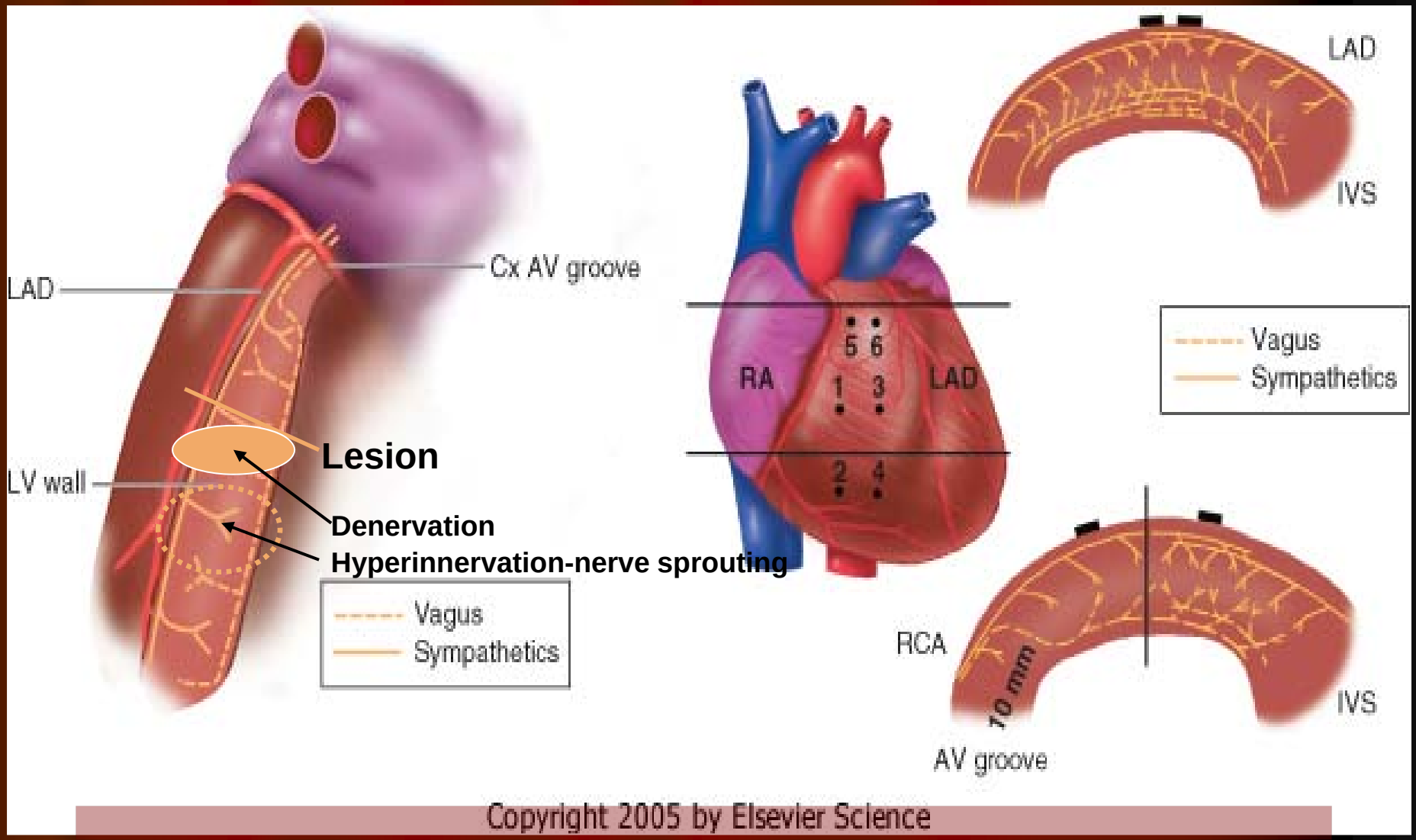
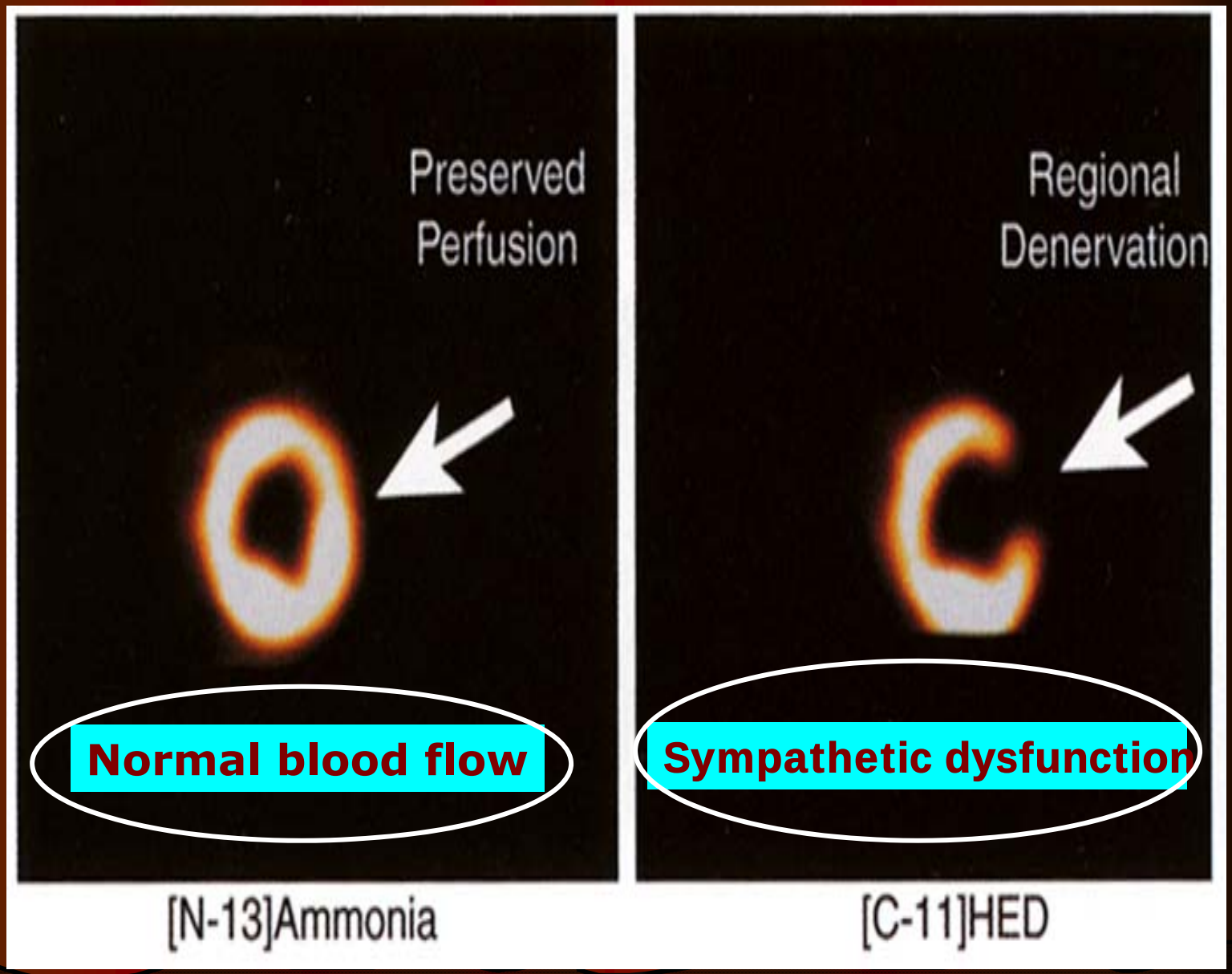
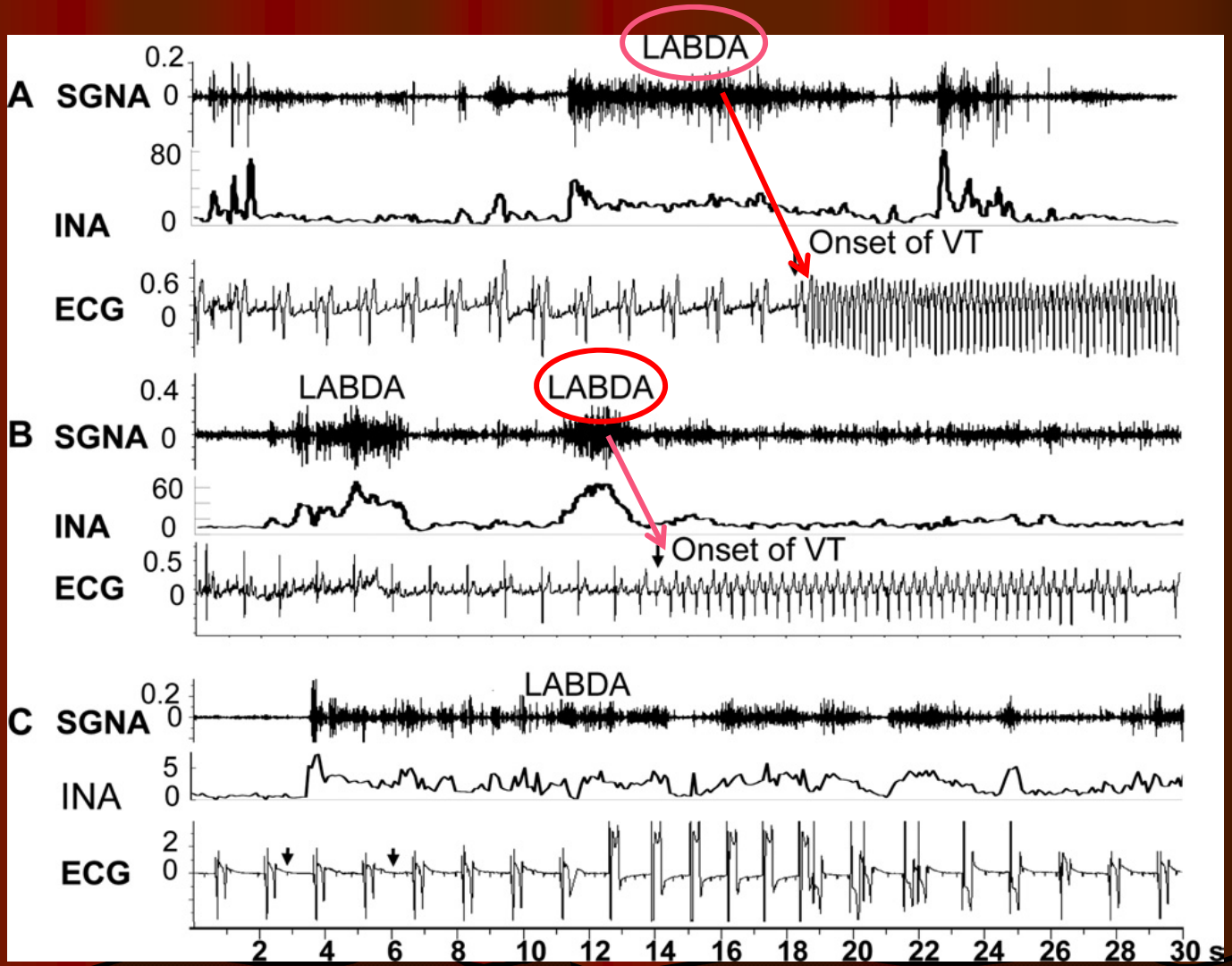


Sympathetic denervation after myocardial infarction

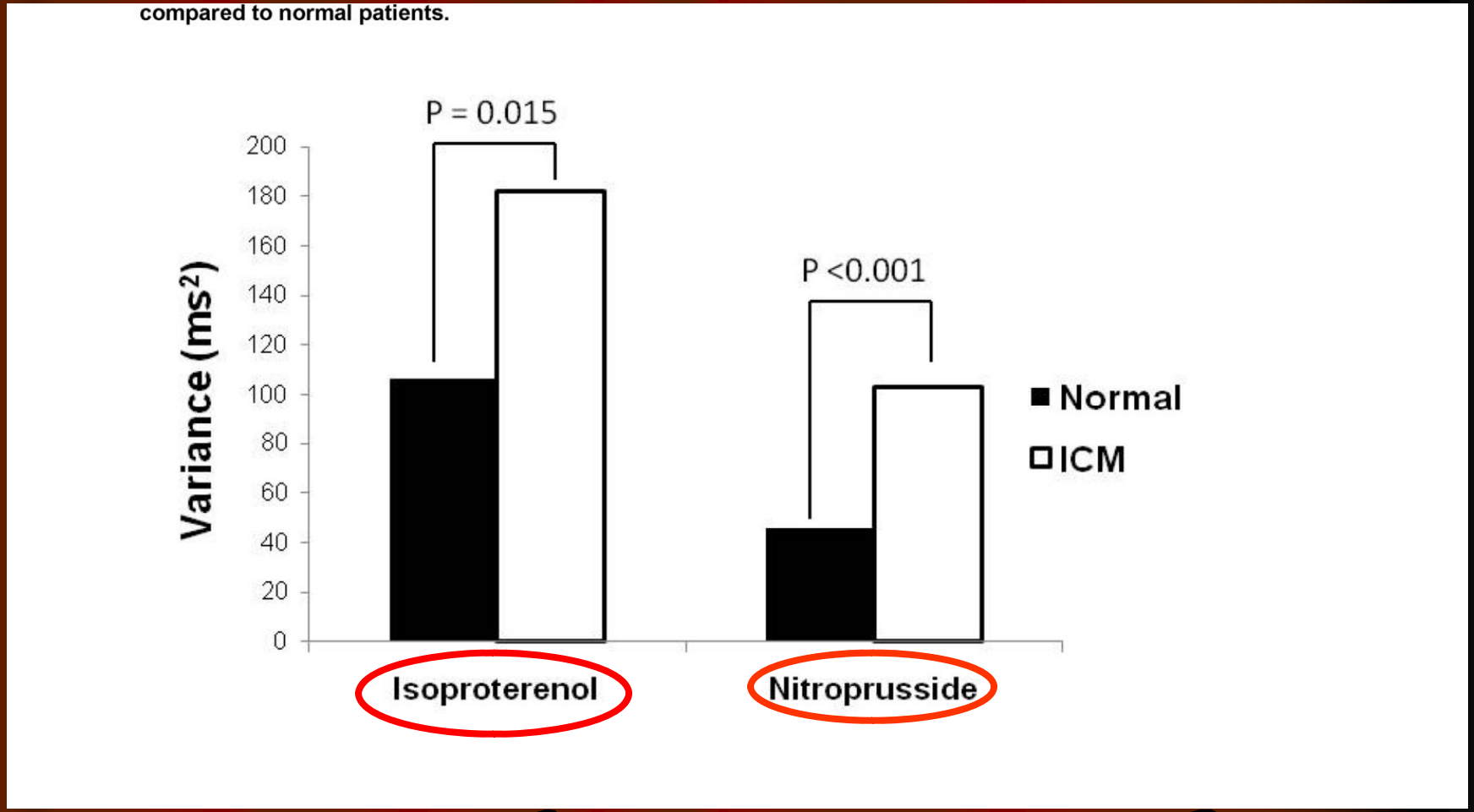


Increased stellate ganglion nerve activity (SGNA) preceding ventricular tachycardia



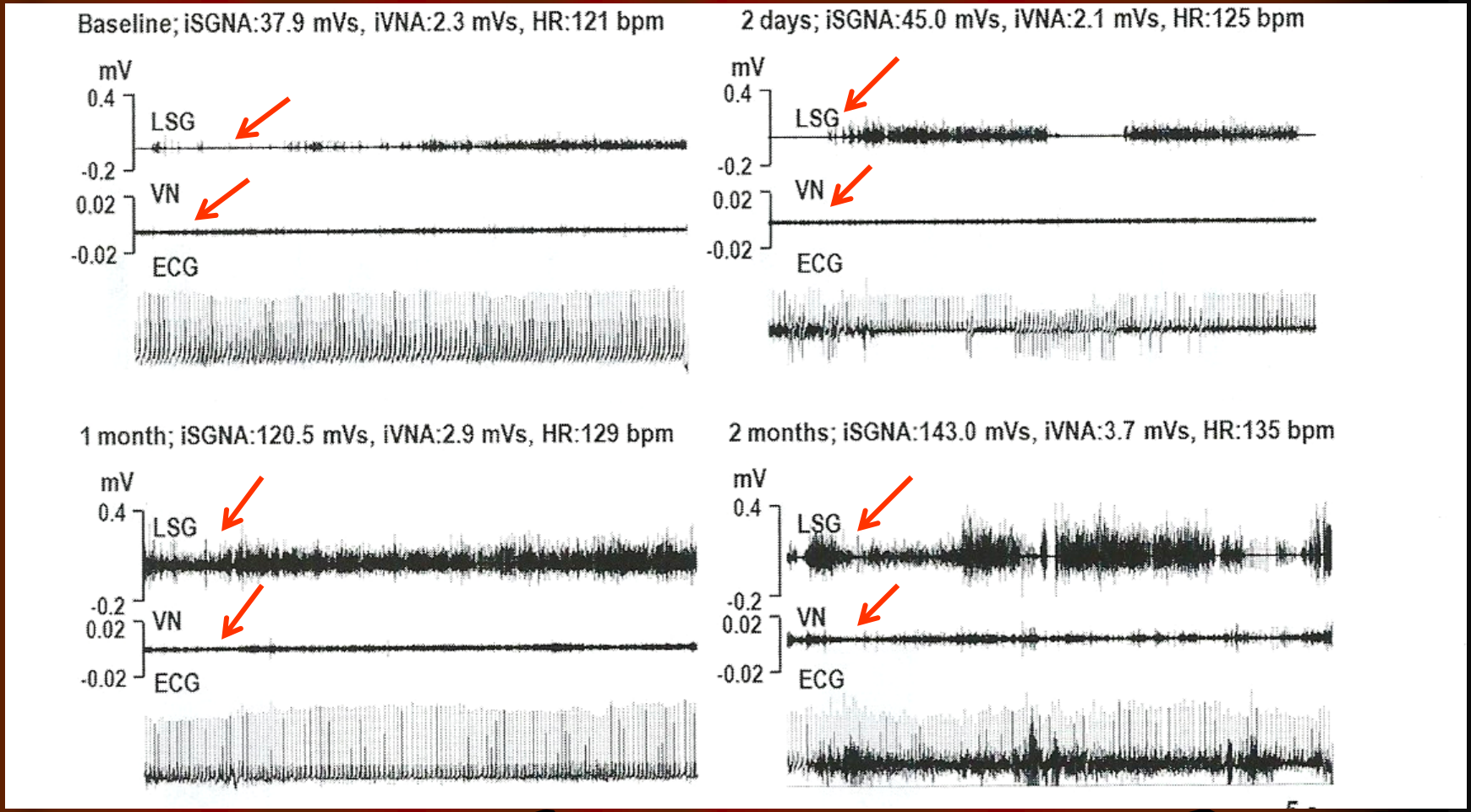
Zhou et al Heart Rhythm 2008;5:131–139

Sympathetic stimulation increases dispersion of repolarization in humans with MI



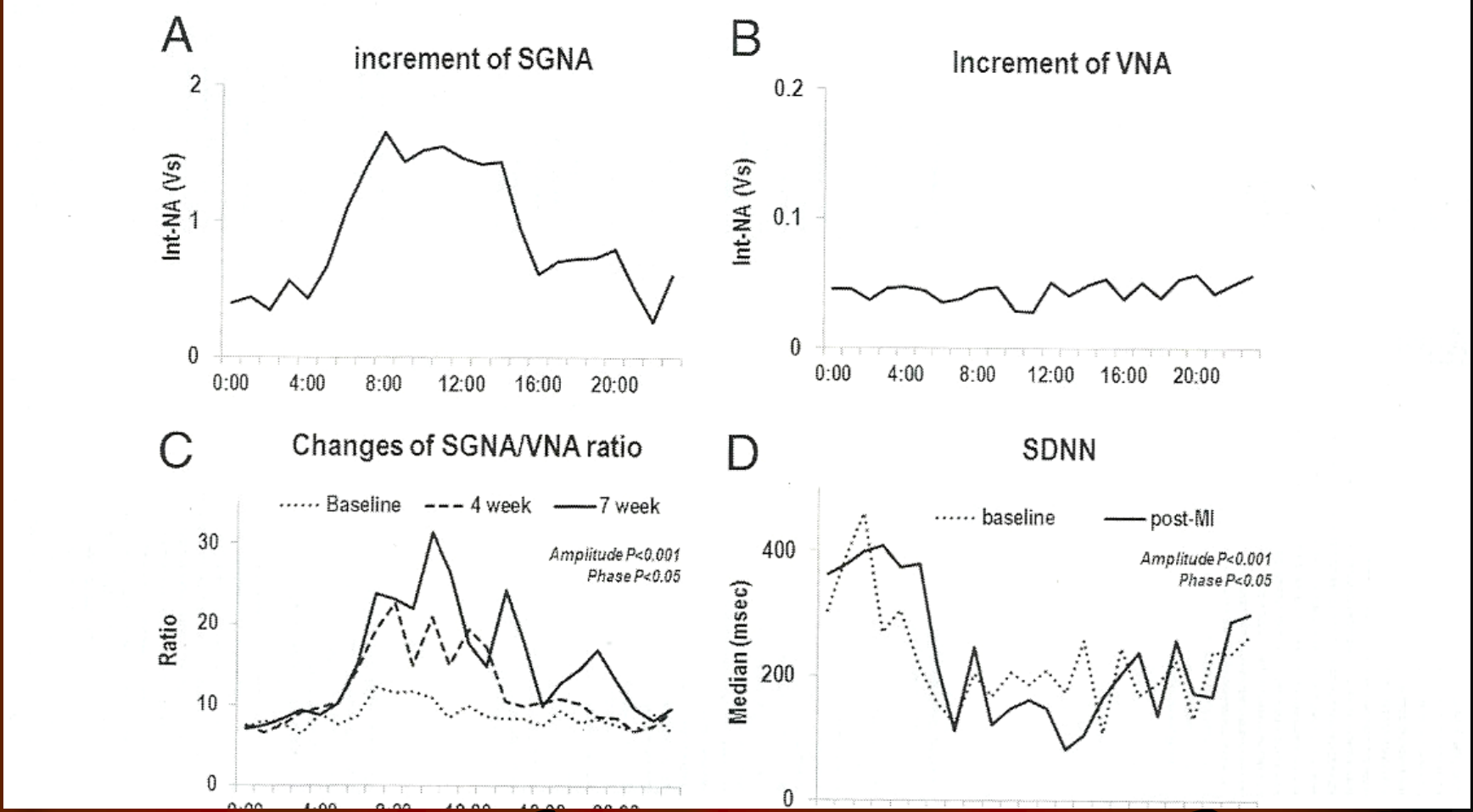
Vaseghi Shivkumar Am J Physiol Heart Circ Physiol (February 17, 2012). doi:10.1152/ajpheart.01106.2011

Simultaneous recordings of stellate ganglion and vagal nerve activity and ECG before and after MI show increase SGNA but flat VNA



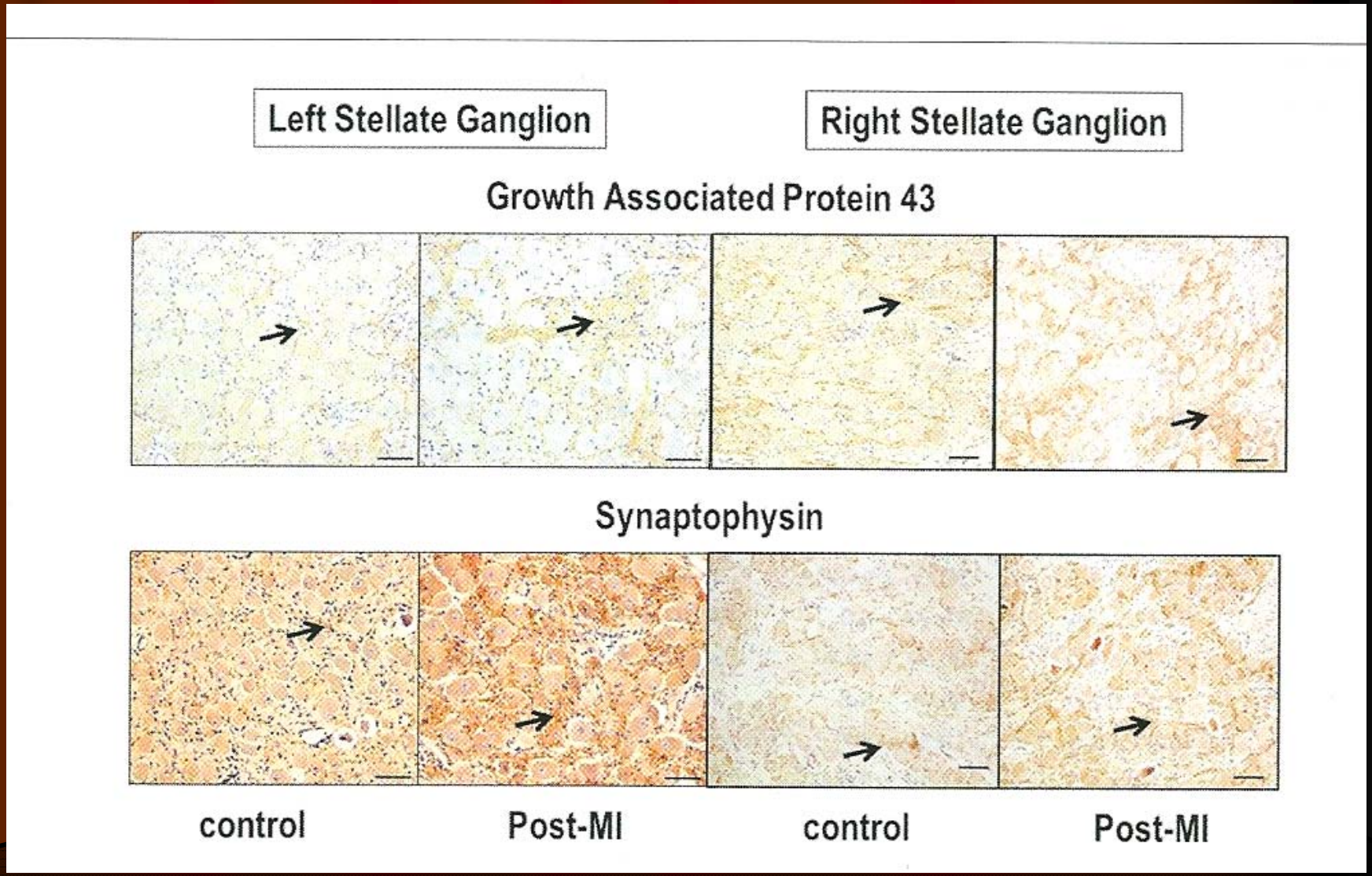
Han et al Electroanatomic remodeling after MI JACC 2012; 59:954-961

Increase in integrated SGNA and ratio SGNA/VNA over 24 hrs after MI show sympathovagal imbalance



Han et al Electroanatomic remodeling after MI JACC 2012; 59:954-961

Immunohistochemical staining show increased immunoreactivity in both SG



Han et al Electroanatomic remodeling after MI JACC 2012; 59:954-961

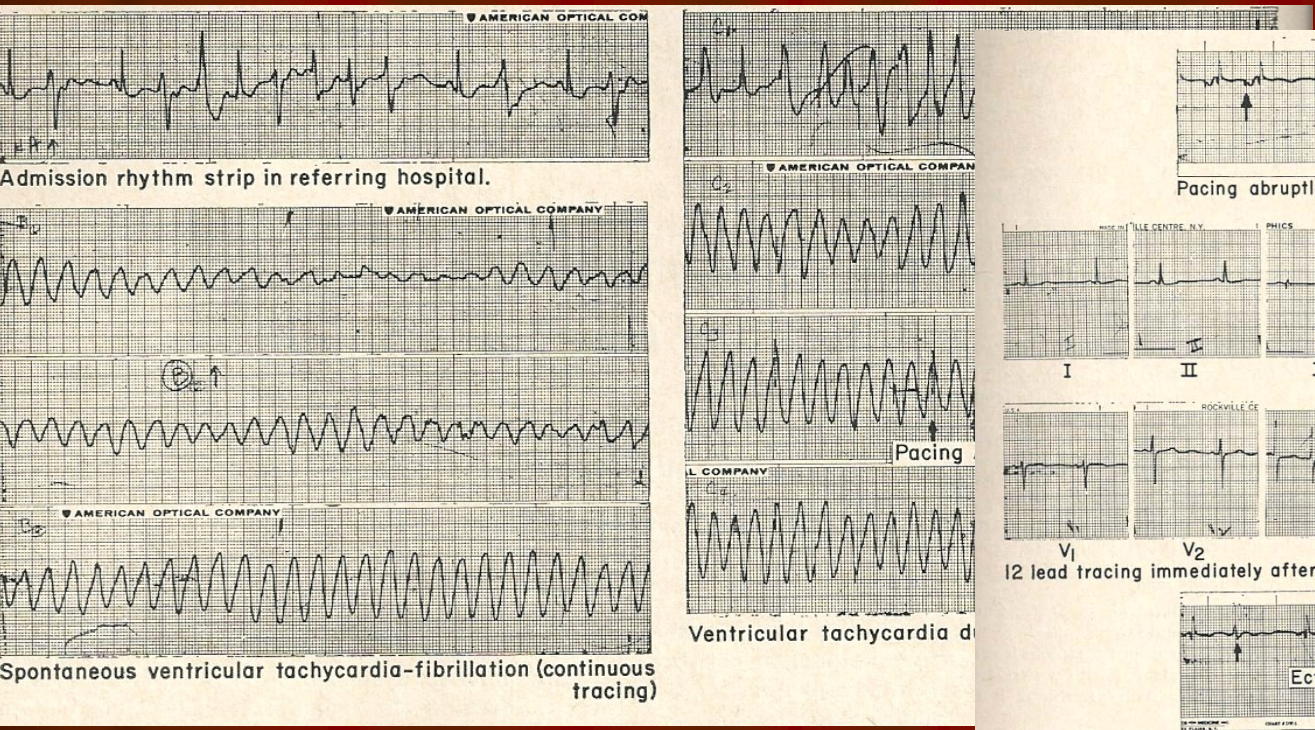
WHAT'S NEW IN THERAPIES OF SYMPATHETIC INHIBITION TO REDUCE SCD?

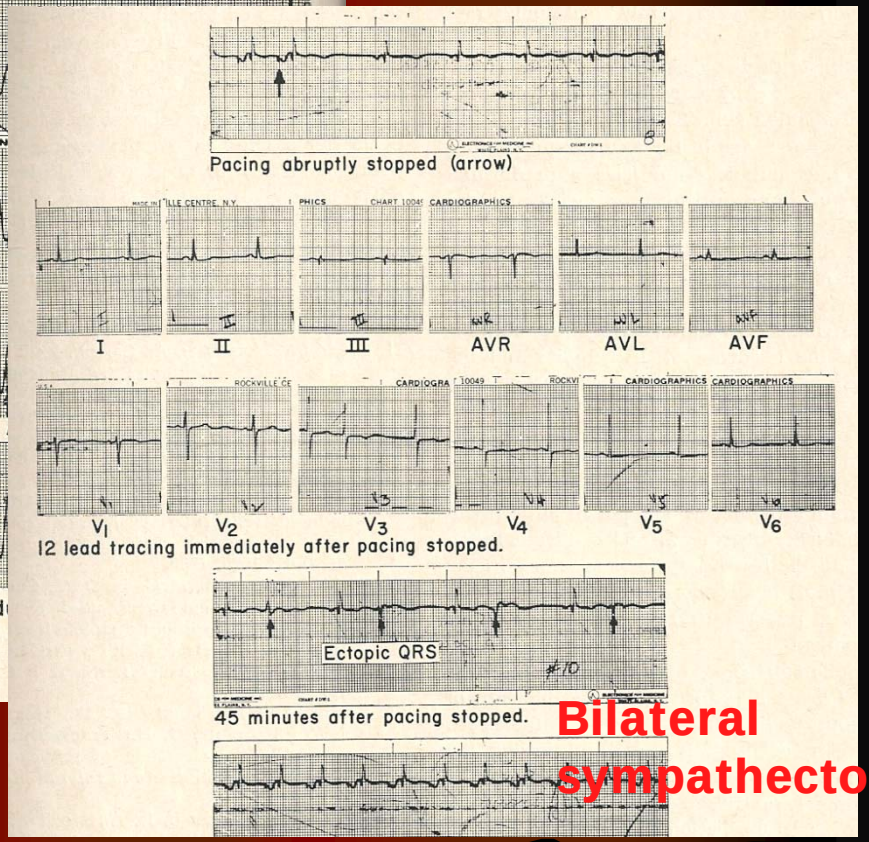
(Some treatments not that new!)

Ann Intern Med. 1968 Mar;68(3):591-7.

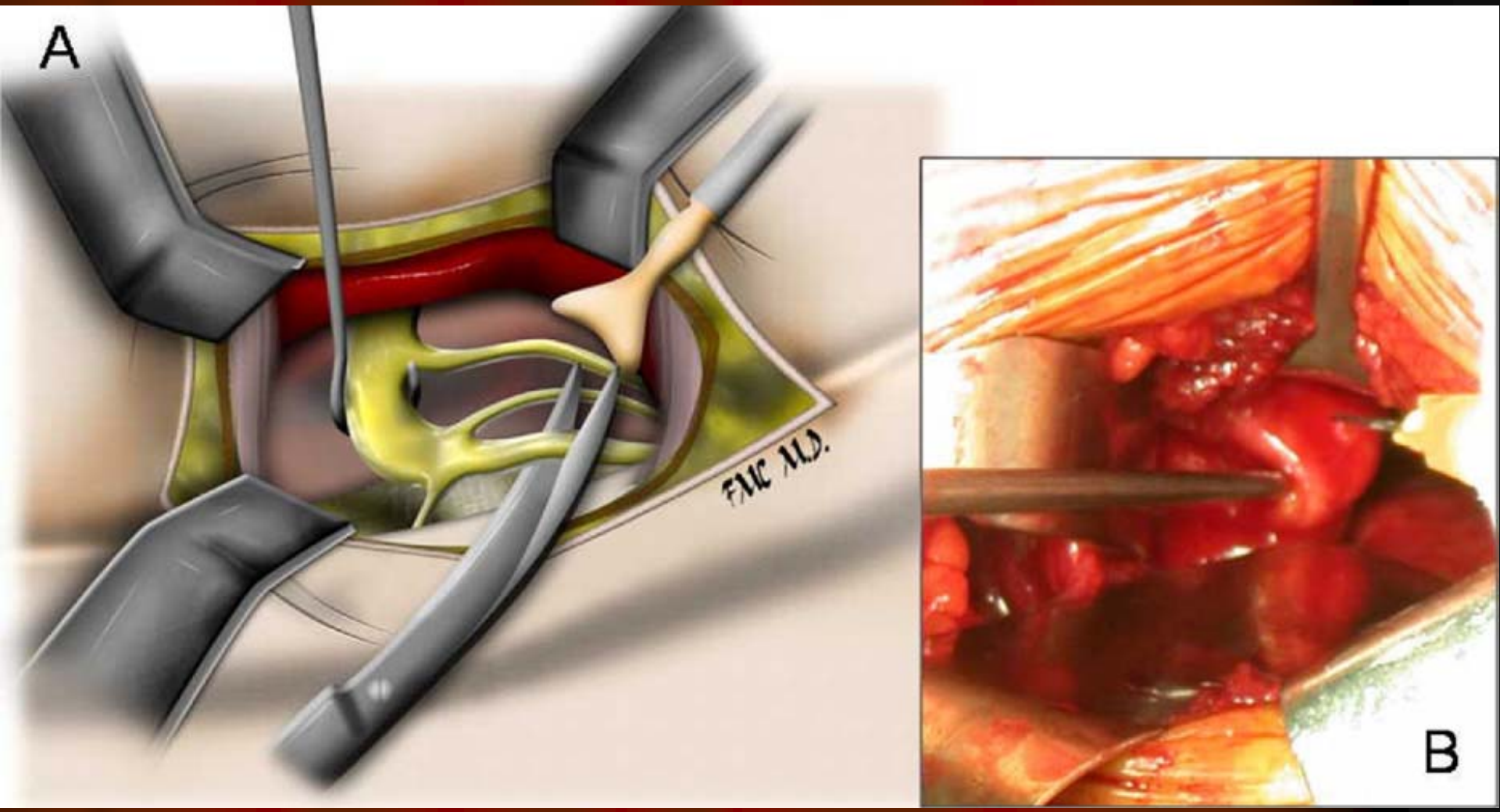
Treatment of ventricular arrhythmia by permanent atrial pacemaker and cardiac sympathectomy.

Zipes DP, Festoff B, Schaal SF, Cox C, Sealy WC, Wallace AG



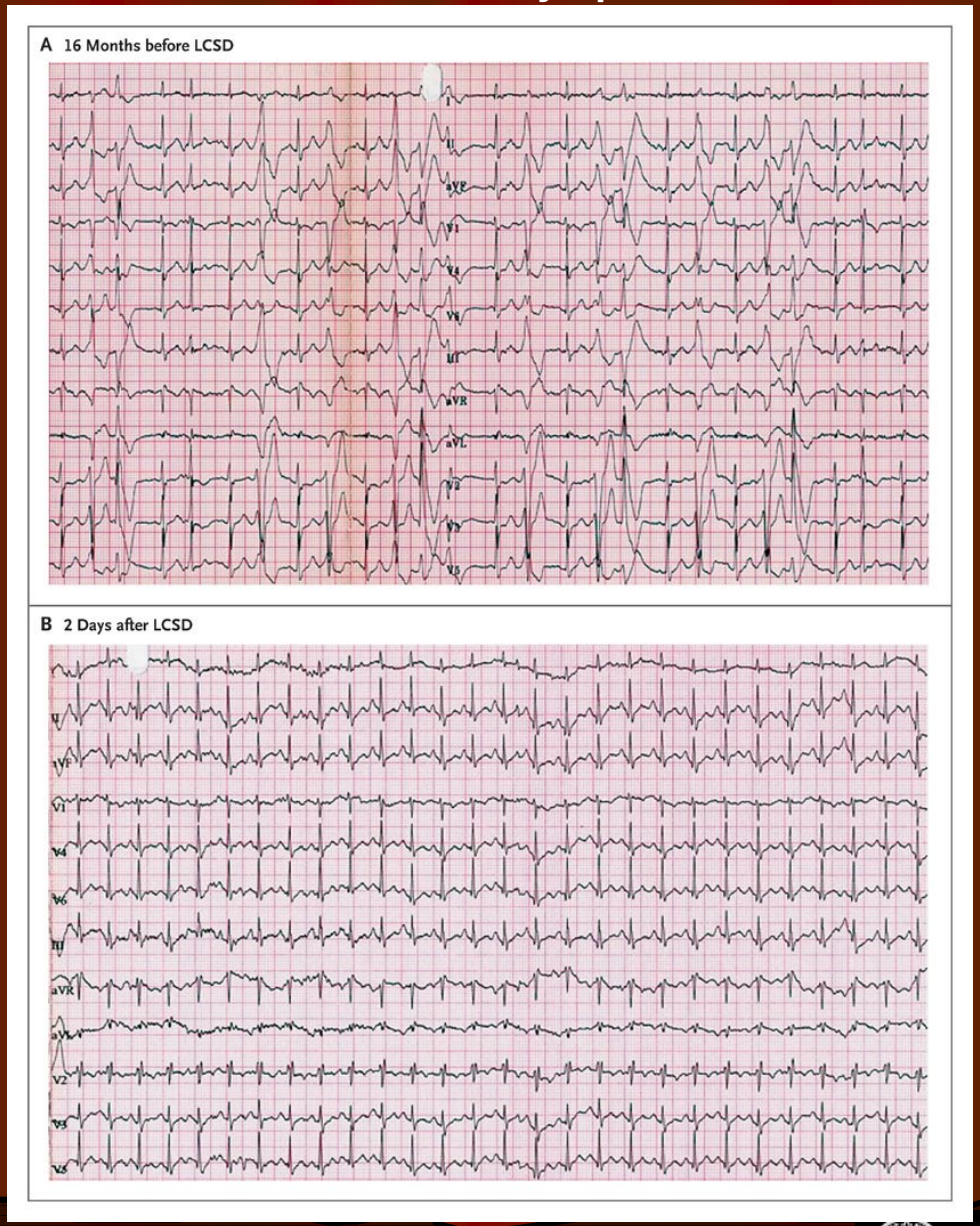


Left Cardiac Sympathetic Surgical Denervation



Odero…Schwartz Heart Rhythm 7:1161 (Aug) 2010

Twelve-Lead Electrocardiograms (ECGs) Obtained from Patient 2 during Exercise Stress Tests before and after Left Cardiac Sympathetic Denervation (LCSD)



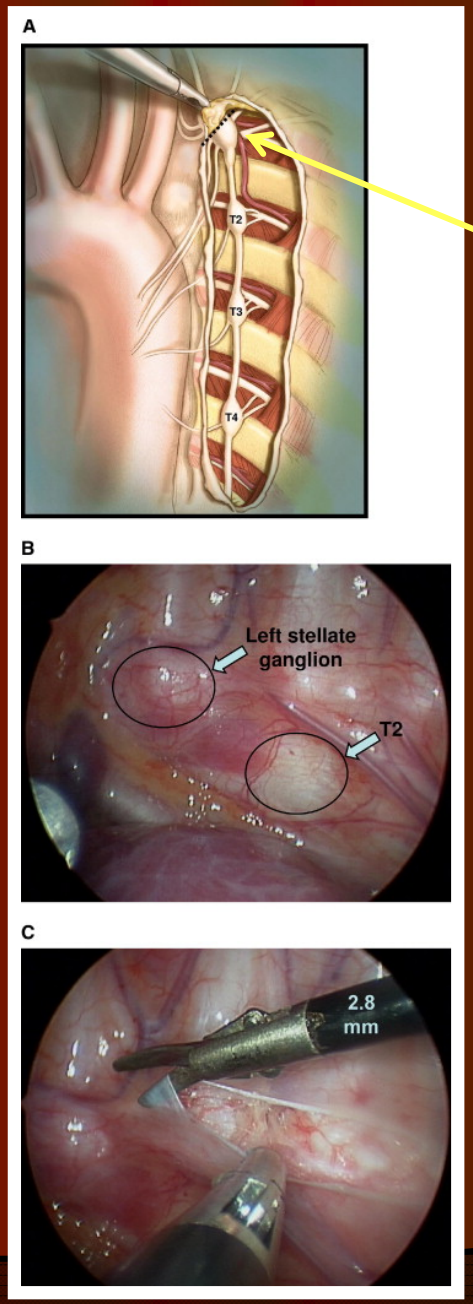
CPVT

LCSD

Wilde AAM et al. N Engl J Med 2008;358:2024-2029

The NEW ENGLAND JOURNAL of MEDICINE

Video-assisted thoracic surgery



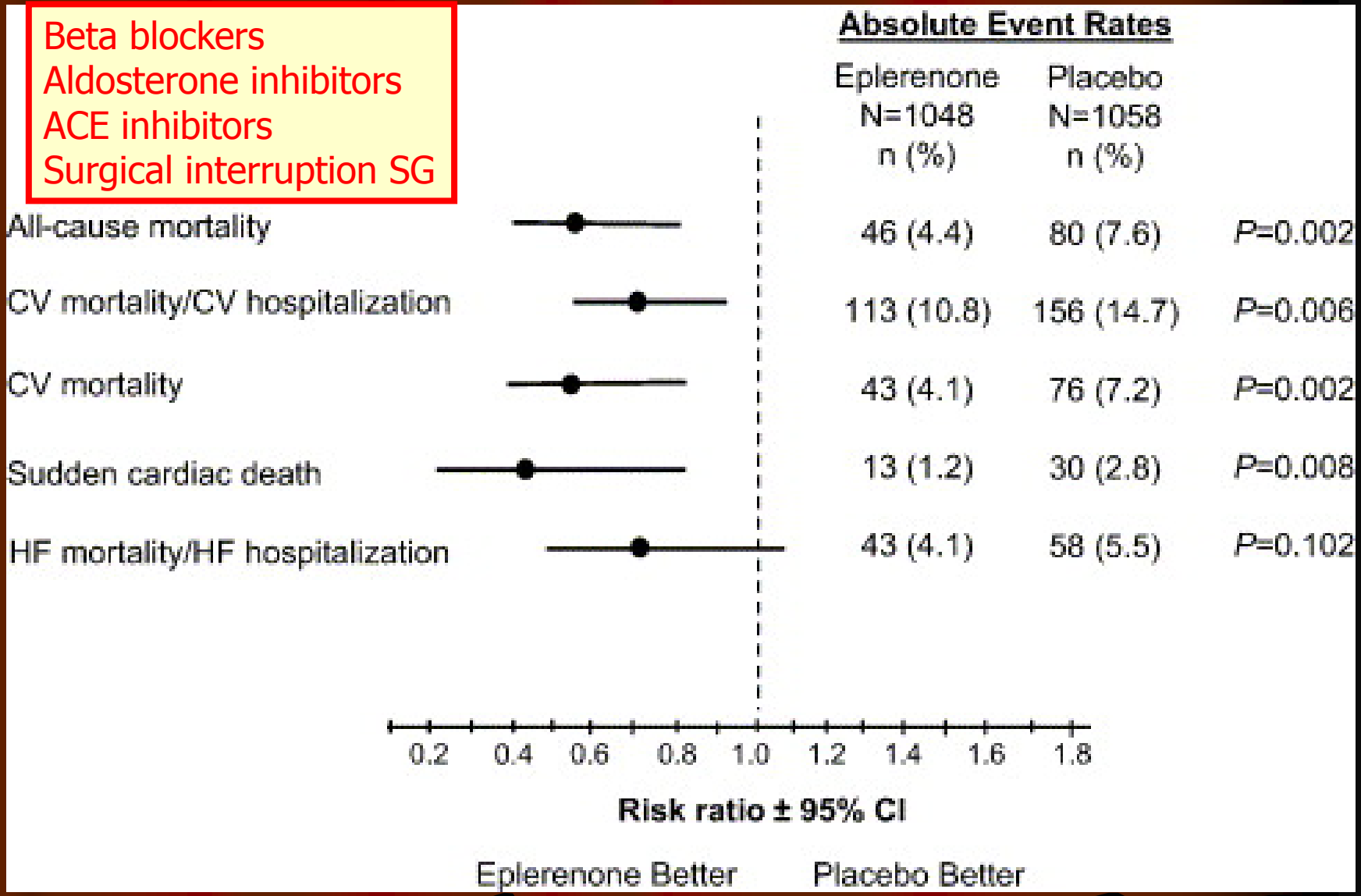
Resection of the lower half of the left stellate ganglion and top 2 or 3 ganglia

For LQT, drug induced (methadone), recurrent ischemic/nonischemic VT

Source: Heart Rhythm 2009; 6:752-759 (DOI:10.1016/j.hrthm.2009.03.024)

Relative risks of mortality and morbidity at 30 days post-randomization in EPHESUS patients with LVEF ≤ 30%

Beta blockers
Aldosterone inhibitors
ACE inhibitors
Surgical interruption SG

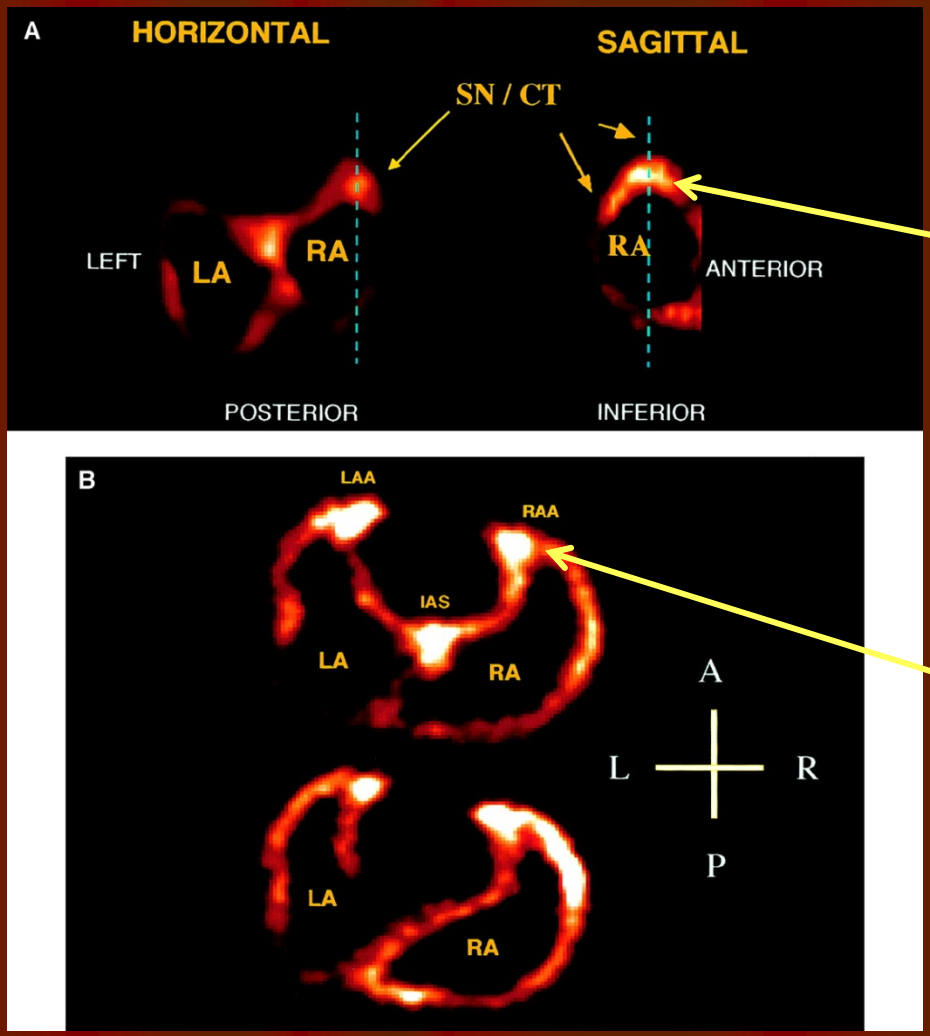


Pitt et al Eur J Heart Fail. 2006 Feb 24

VAGAL STIMULATION CAN BE USED TO REGULATE SYMPATHETIC EFFECTS:

Vagal stimulation opposes sympathetic action at prejunctional (NE release) and post junctional (cell) levels

PET Images in dogs after pacing induced AF: Increased sympathitic innervation



Control

Atrial fibrillation

Circulation

Jayachandran, Olgin, Zipes Circulation 2000;101:1185-1191

American Heart Association
Learn and Live

Vagal stimulation for atrial fibrillation

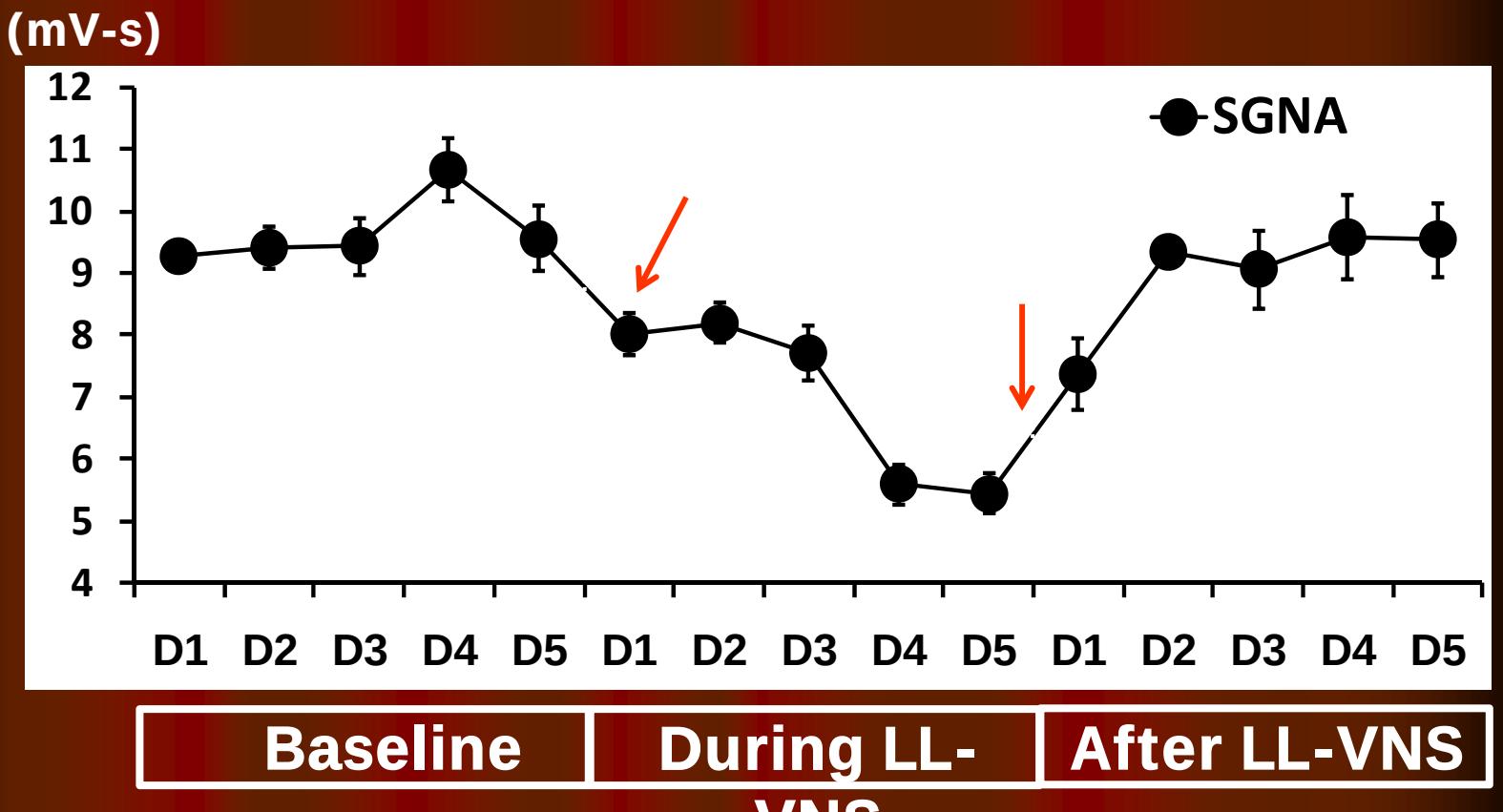
- Vagal stimulation is “pro-fibrillatory” in the atrium but anti fibrillatory in the ventricle
- Could low levels of vagal stimulation be anti-sympathetic and be antiarrhythmic?

Low-Level Vagus Nerve Stimulation

- Low-level vagus nerve stimulation = LL-VNS
- Left-sided cervical vagus nerve
- Stimulus strength: 1 V below the threshold needed to reduce the sinus rate (4±2 V, range 1-6 V)

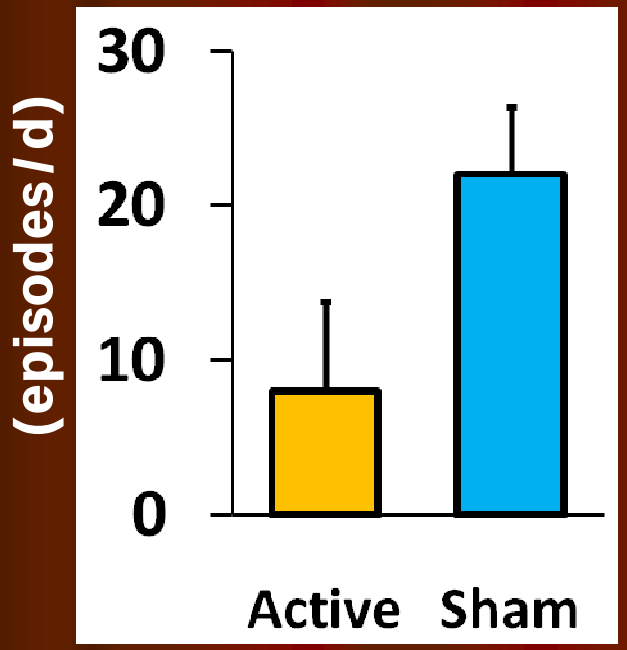
Shen et al.Circulation 2011;123:2204-12

Daily Changes of SGNA

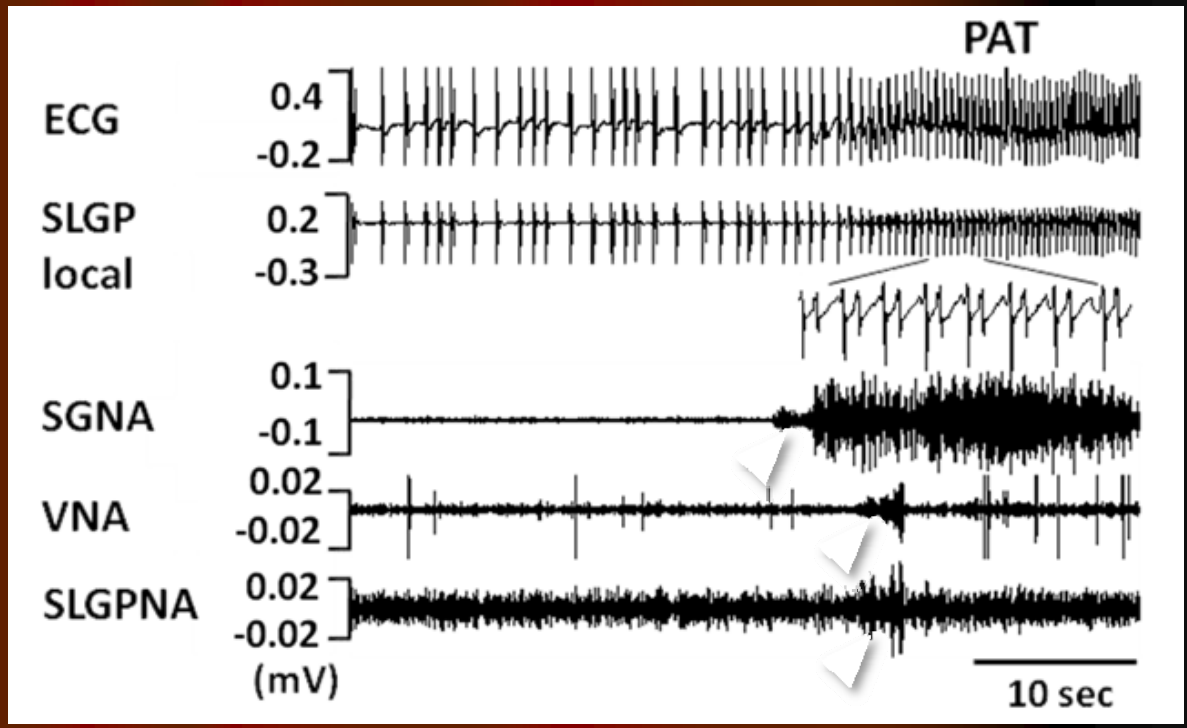


Paroxysmal Atrial Tachycardias

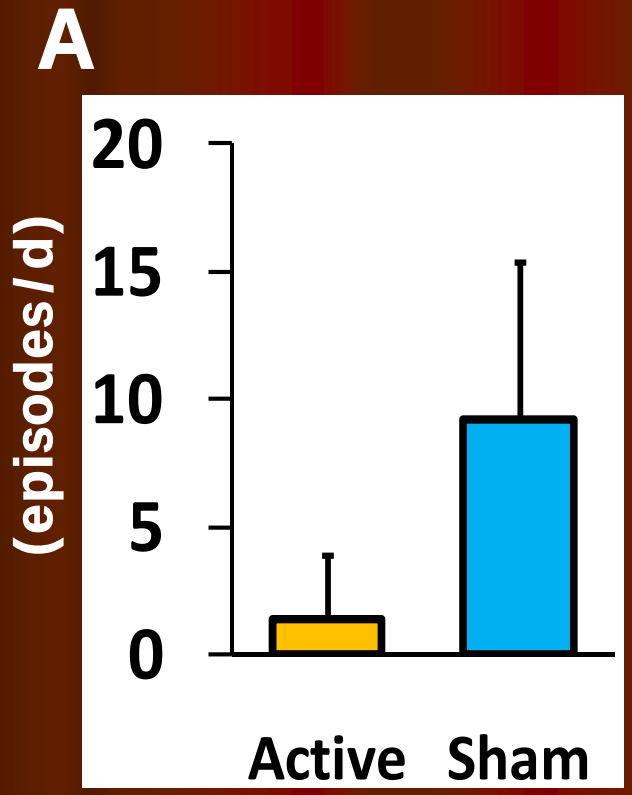
A

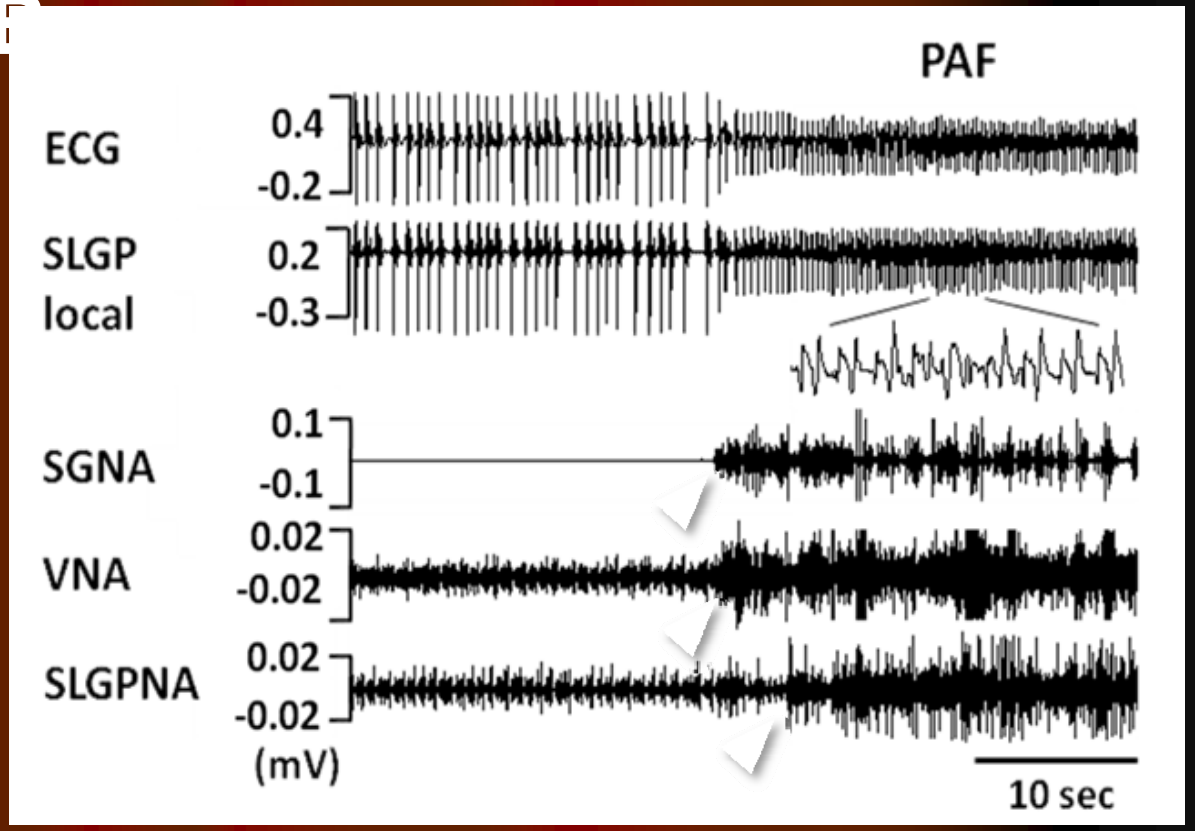


B



Paroxysmal Atrial Fibrillation



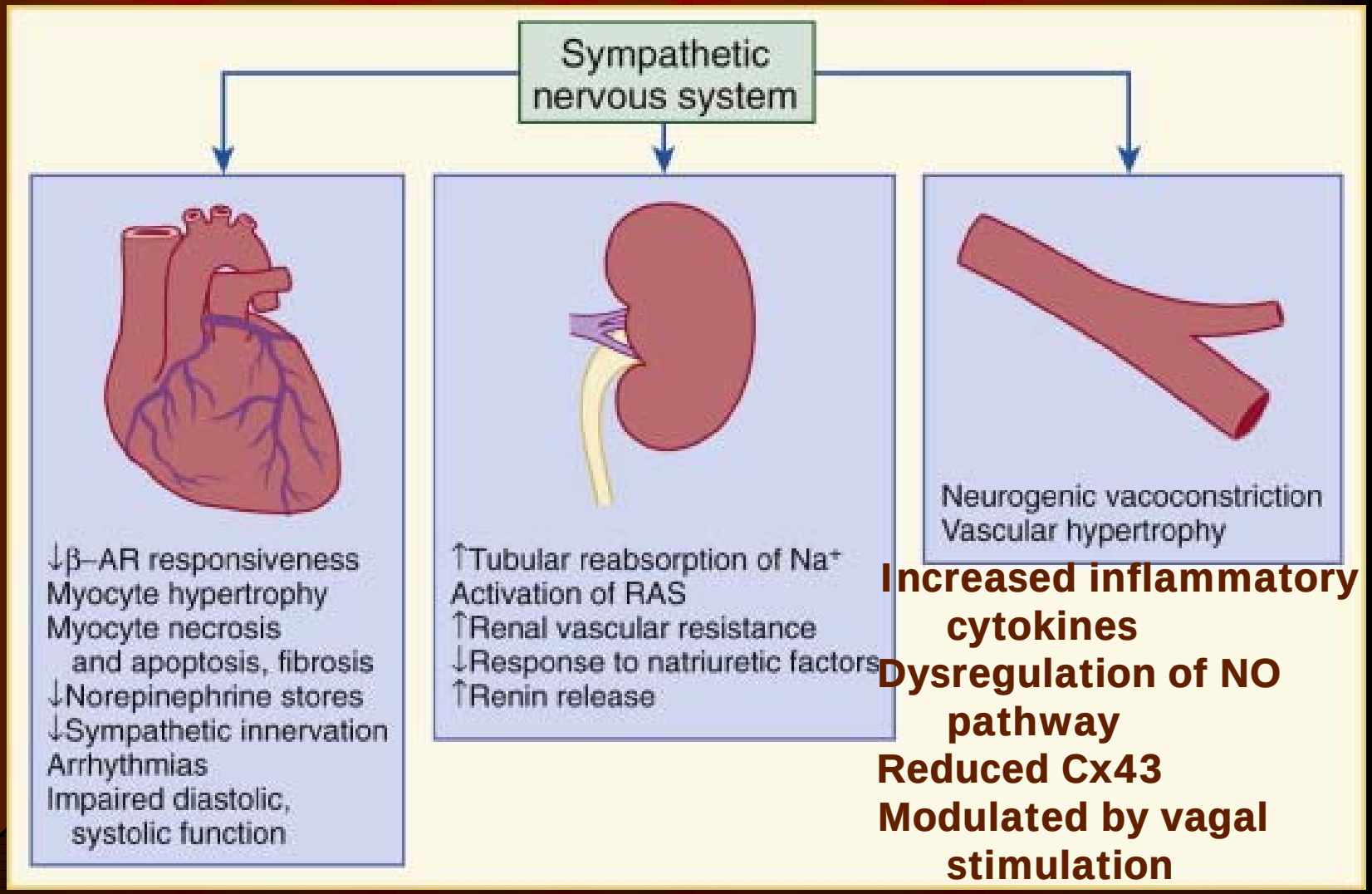


Conclusions

- Chronic LL-VNS reduces SGNA and tyrosine hydroxylase-positive nerve density in the left stellate ganglion.
- It also suppresses the paroxysmal atrial tachyarrhythmias in ambulatory dogs.
- The remodeling in the left stellate ganglion underlies the antiarrhythmic mechanisms of LL-VNS.
- Could this be a new treatment for PAF?

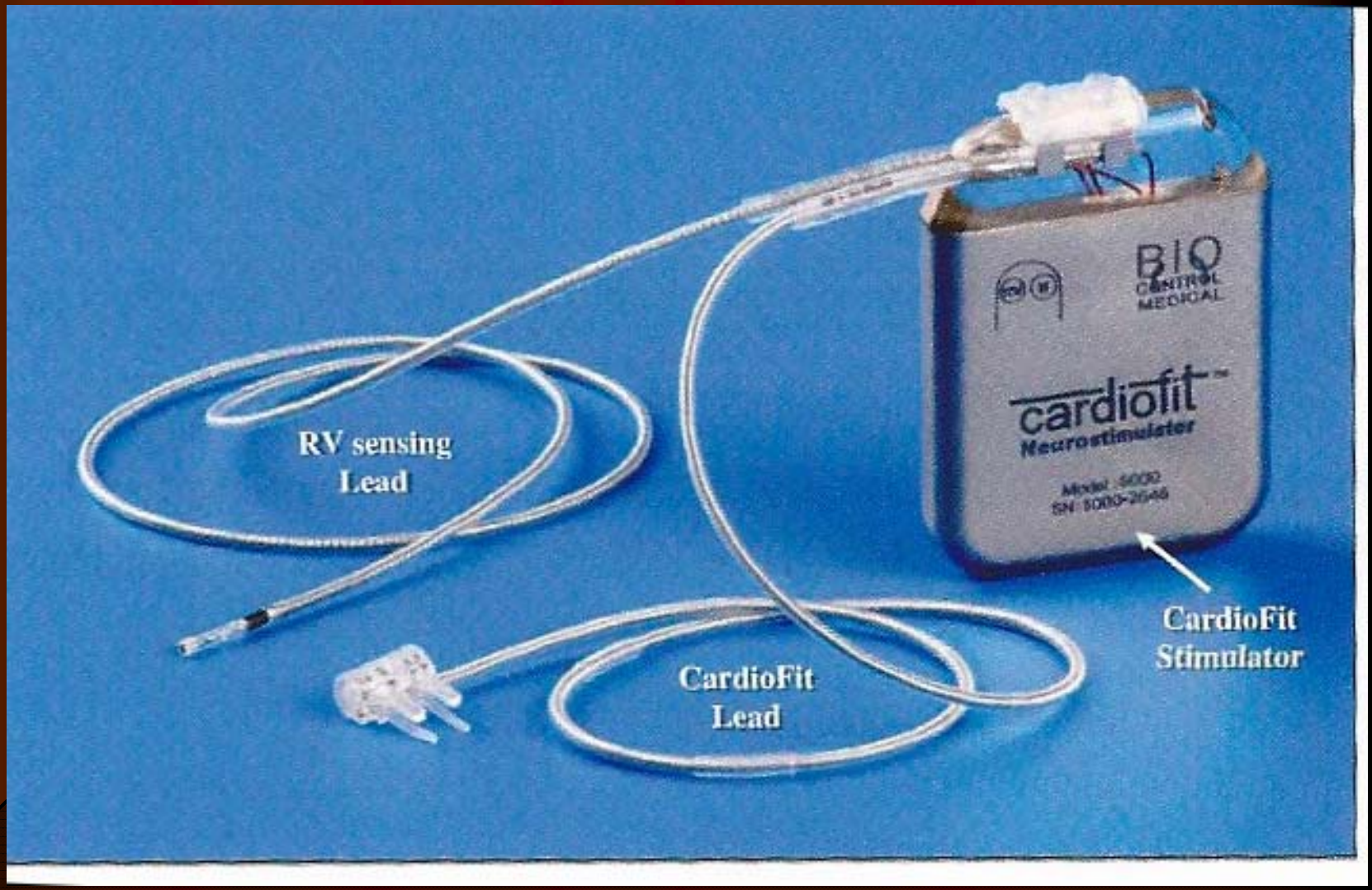
What about chronic vagal nerve stimulation for ventricular arrhythmias and heart failure?

Increased sympathetic activity affects cardiac, renal, and vascular function



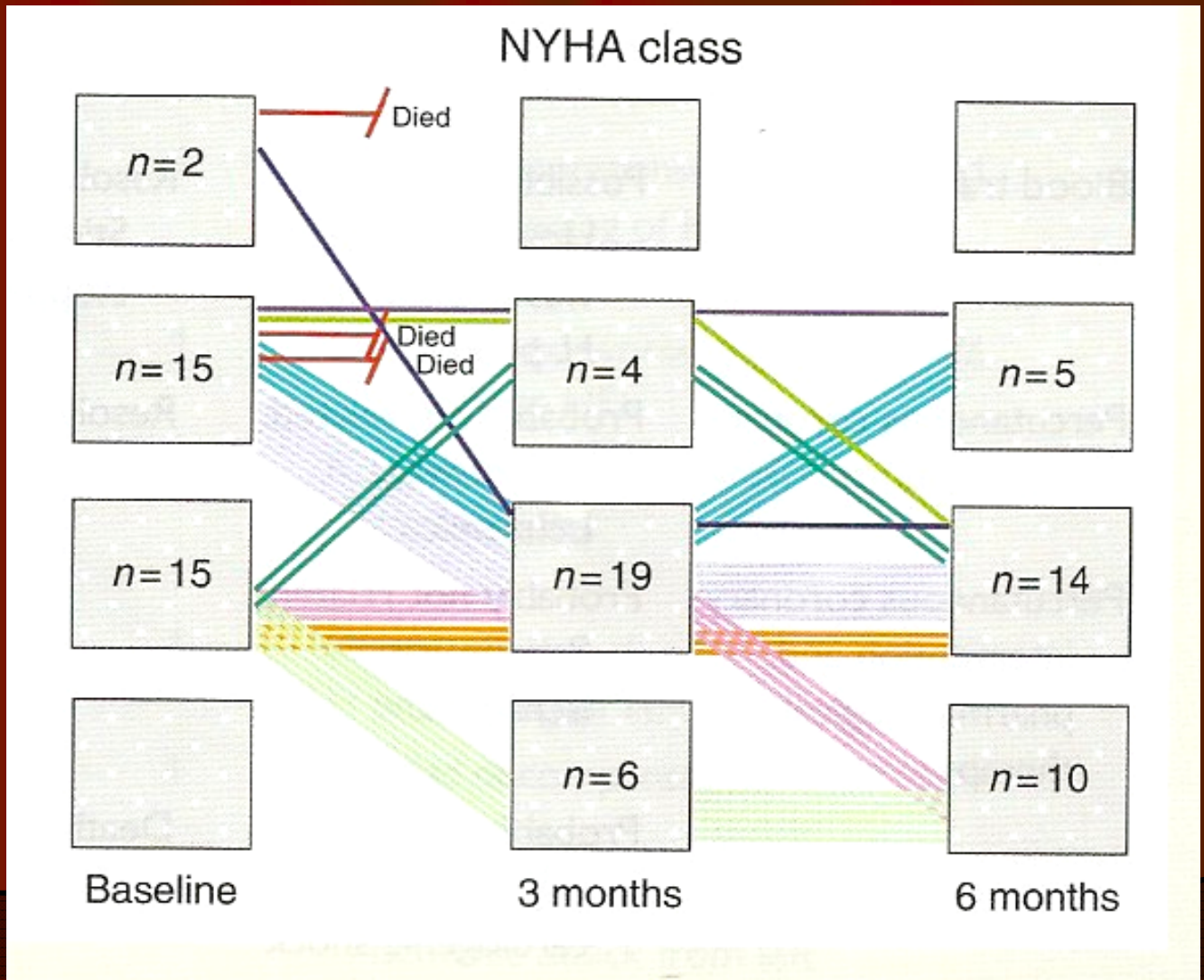
D. Mann

Chronic right vagal nerve stimulation



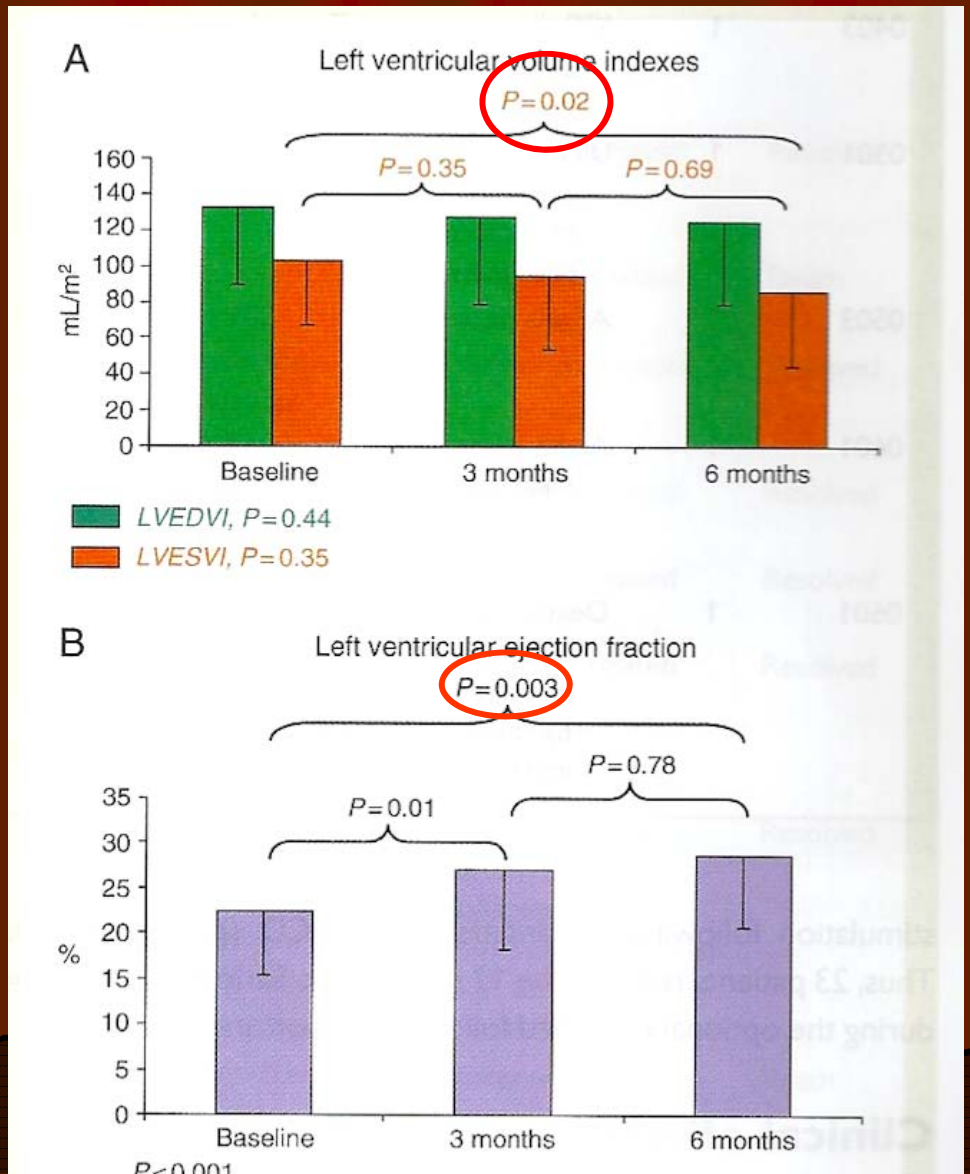
Chronic vagus nerve stimulation for HF

DeFerrari et al European Heart Journal 2011; 32:847



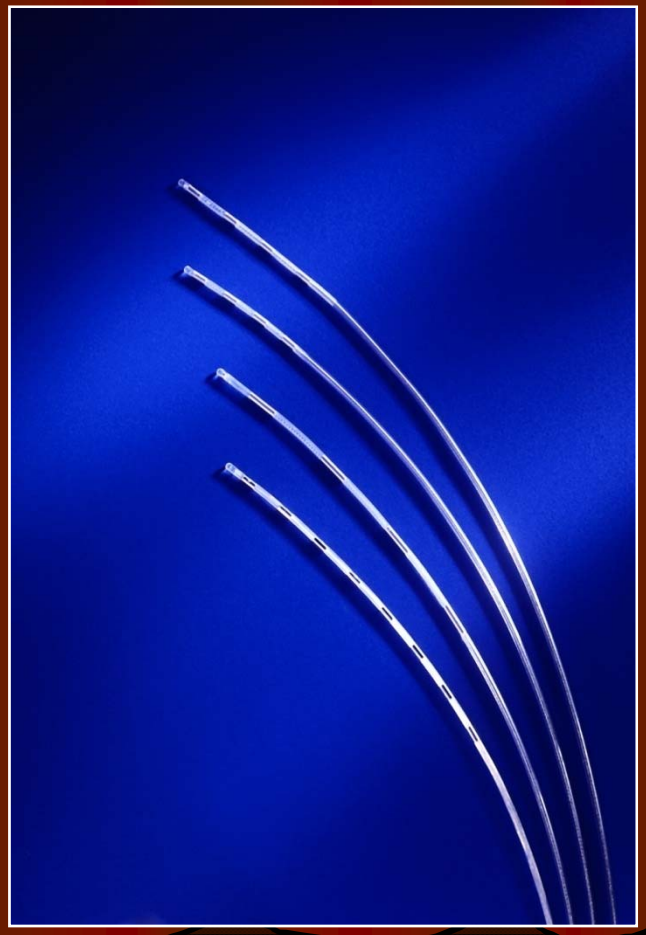
Chronic vagus nerve stimulation

DeFerrari et al European Heart Journal 2011; 32:847

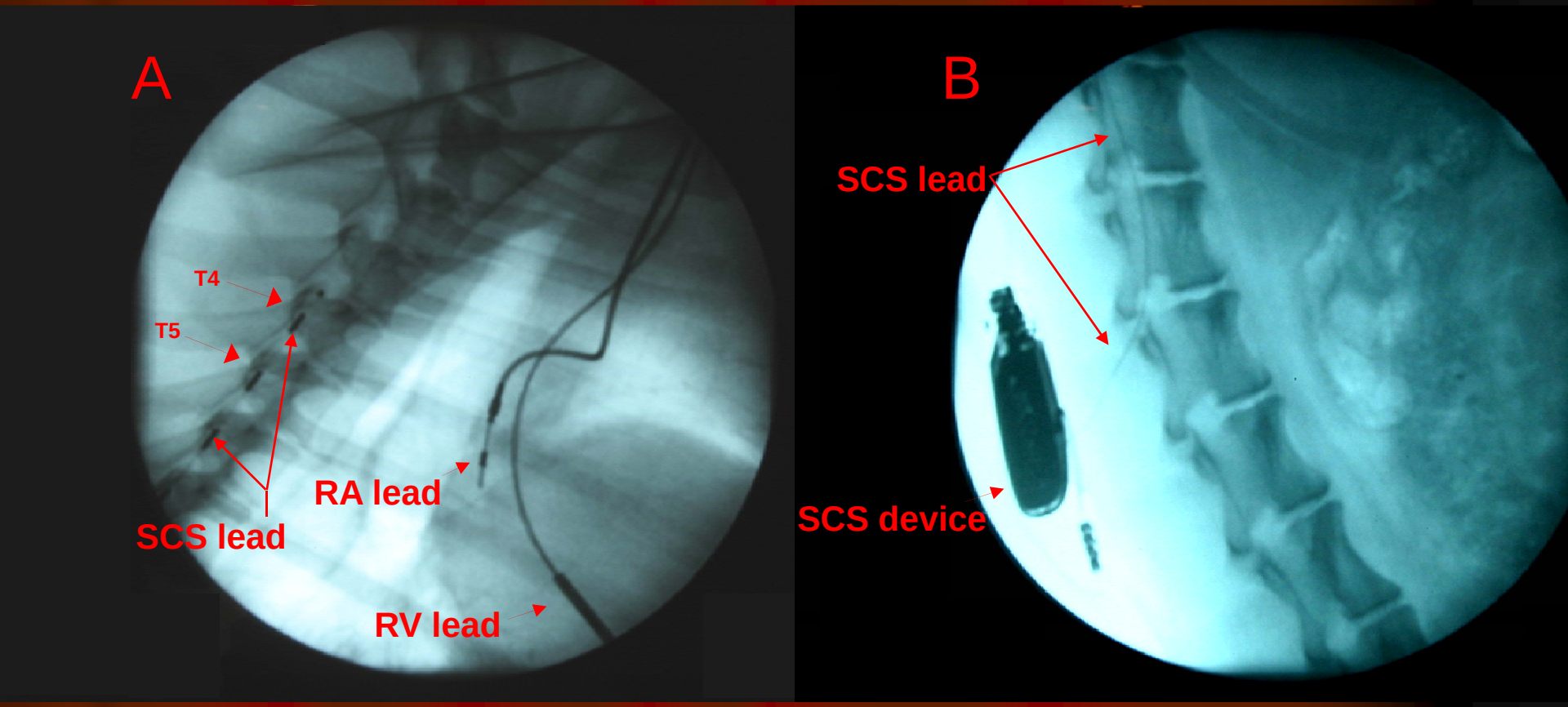


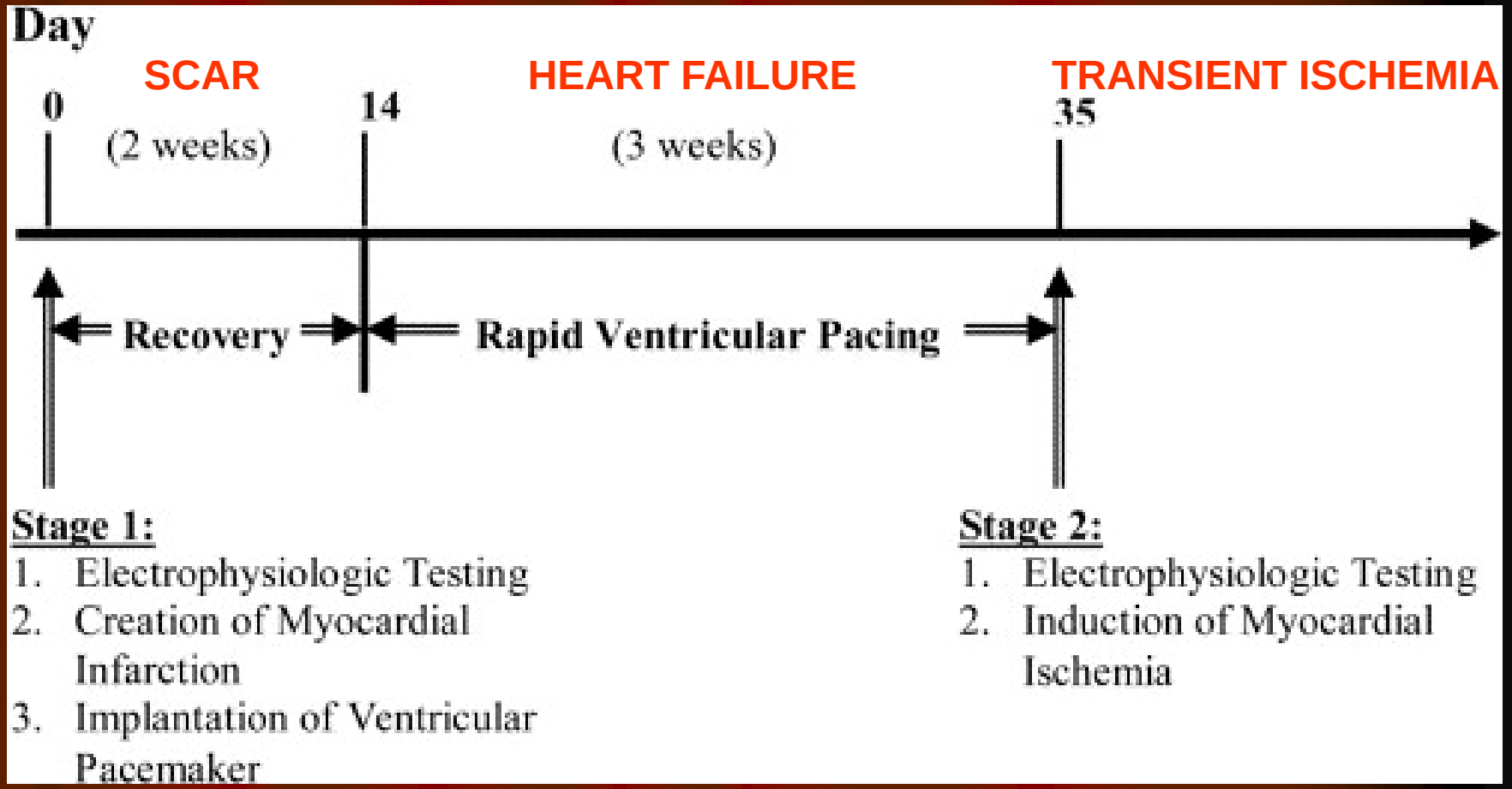
Neurostimulation Devices To Modulate Sympathetic Activity

Spinal cord stimulation



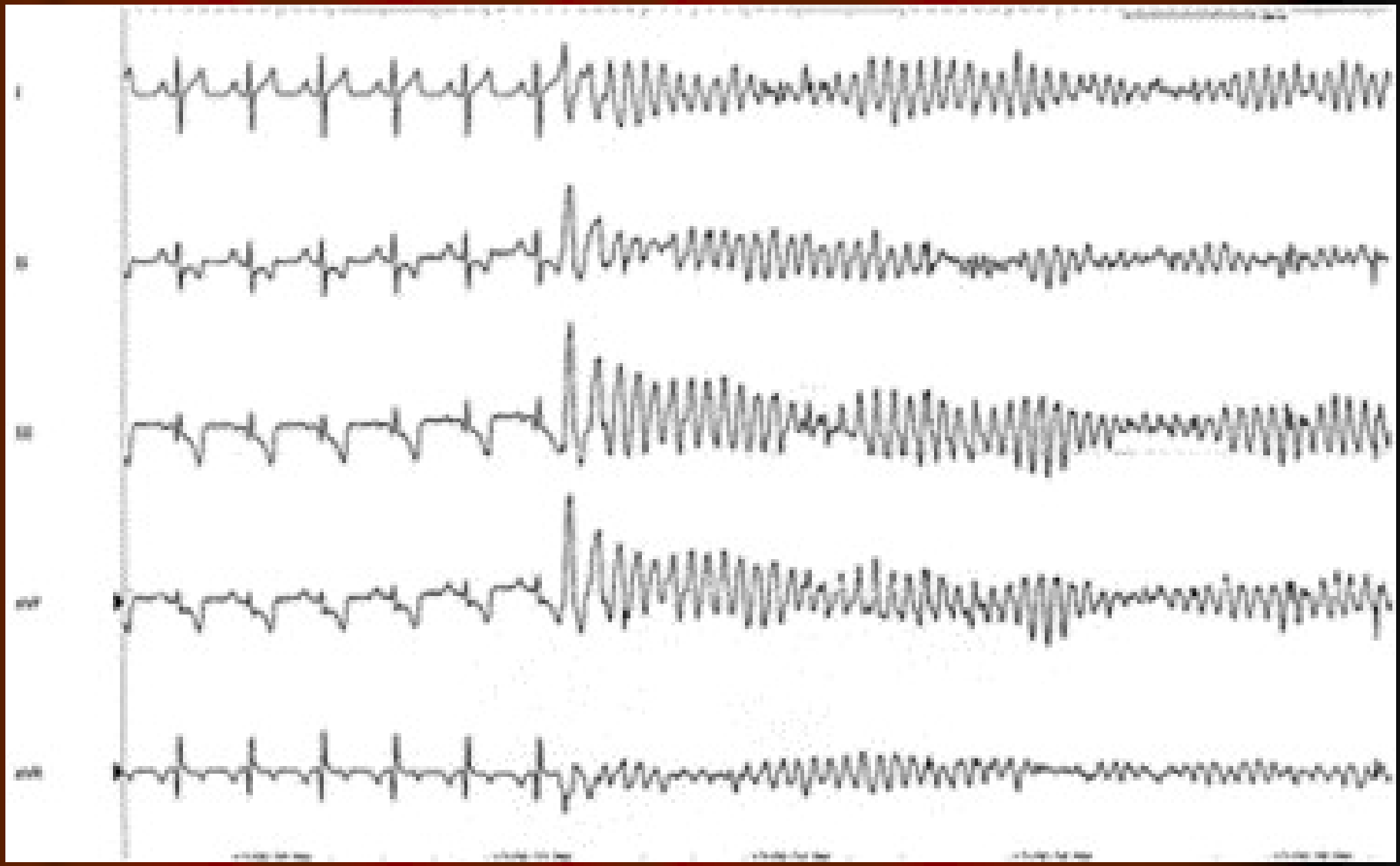
SCS Implantation





Issa et al Heart Rhythm. 2005 ; 2:979-983.

POLYMORPHIC VENTRICULAR TACHYCARDIA-FIBRILLATION

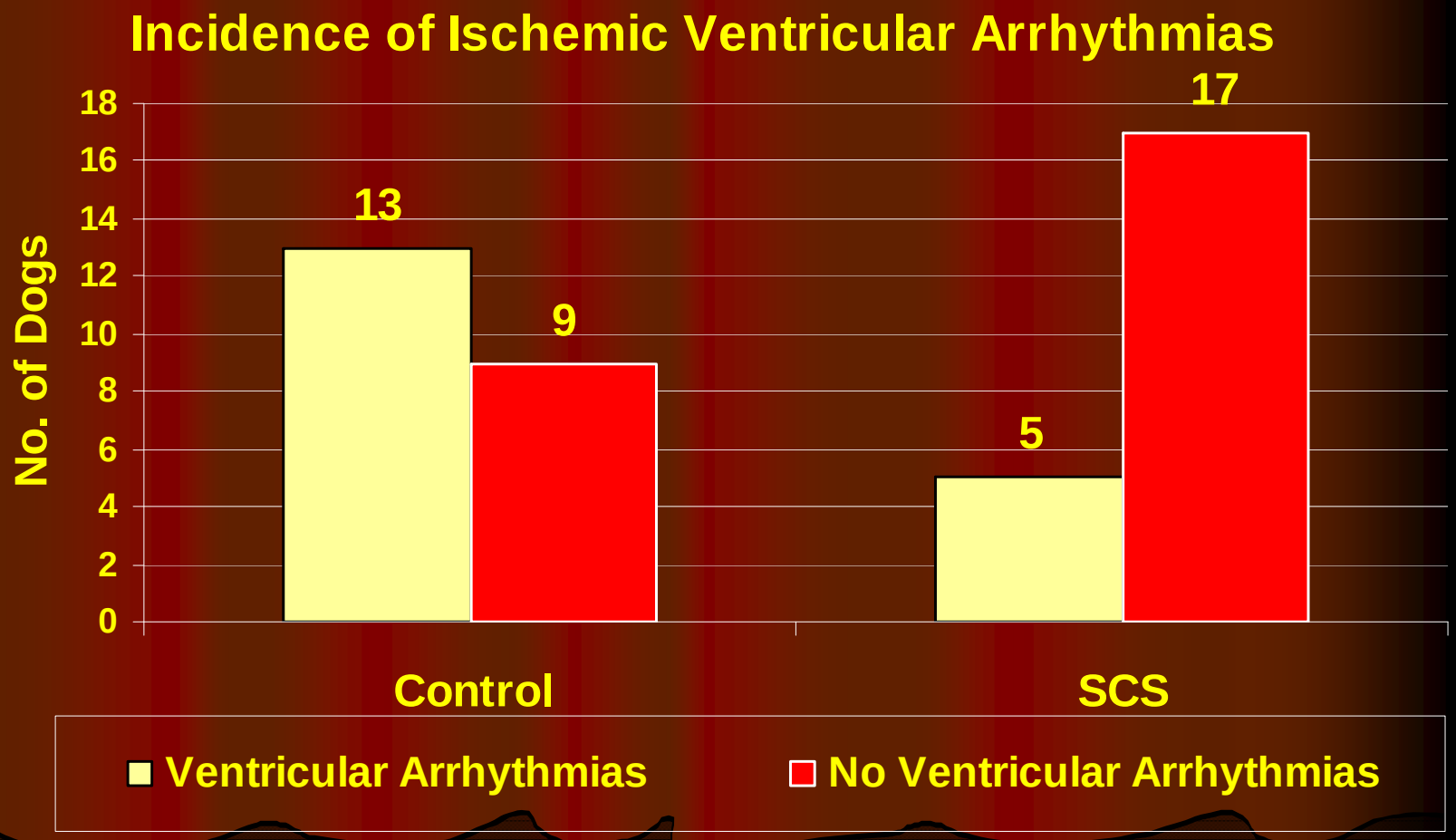


Issa et al Heart Rhythm. 2005 ; 2:979-983.

MONOMORPHIC VENTRICULAR TACHYCARDIA

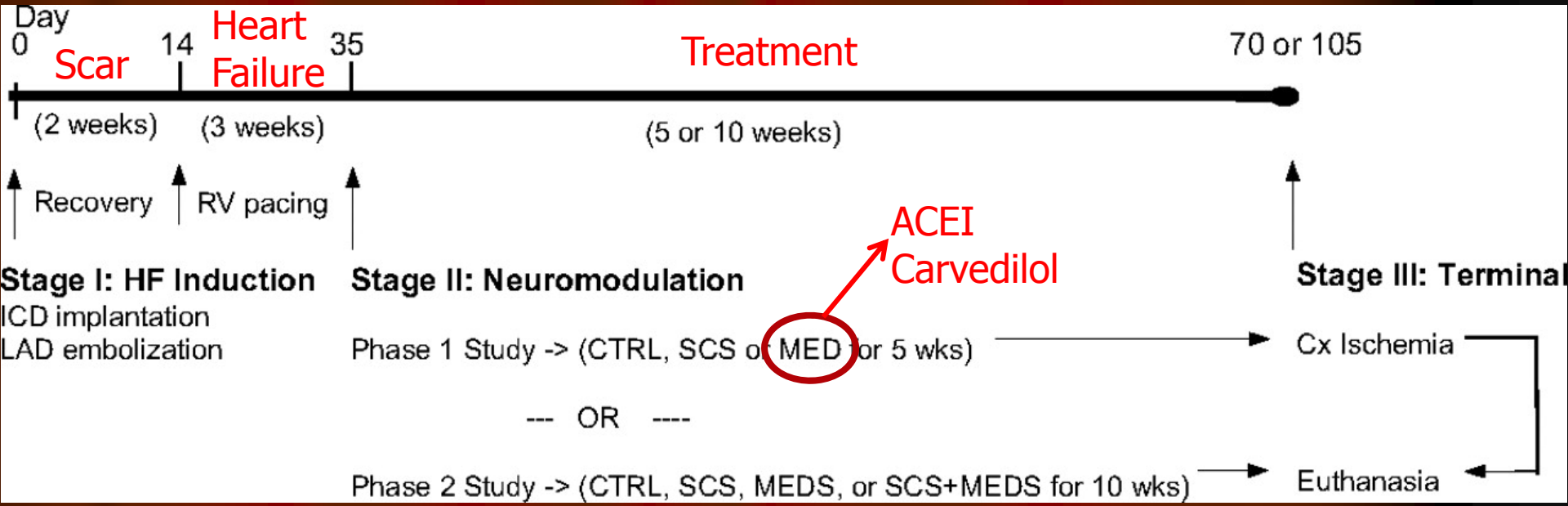
Issa et al Heart Rhythm. 2005 ; 2:979-983.

Results of Spinal Cord Stimulation



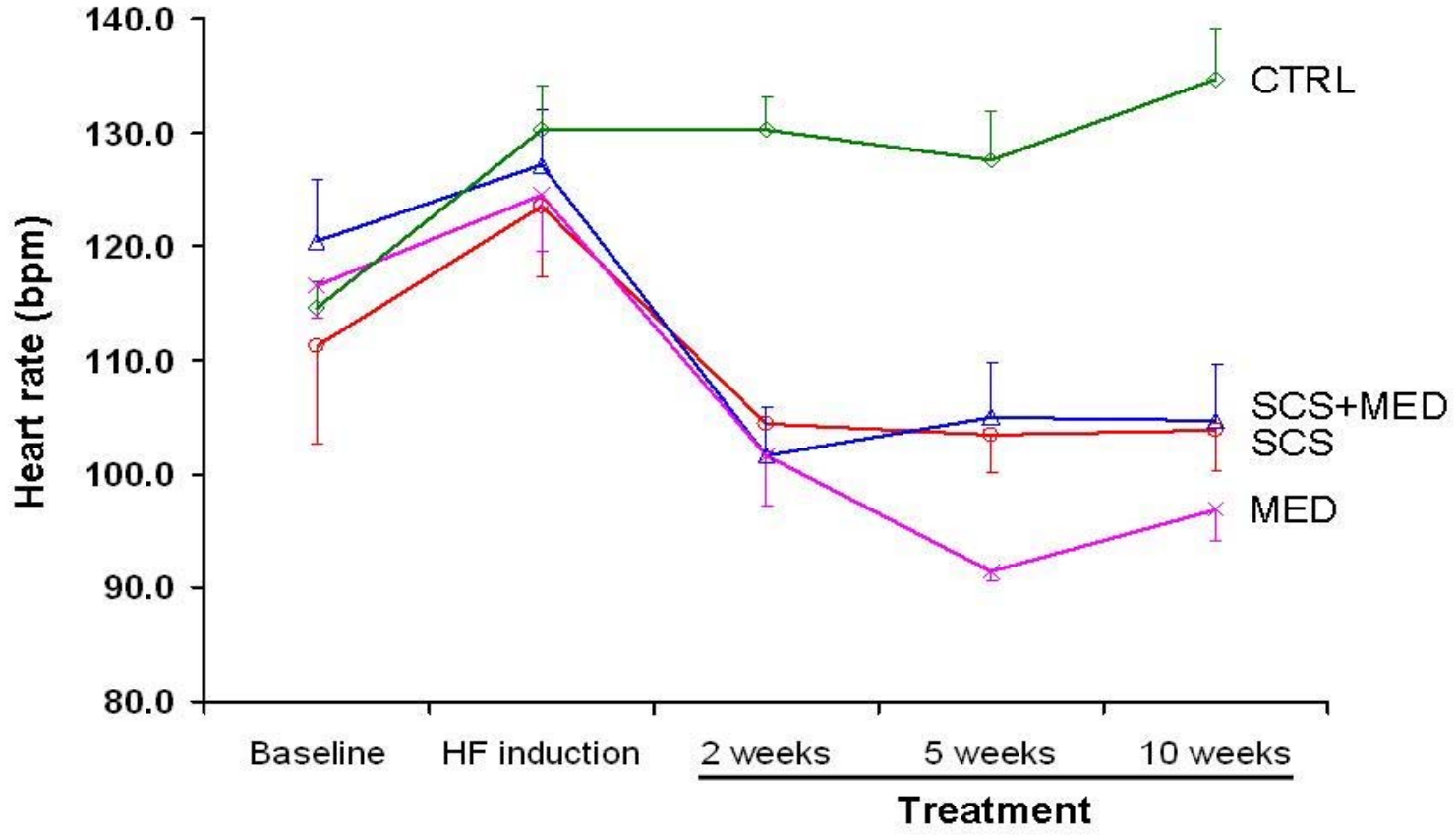
Issa et al Circulation 111:3217-3220, 2005

Research timeline and experimental design



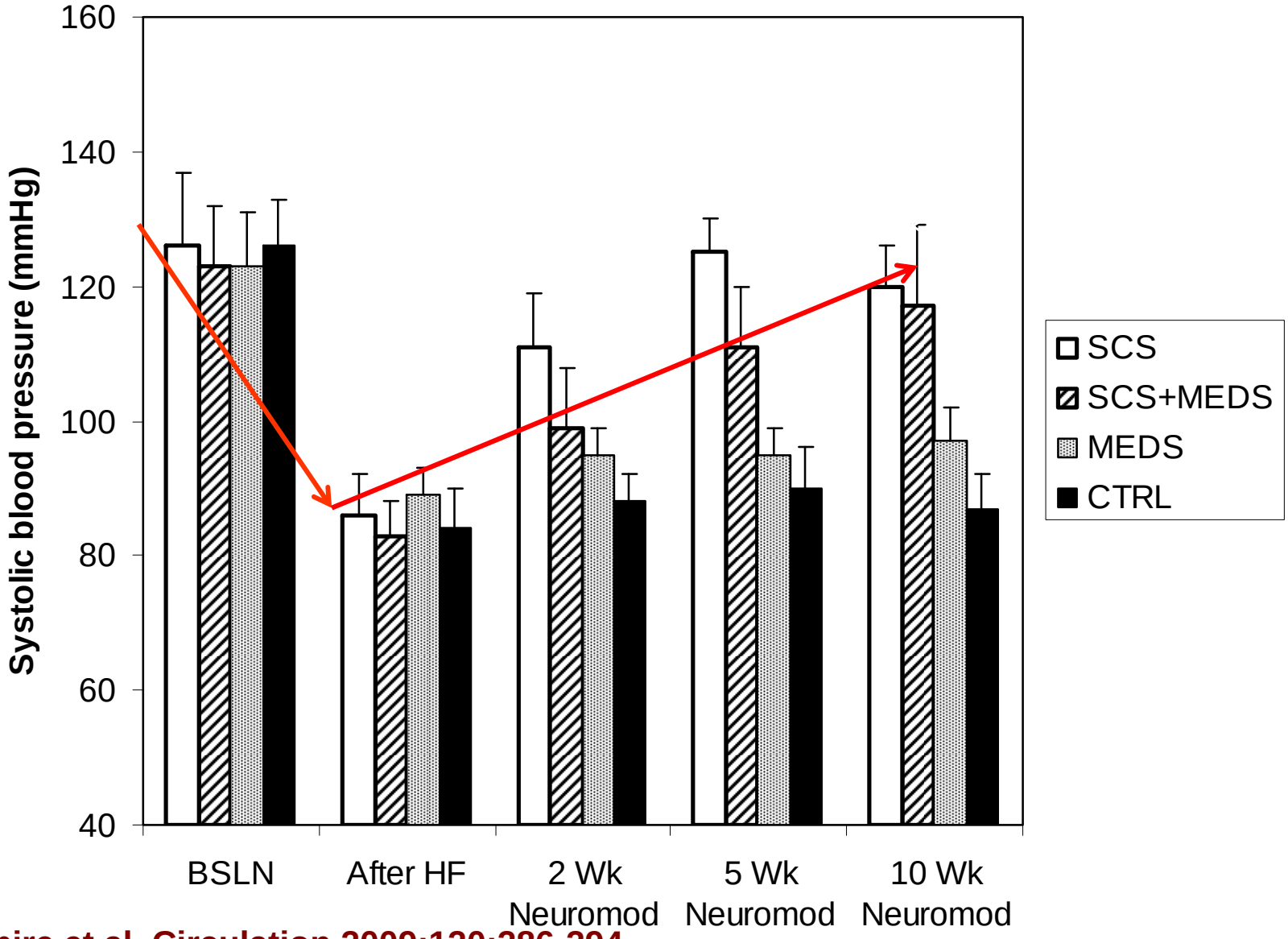
Lopshire et al. Circulation 2009;120:286-294

Stage 2: HR effects



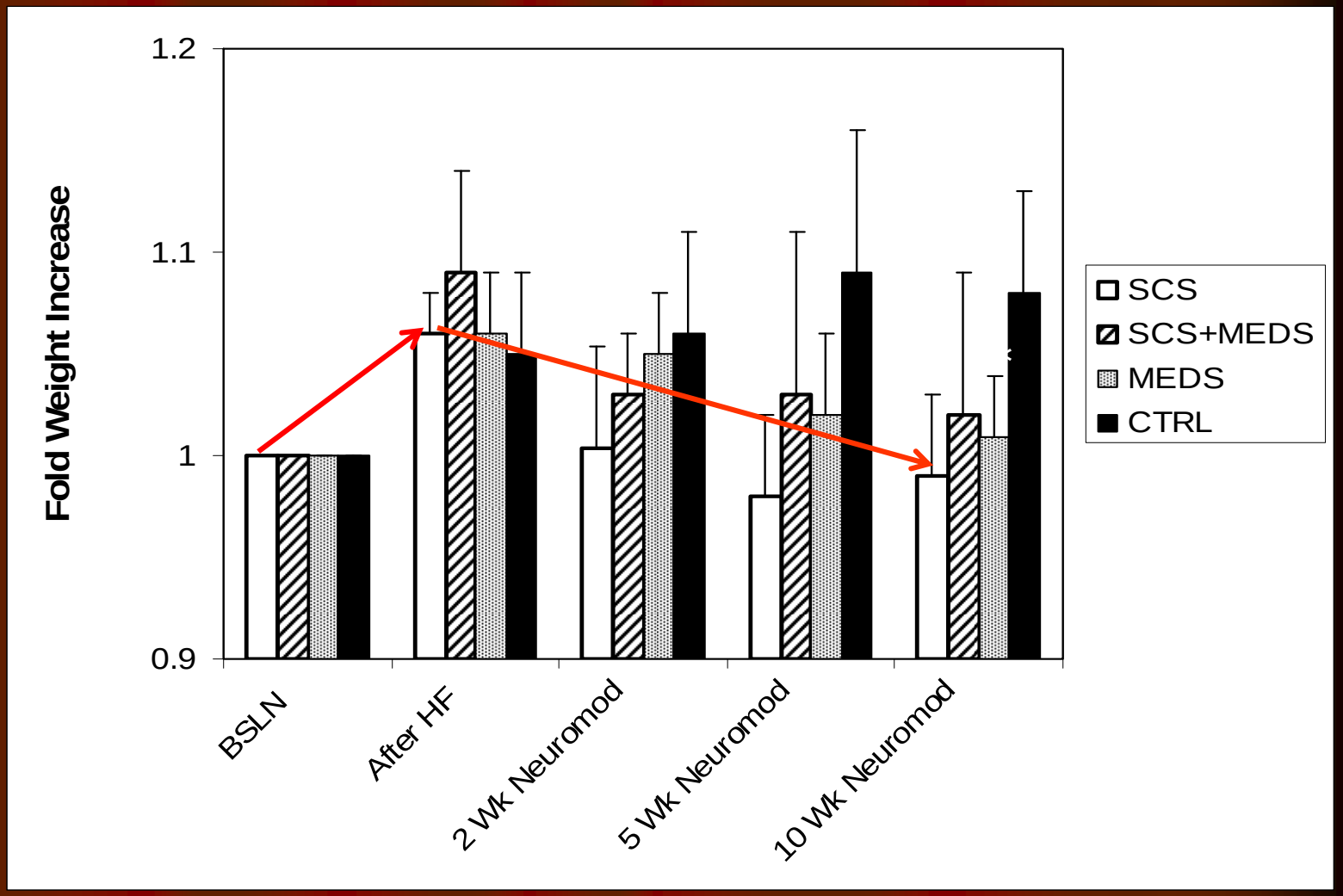
Lopshire et al. Circulation 2009;120:286-294

Stage 2: BP effects



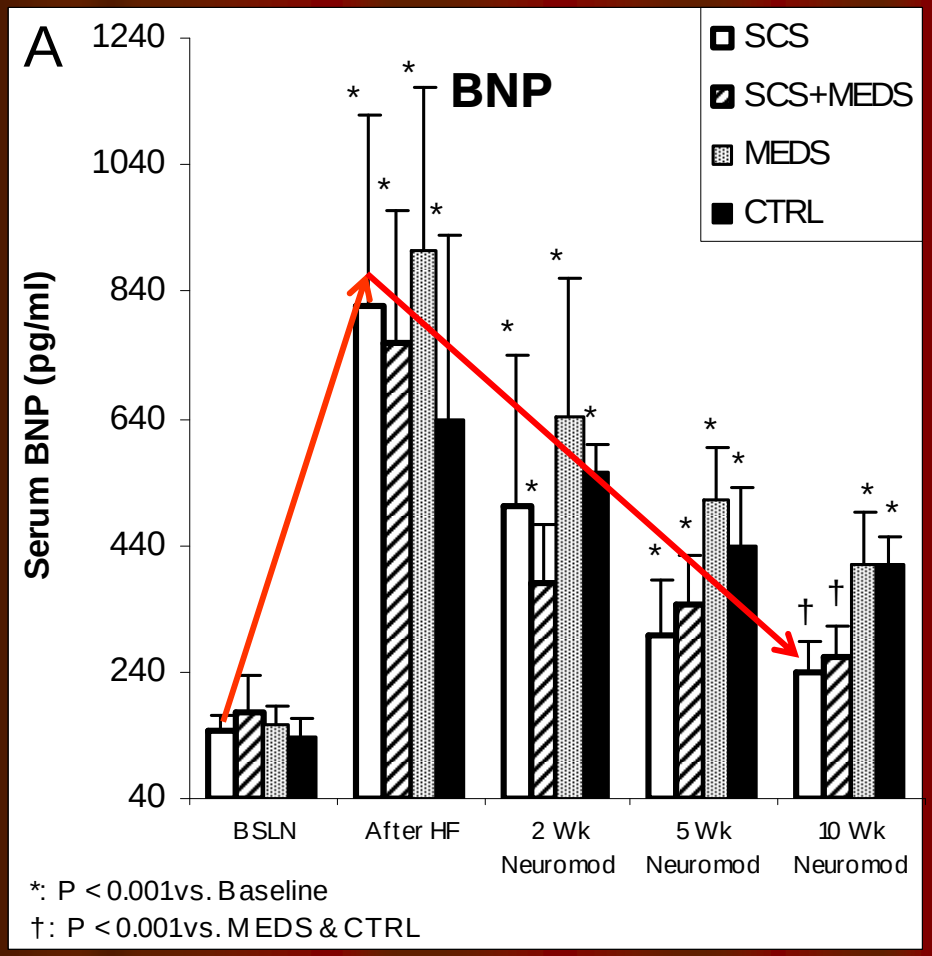
Lopshire et al. Circulation 2009;120:286-294

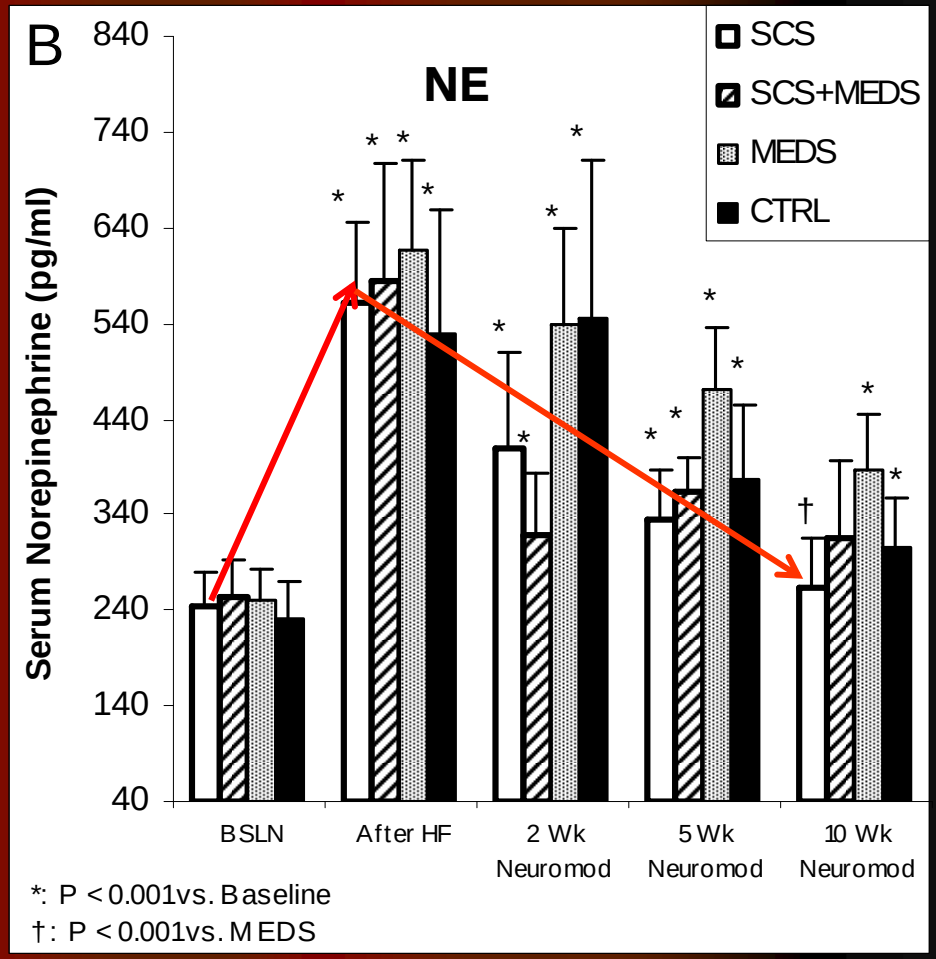
Stage 2: Body weight



Lopshire et al. Circulation 2009;120:286-294

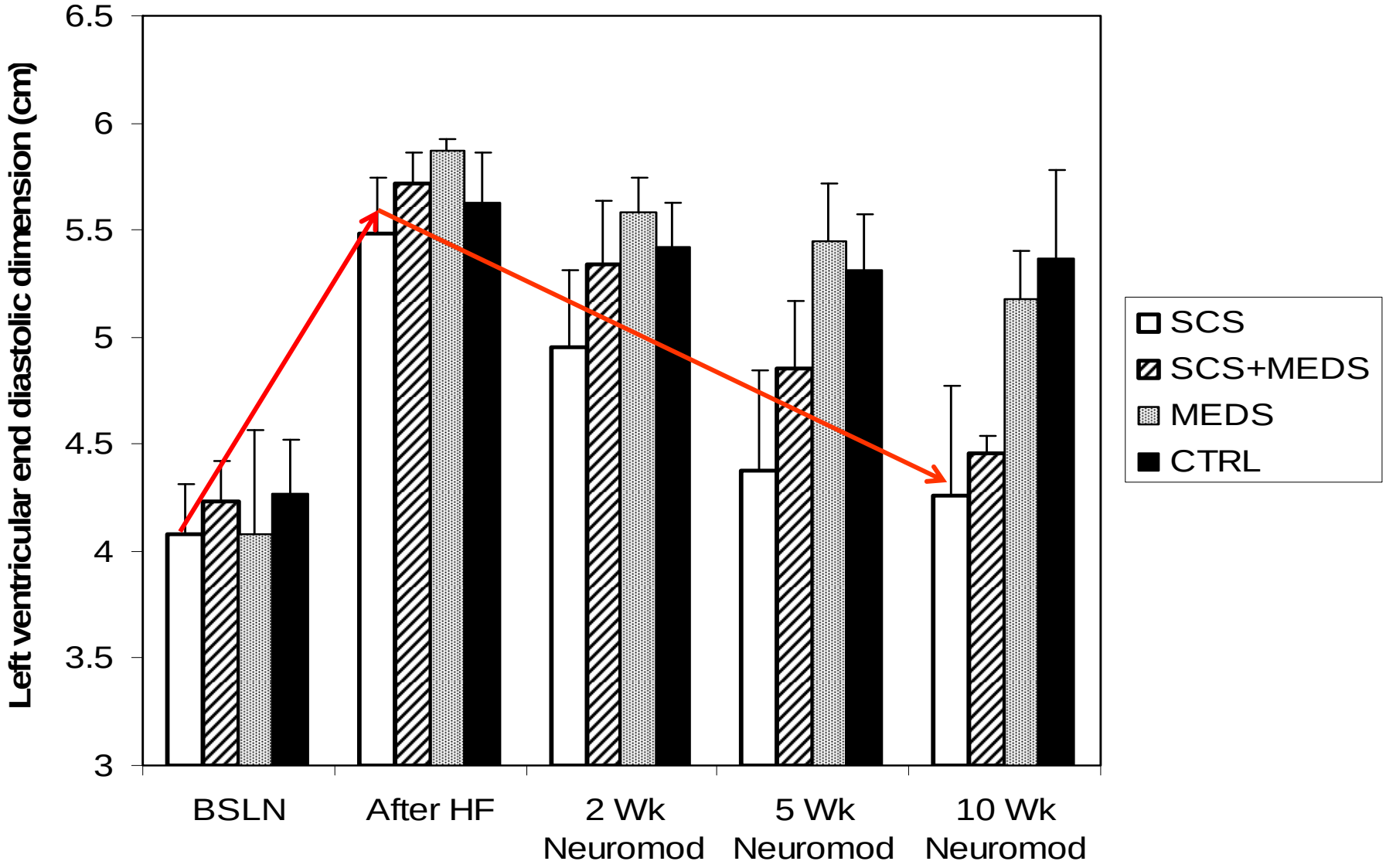
Serum markers and neuromodulation





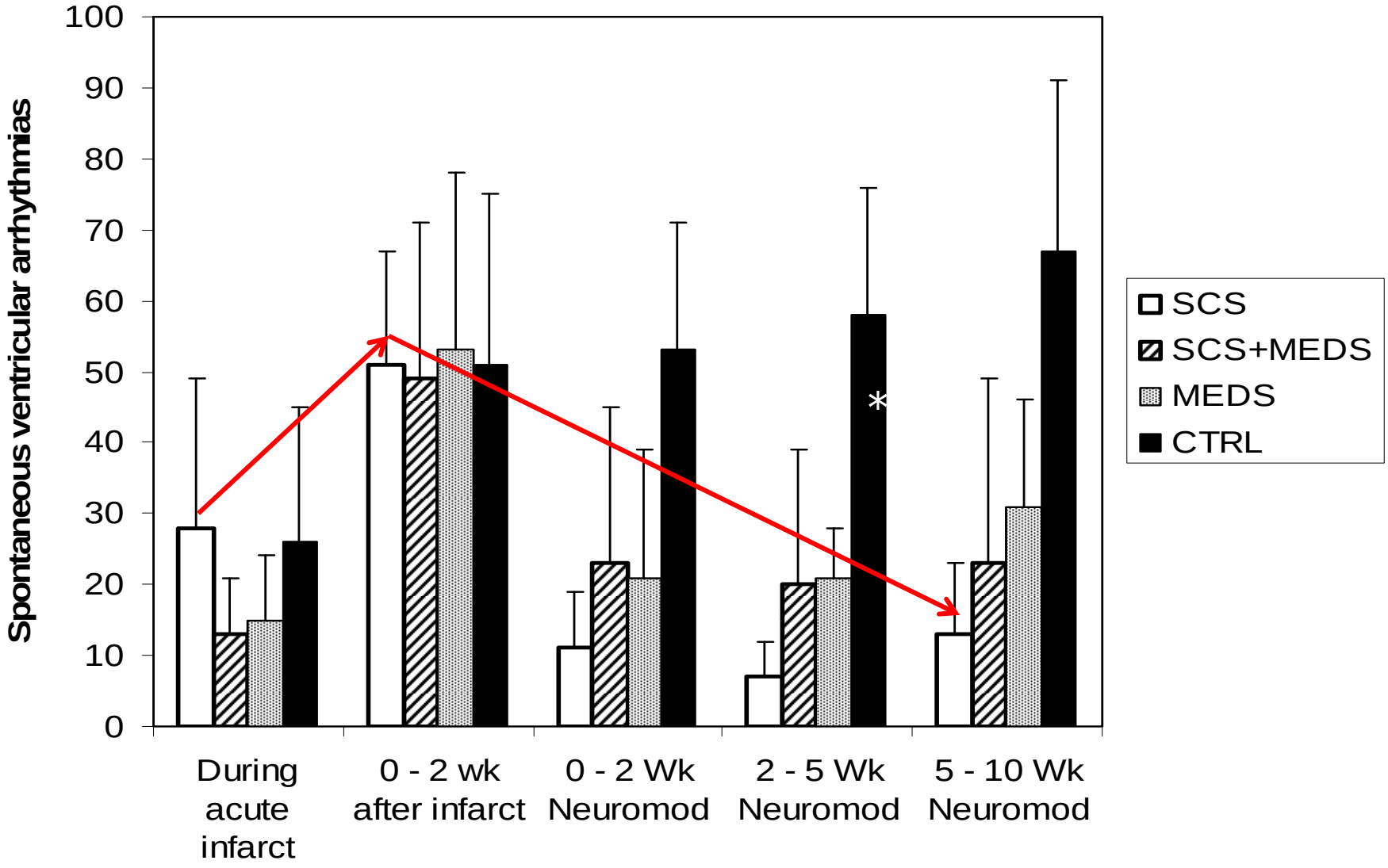
Lopshire et al. Circulation 2009;120:286-294

Neuromodulation in heart failure – LV dimension effects (LVEDD)



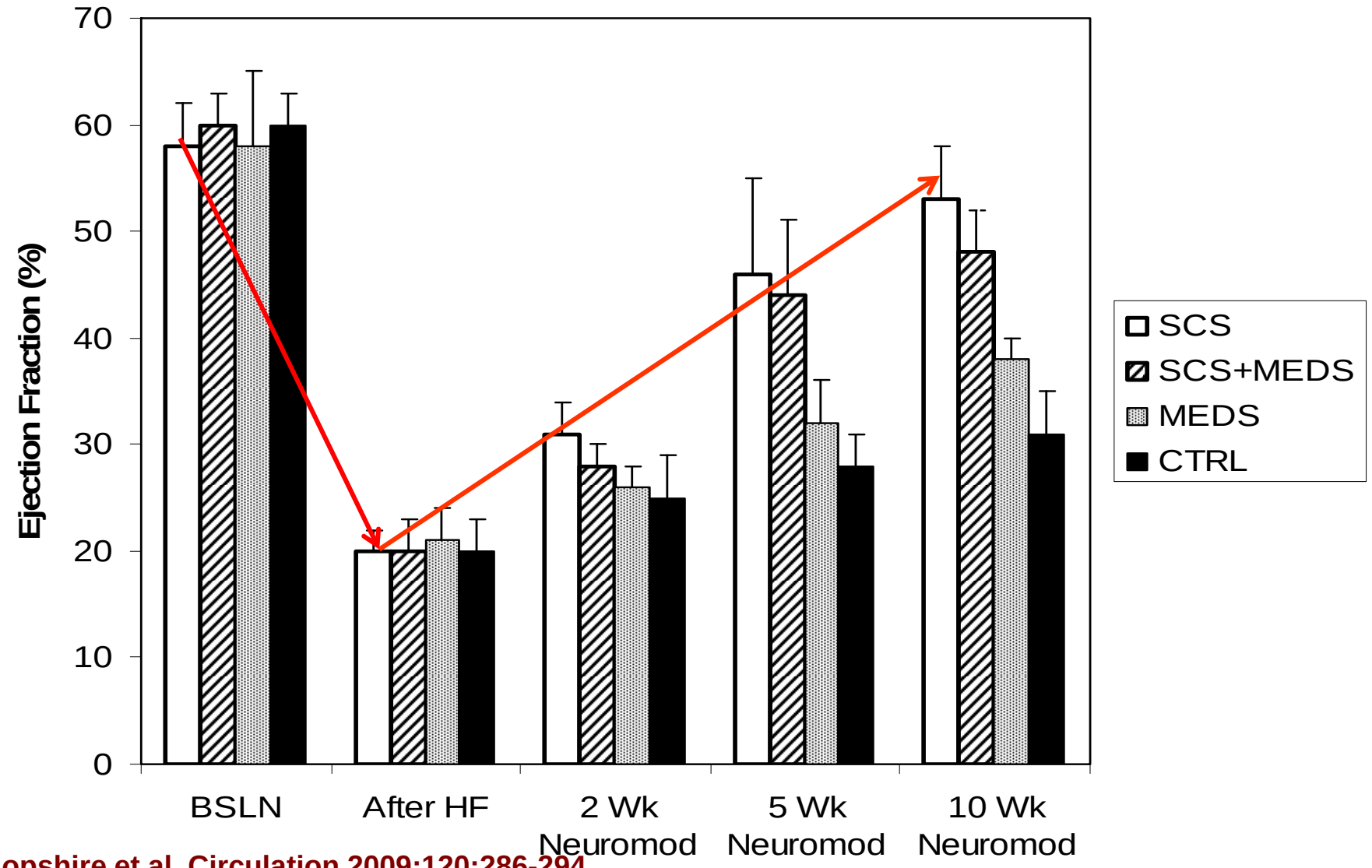
Lopshire et al. Circulation 2009;120:286-294

Neuromodulation in heart failure – Ventricular arrhythmias



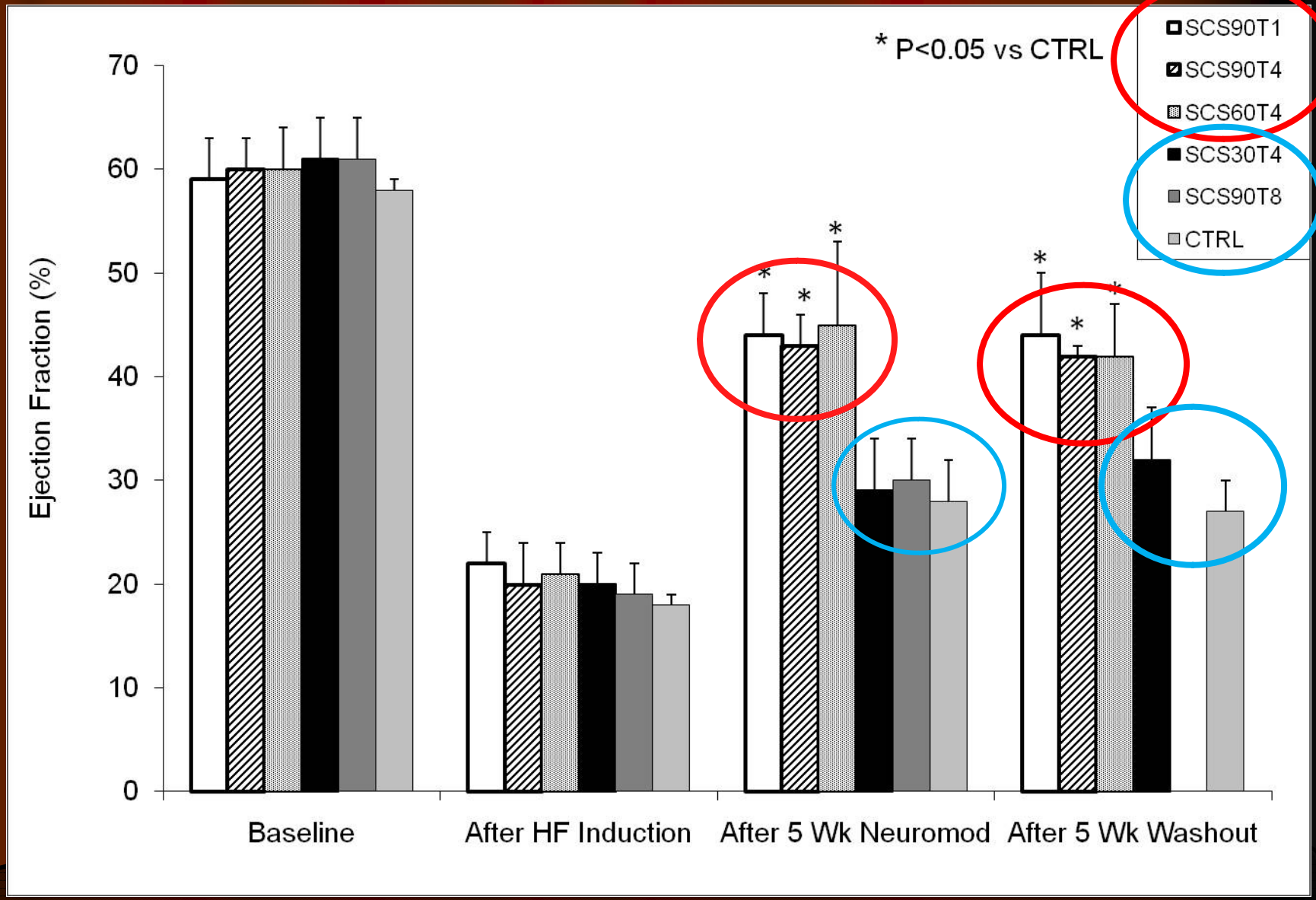
Lopshire et al. Circulation 2009;120:286-294

Stage 2: Ejection fraction



Lopshire et al. Circulation 2009;120:286-294

Ejection Fraction after SCS (Unpublished)



Lopshire et al Presented at HRS

CONCLUSIONS

- SCS T1-T4 significantly improved cardiac contractile function and decreased ventricular arrhythmias in a canine model of healed myocardial infarction and heart failure

Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure

DEFEAT-HF

H. Theres (Europe)
D. Zipes (US)
Principal Investigators

Spinal Cord Stimulation (SCS) for Heart Failure

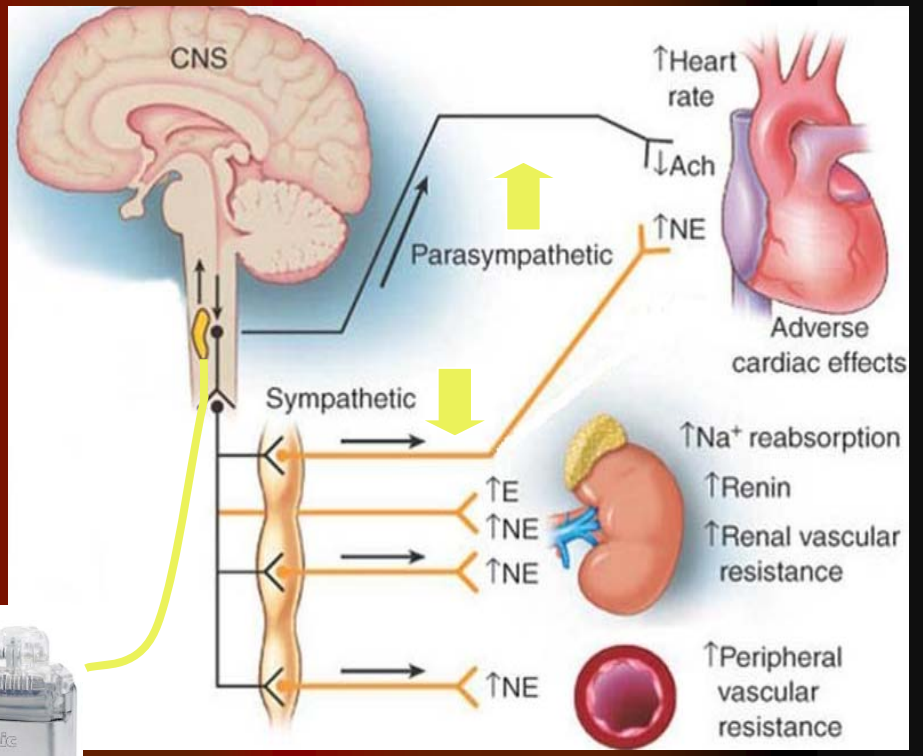
Sympathetic Inhibition
Parasympathetic Stimulation

Application

- Spinal Cord Stimulation applied at level of the heart
- No new technology needed

Evidence

- Hypothesis: SCS reduces cardiac sympathetic drive
- Mixed pre-clinical HF results:
  - Strong results in post-infarct high rate pacing HF model
  - Modest results in micro-embolism HF model

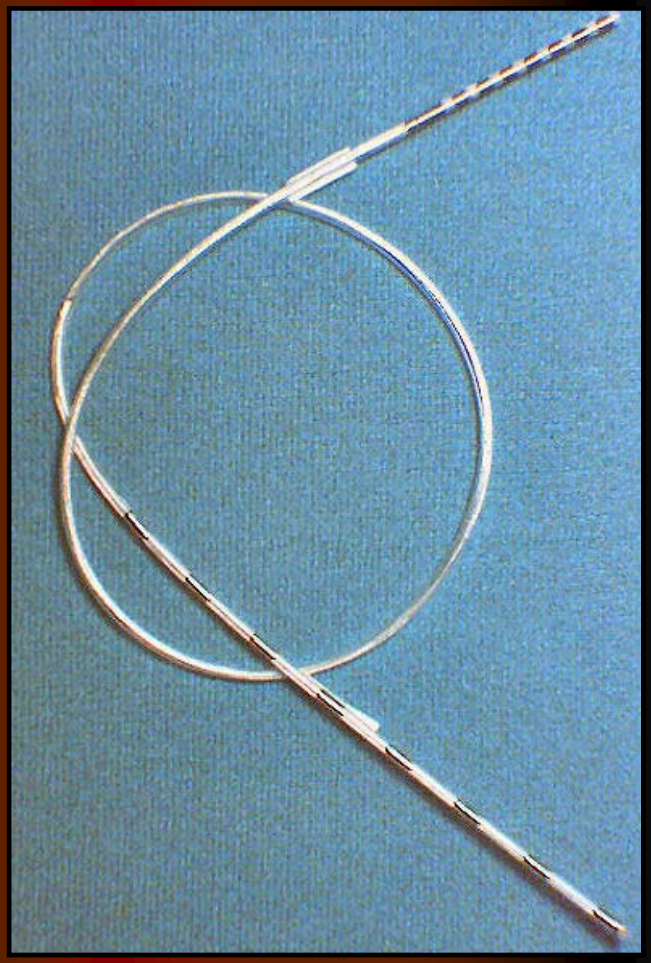


From Mann, "Pathophysiology of Heart Failure" in Braunwald's Heart Disease, p543

Autonomic modulation to normalize neural control of the heart and cardiovascular system

PrimeADVANCED™ SCS Implant

Model 37702 PrimeADVANCED™ INS



Model 3777 Octad Percutaneous Lead
Model 37081 Lead Extension

Study Purpose

Determine feasibility of spinal cord stimulation (SCS) as a chronic therapy for heart failure (HF)

- Single percutaneous lead
- Target: T2-T4 level of the spinal cord

Study Objectives

Primary objective:

- To evaluate the reduction in left ventricular end systolic volume index (LVESVi) after 6 months of SCS therapy in the Treatment arm compared to the Control arm

Secondary objectives:

- To characterize the change in peak oxygen uptake between the Treatment arm and Control arm
- To characterize the change in proBNP between the Treatment arm and Control arm

Additional Analyses:

- Change in QOL
- Adverse Events
- Frequency of hospitalizations for HF or CV events
- Changes in NYHA functional class
- Holter data analysis

Key Inclusion Criteria

- LVEF of 35% or less
- NYHA functional Class III at the time of screening
- QRS duration less than 120 ms
- LVEDD of 55 mm – 80 mm
- Stable medical therapy for HF prior to enrollment*
- Serum creatinine ≤3.0mg/dL
- 18 years or older

* *Stable medical therapy is defined as no increase or decrease greater than 50% for two weeks in diuretics, and no increase greater than 100% or decrease greater than 50% for one month in ACE and ARB and for three months in Beta Blockers*

Current Status

- 23 sites are actively recruiting patients: U.S., Europe, Canada
- Study goal = 70 successful implants to ensure 60 subjects reach 6 months of follow-up
- Recruitment on schedule and plan to finish in the next several months

Autonomic modulation trials using class III

Trial	Sponsor	Therapy
INOVATE-HF	BioControl	VNS
NECTAR-HF	BSX	VNS
SCS HEART	STJ	SCS
Neurostimulation of Spinal Nerves That Affect the Heart	The Methodist Hospital System – Dr. Torre	SCS

If successful, VNS directly or via spinal cord stimulation will reduce VAs and improve LV function, providing a significant advance in treating patients with heart failure.

In summary, many mysteries about sudden death remain to be written and explained.

THANK YOU FOR YOUR ATTENTION