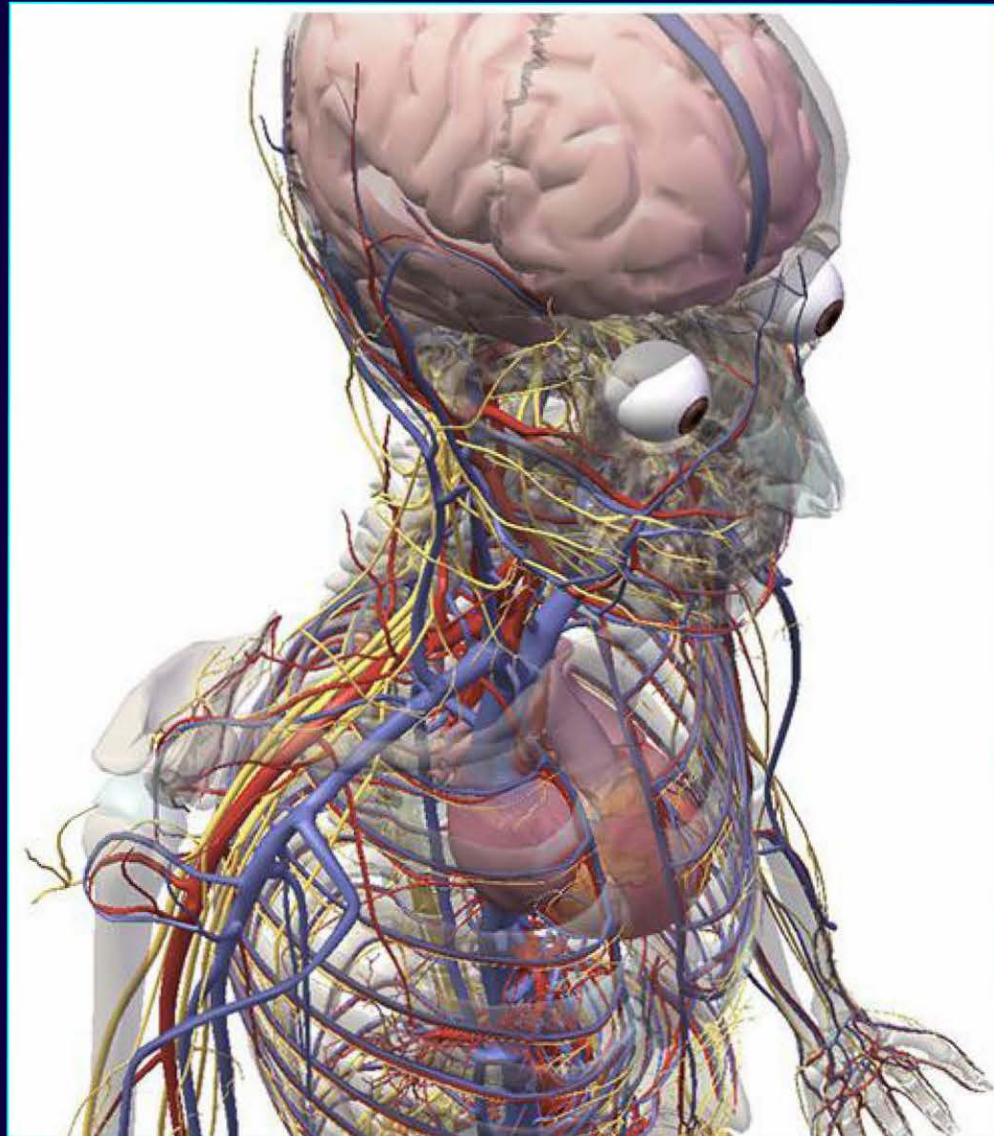


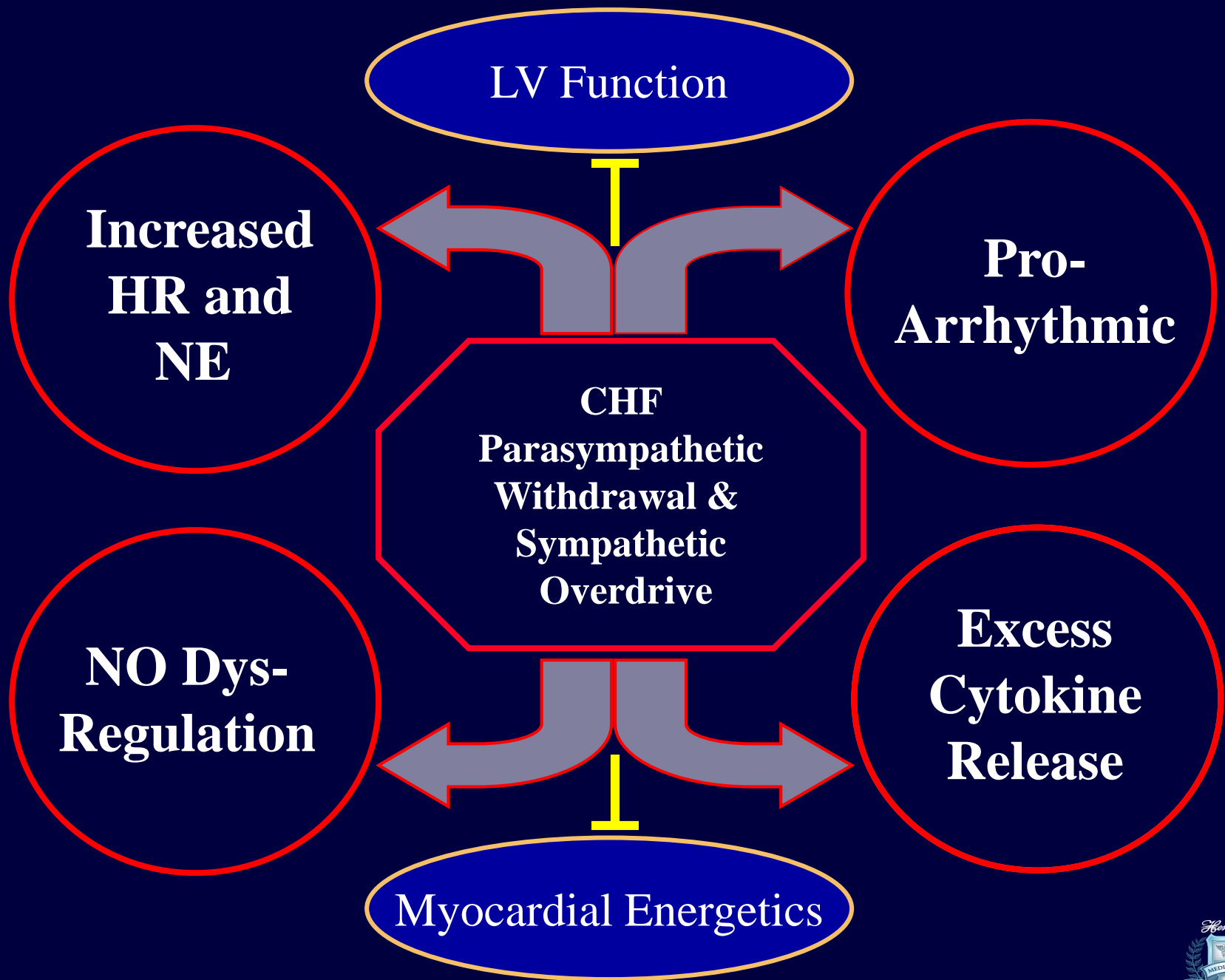
Modulation of Cardiac Efferent Signaling: A New Strategy for Heart Failure Therapy? *Technology Response: Heart Failure*

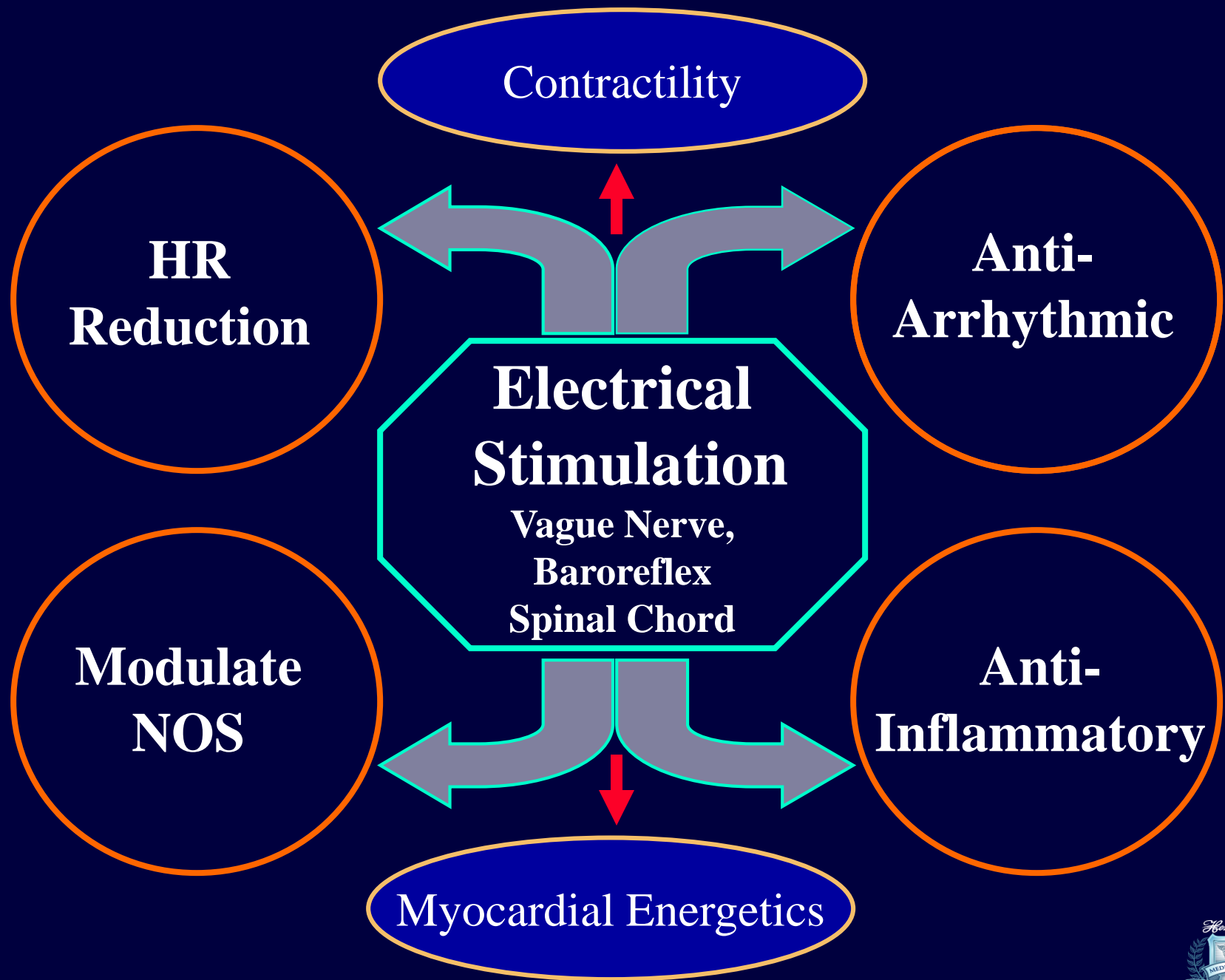
Hani N. Sabah, Ph.D., FACC, FCCP, FHRS
Professor of Medicine, Wayne State University
Director of Cardiovascular Research
Henry Ford Health System



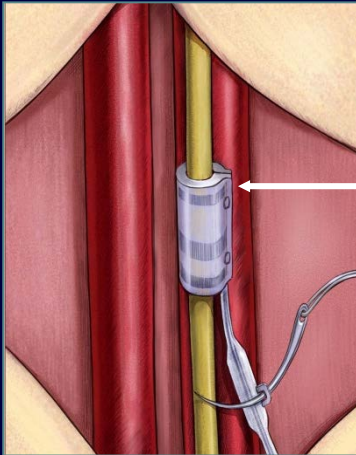
Neuromodulation for Treatment of Heart Failure





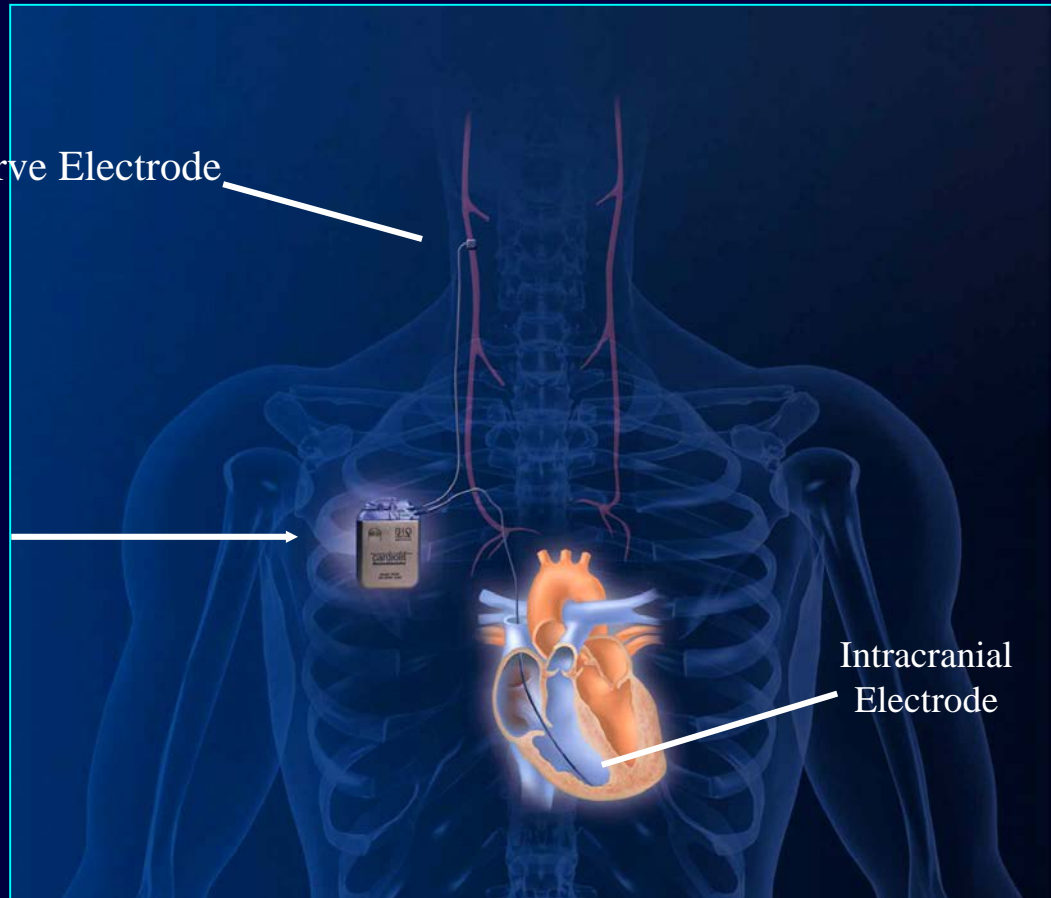


Vagus Nerve Stimulation



Vagus Nerve Electrode

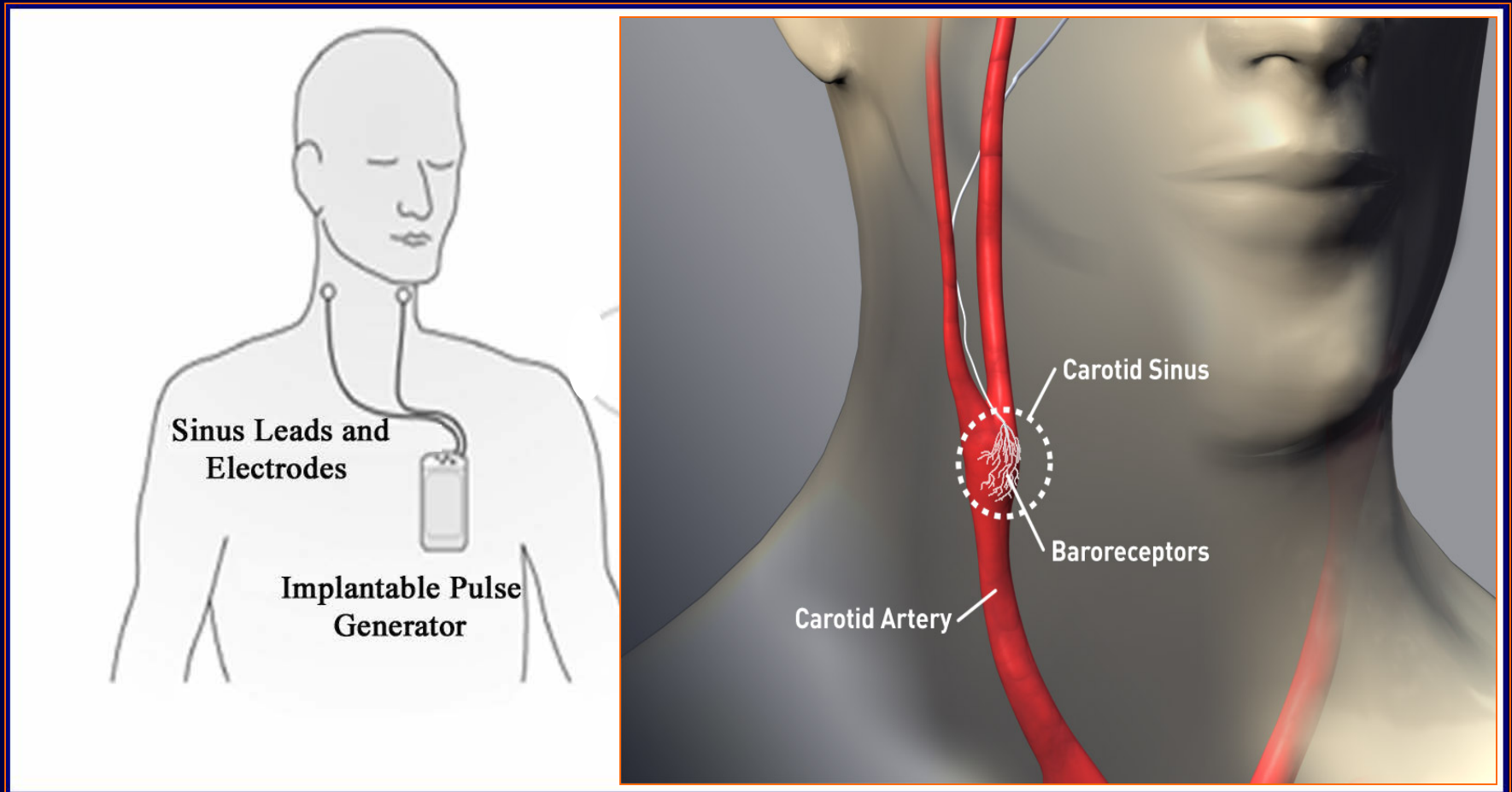
Stimulator



Intracranial
Electrode

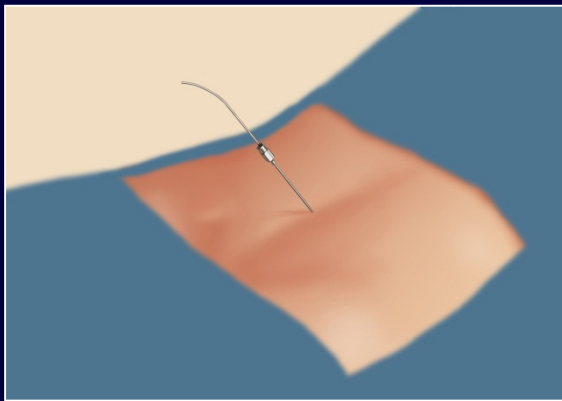
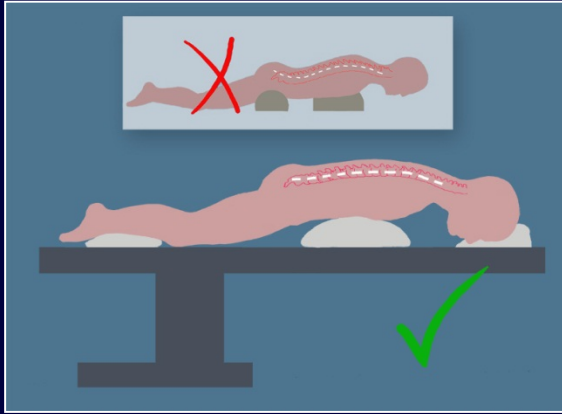
RheosTM

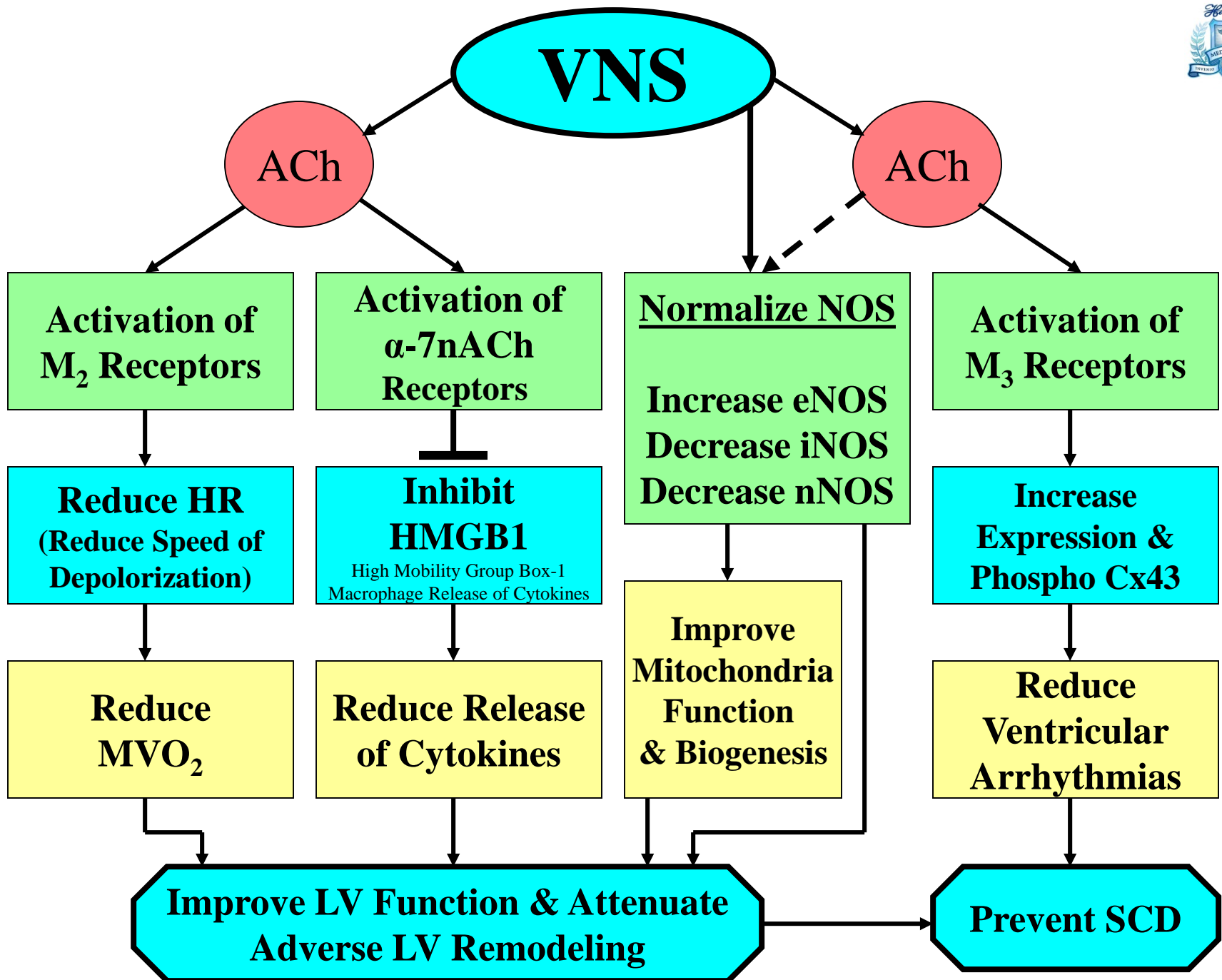
Electrical Activation Carotid Baroreflex System

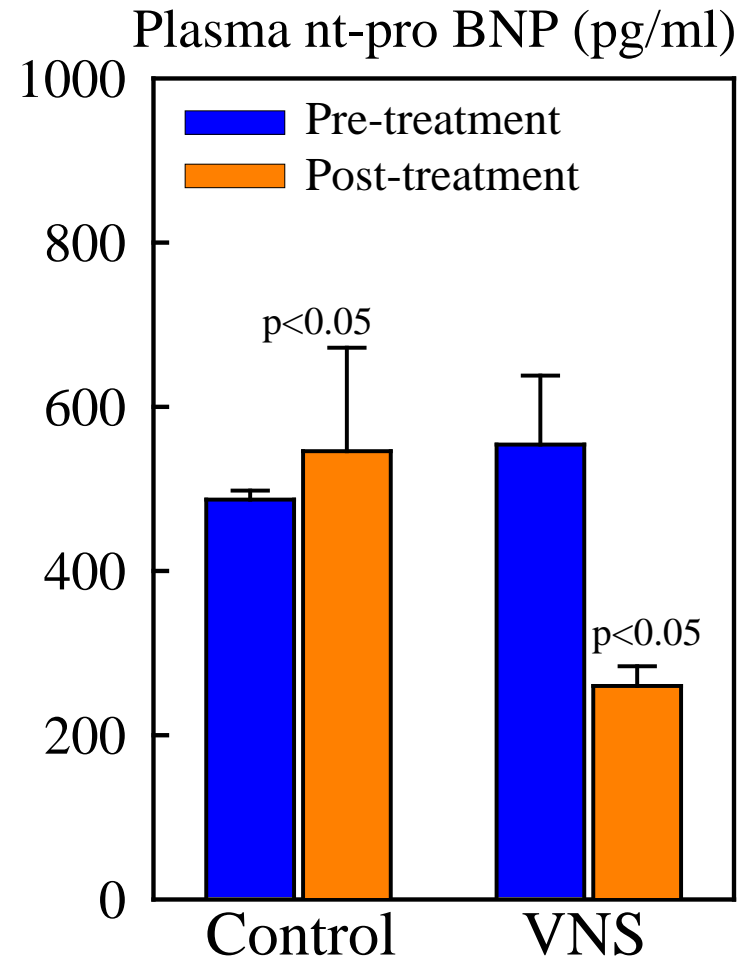
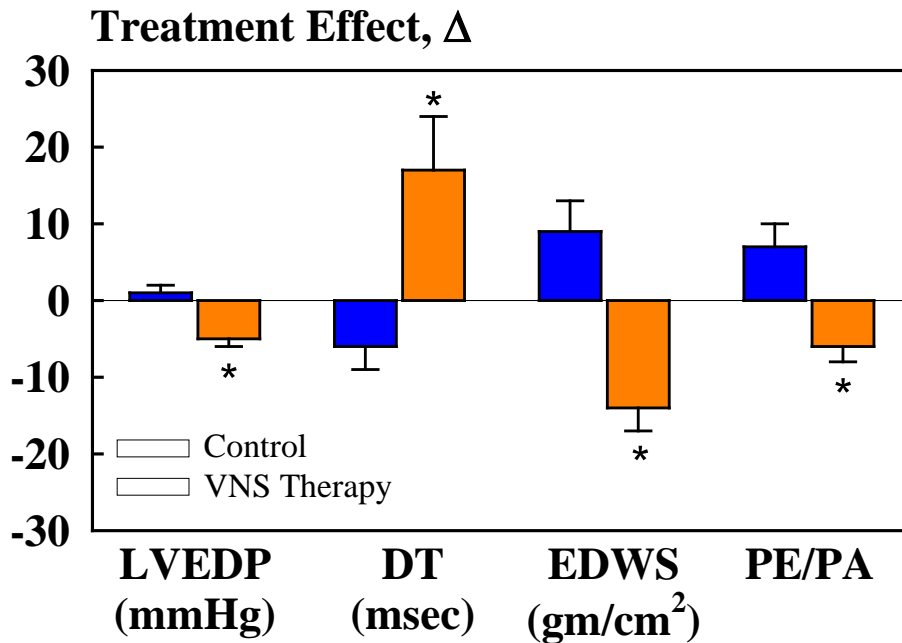
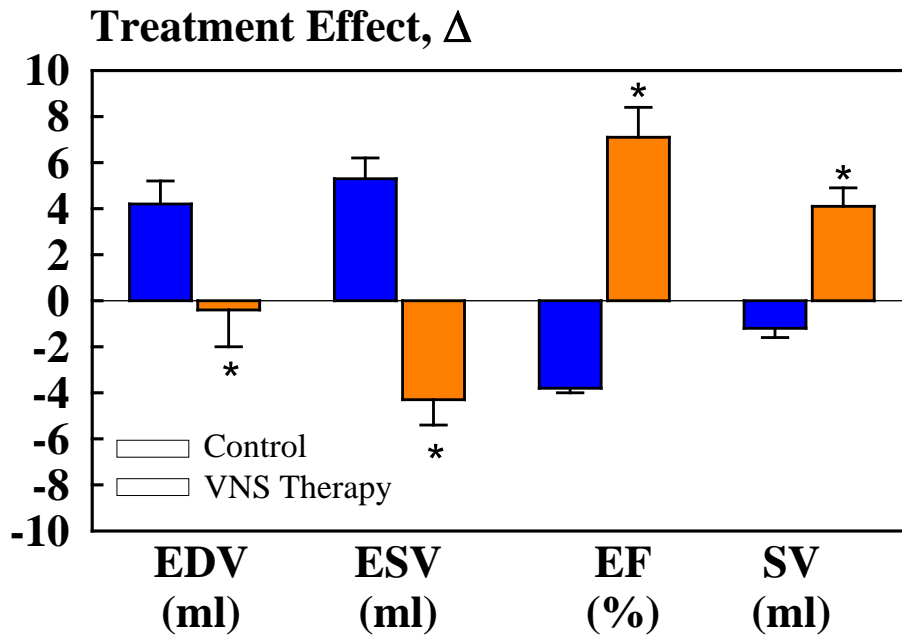


Spinal Cord Stimulation

Implantation in Epidural Space

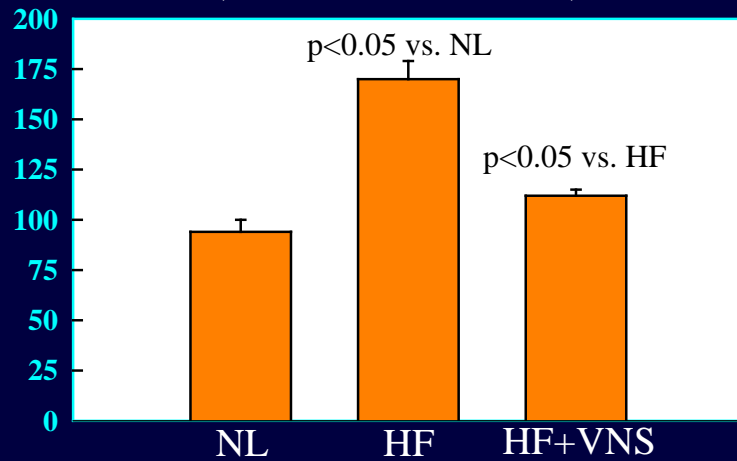






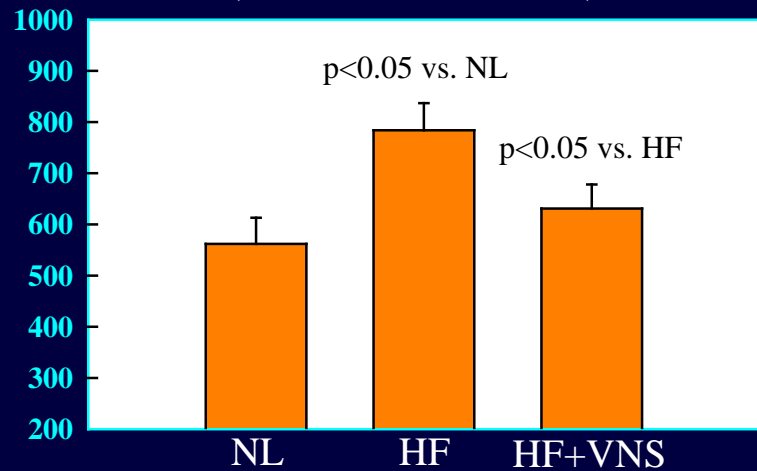
Protein Expression of TNF α

(densitometric units)

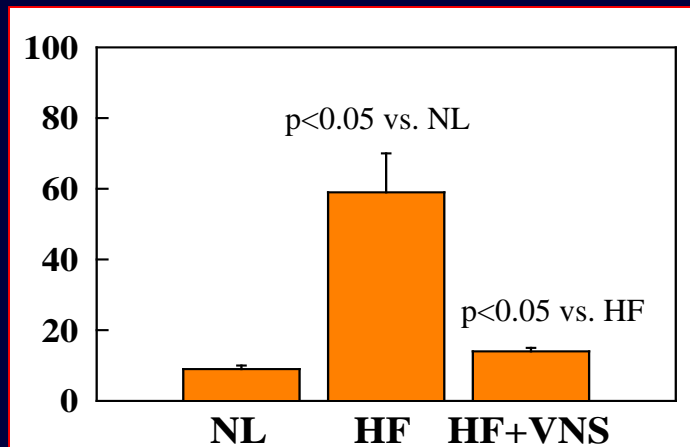


Protein Expression of IL-6

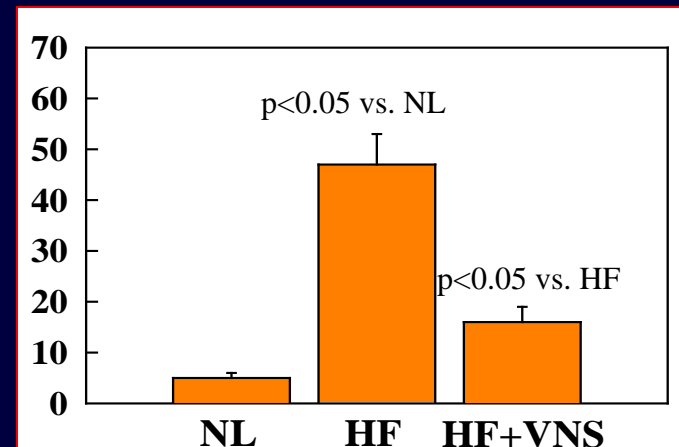
(densitometric units)



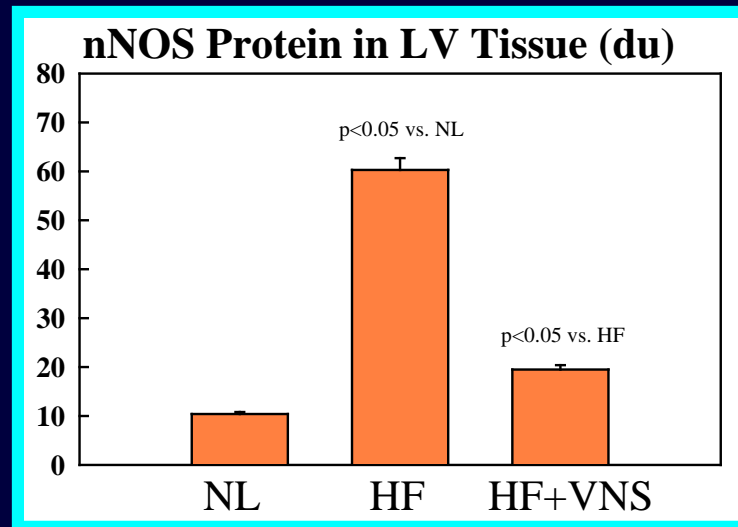
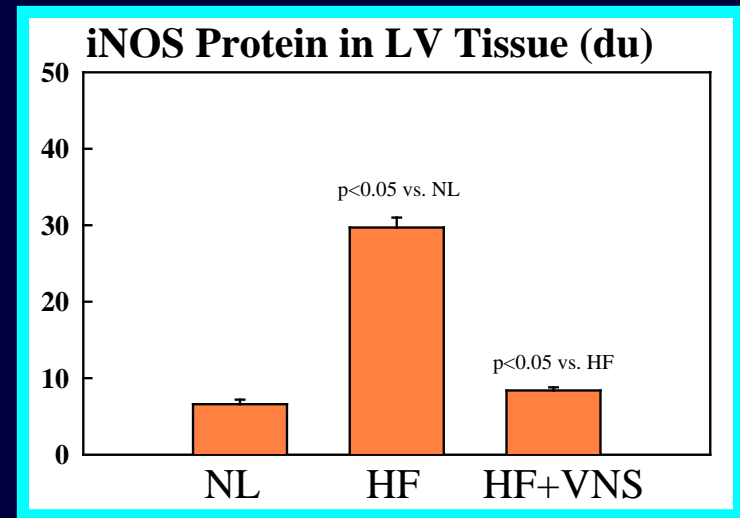
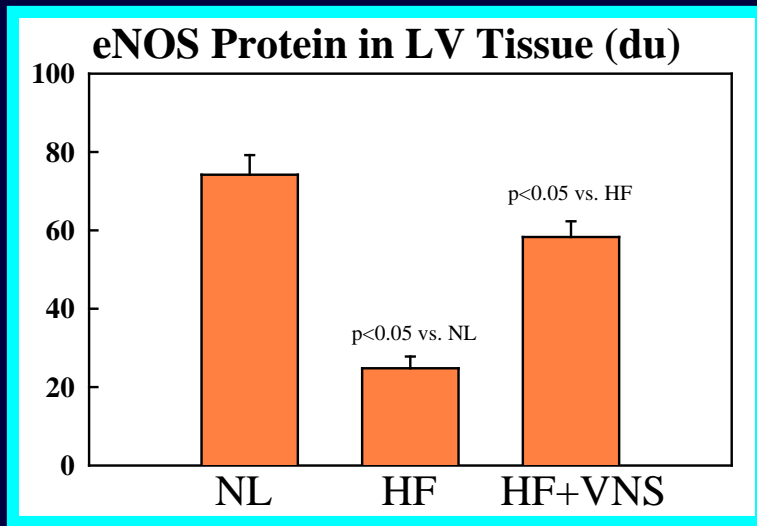
TNF α Plasma Levels (pg/ml)



IL-6 Plasma Levels (pg/ml)



Expression of Nitric Oxide Synthases in LV Tissue



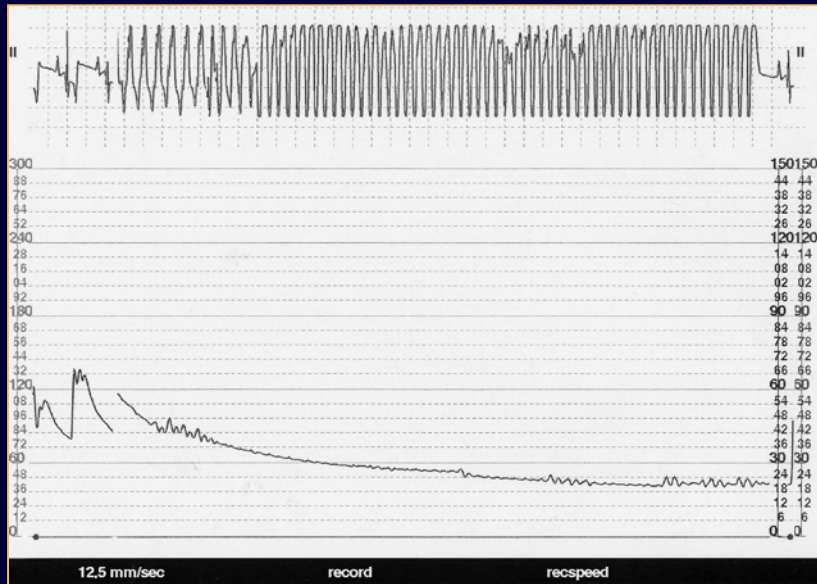
Δ LV Systolic Indexes Treatment Effect



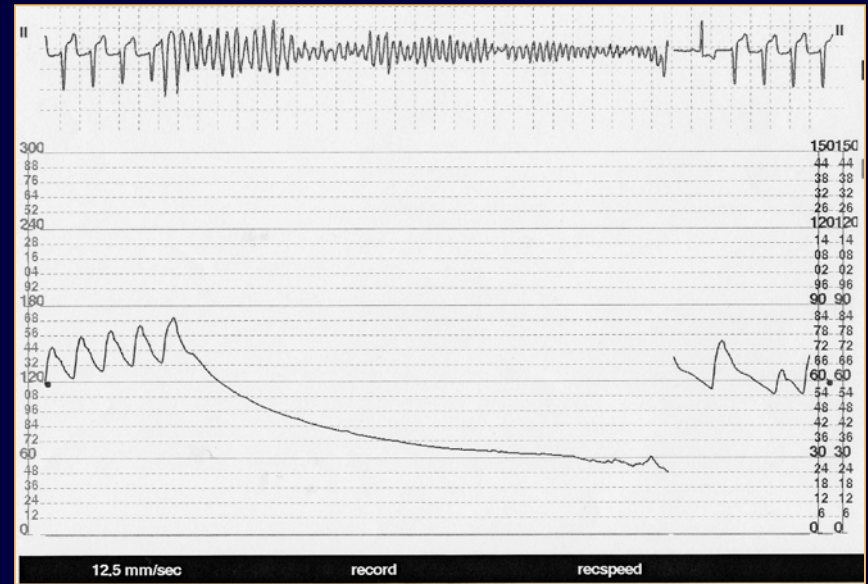
Sabbah et al, Circulation Heart Failure, 2011



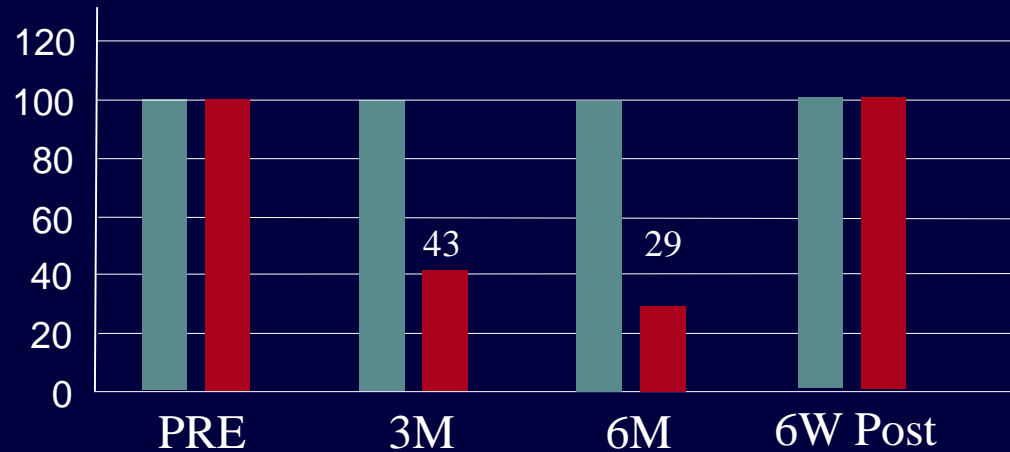
Control



BAT-Treated



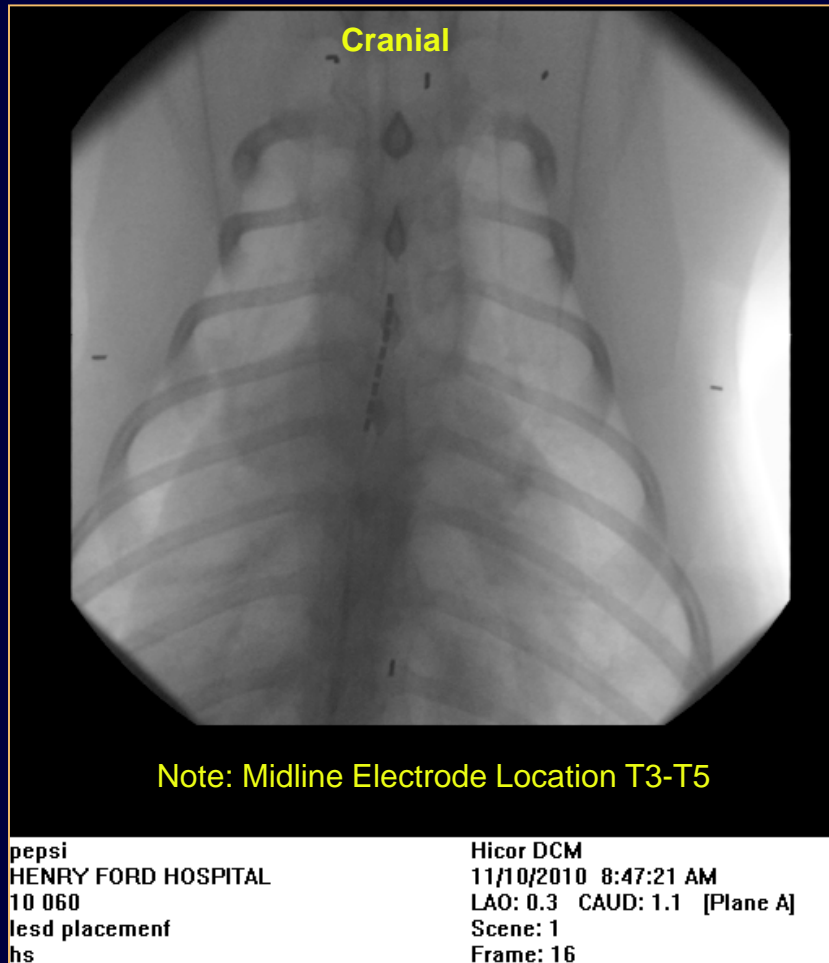
Percent of Dogs Induced into VT or VF



Control (n = 7)
BAT (n = 7)

Wang...Sabbah et al, Circulation 2008

Fluoroscopic Image of Implant in Epidural Space



- Single, Linear ST 50cm 8 Contact Lead
- Epidural Access: L2/L3 or L3/L4
- Lead Placement: T3-T5
- Stimulation: Bipolar
- Frequency: 50 Hz
- Pulse Width: 200 μ s
- Amplitude: Set to 90% Motor Threshold
(0.2 to 1.9 mA)

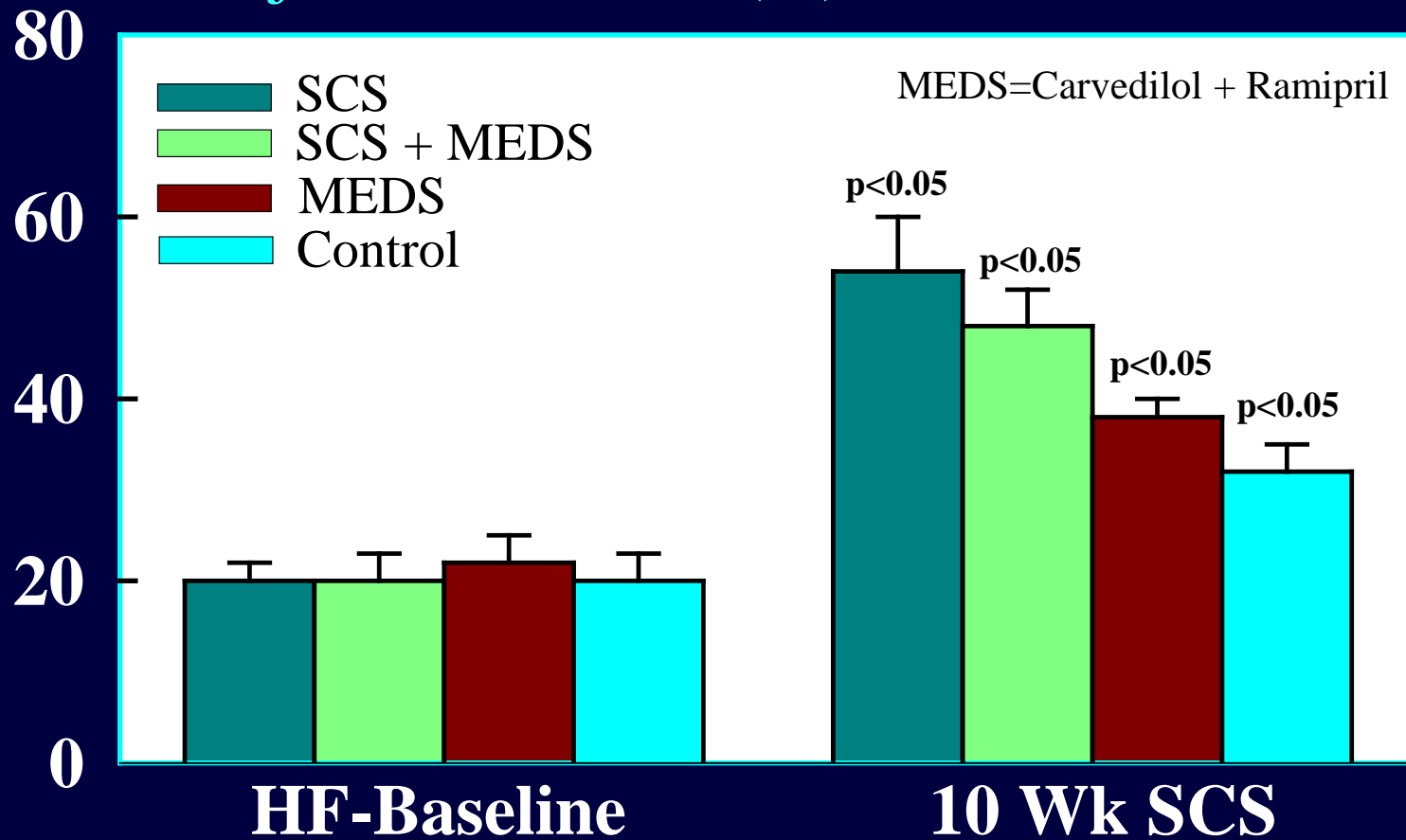
Electrodes 1 and 3: Cathodes, 50%

Electrodes 6 and 8: Anodes, 50%



SCS in Dogs with Post AMI Heart Failure

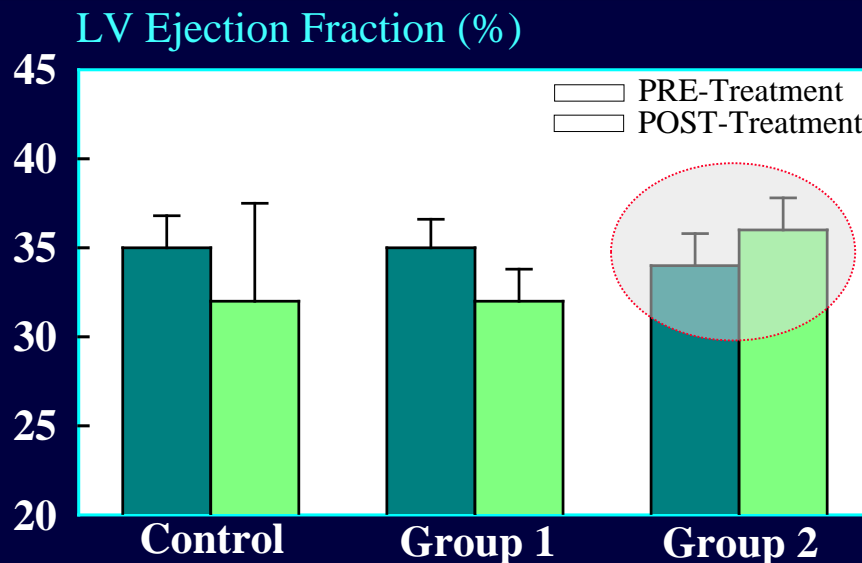
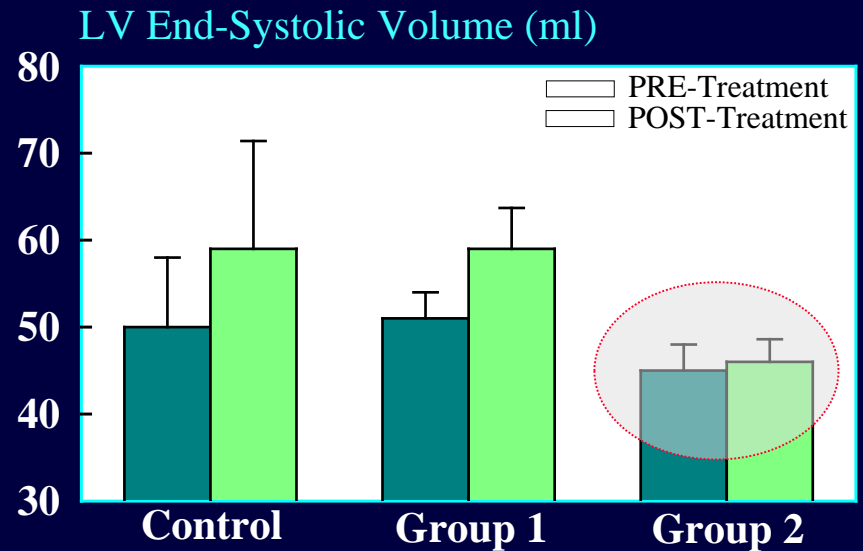
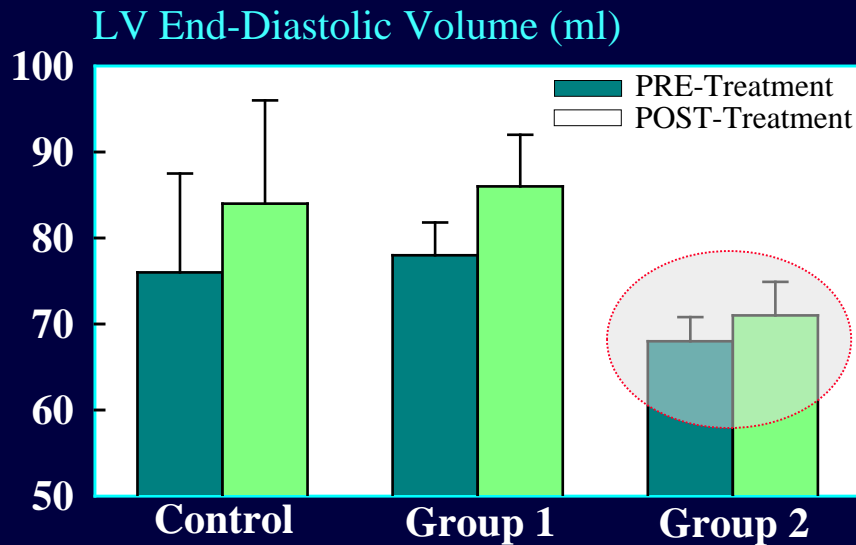
LV Ejection Fraction (%)



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



Pilot SCS Study in Dogs with HF

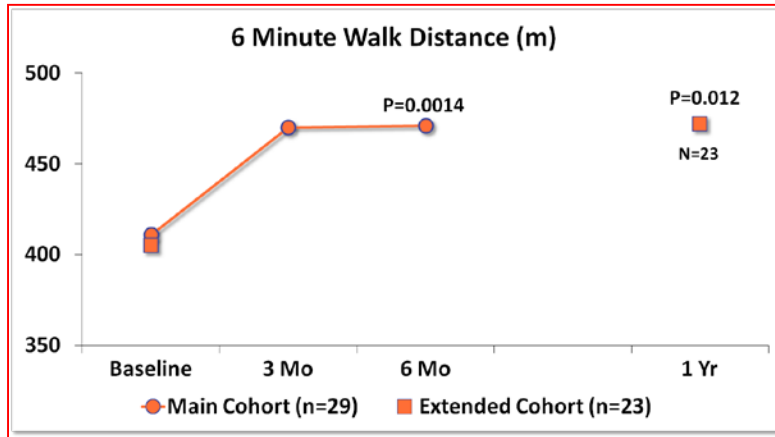


Clinical Experience Pilot Study

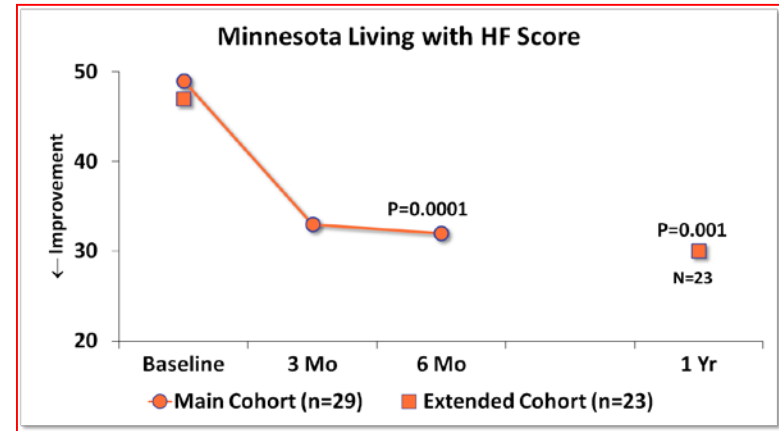
32 patients implanted as part of a
European Safety/Feasibility Trial



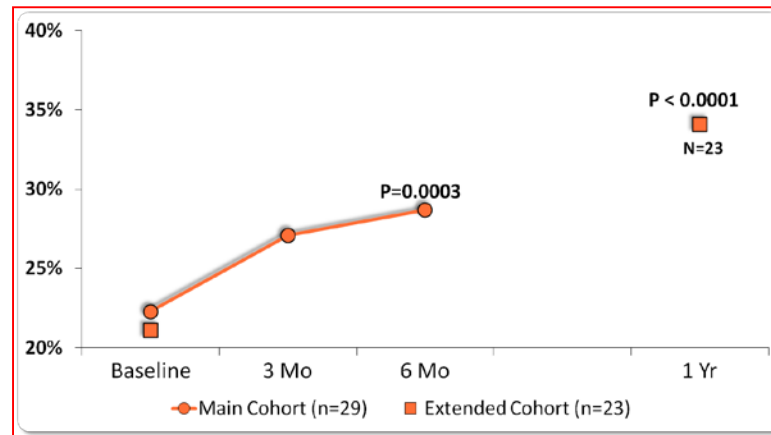
Exercise Capacity – 6 min Walk



MLHFQ



LV Ejection Fraction



P-values are versus paired baseline

*A Randomized Study to Investigate the
Safety and Efficacy of Cardio Fit® for the
Treatment of Subjects with Heart Failure
and Left Ventricular Dysfunction*



CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use

NECTAR-HF Clinical Feasibility Trial

- **NEuroCardiac TherApy for Heart Failure (NECTAR-HF)**

96 patient, VNS vs. OMT, 2:1 randomization

6 months follow-up NYHA III, EF $\leq 35\%$

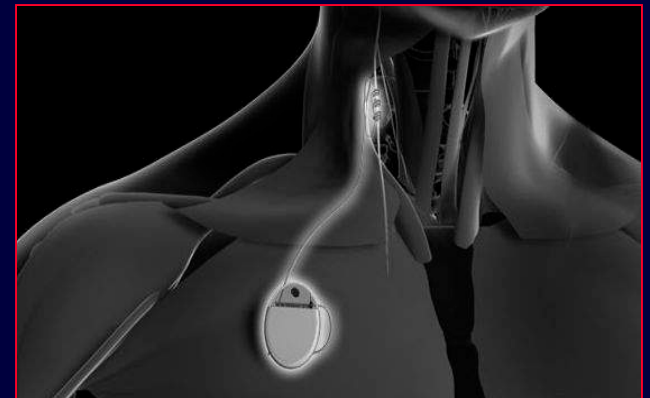
Presented at ESC 2014

No significant improvement in EF or ESV (echo)

Significant improvement in NYHA

Significant improvement in MLHFQ

Nearly 80% of patients on VNS received a stimulation current between 0.5 and 1.0 mA
far below what is needed to activate nerve B-fibers
(2 week titration period)



ANTHEM-HF Clinical Feasibility Trial

Autonomic **N**eural Regulation **T**herapy to **E**nhance **M**yocardial Function in **H**eart **F**ailure

60 patient (randomized to Left VNS n=31 or Right VNS n=29)

6 months follow-up NYHA III, EF \leq 35%

Presented at ESC 2014

Significant improvement in EF (L=R)

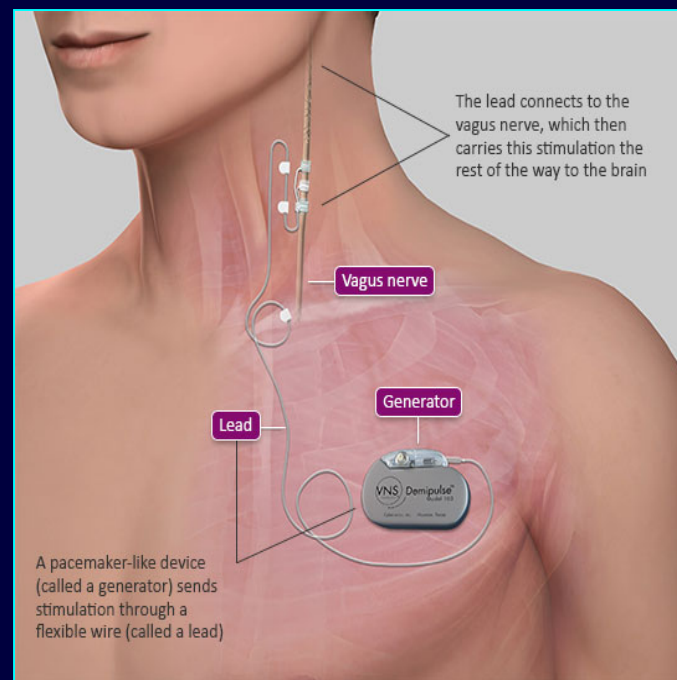
Significant improvement in 6 minute walk (R>L)

Significant improvement in MLHFQ (L=R)

All patients received a stimulation current between

2.0 \pm 0.6 mA with constant 10Hz frequency

(10 week titration period)

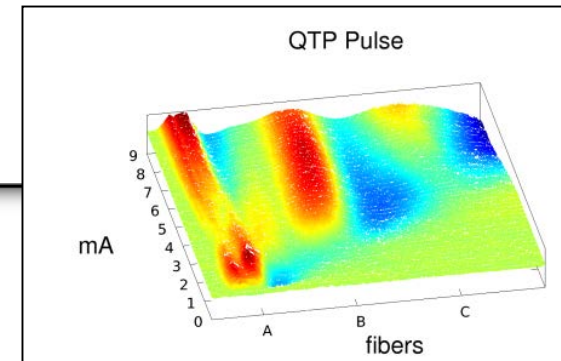
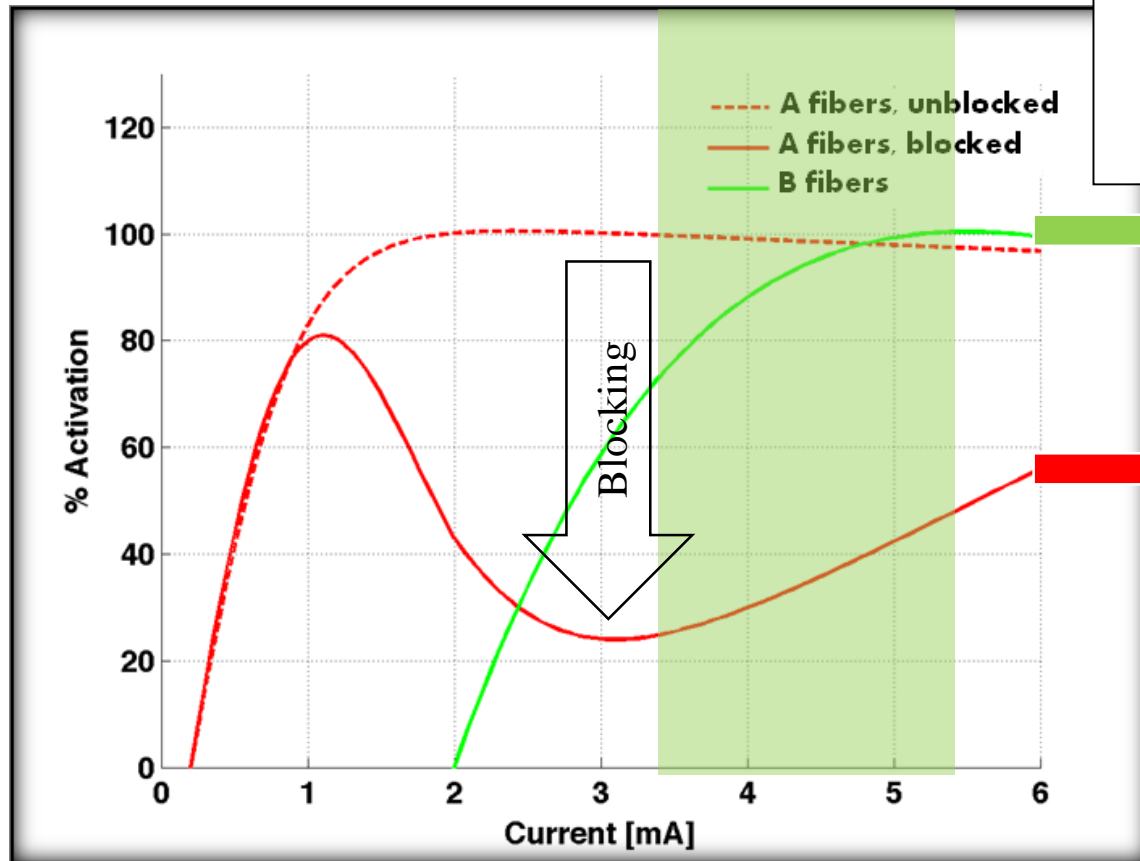


Defeat HF Trial - Failed

- **Determine the feasibility of chronic SCS stimulation in heart failure patients**
- **Multi-center, randomized (3:2 randomization)**
- **30 study centers; 195 subjects**
- **Two arm: Treatment vs. Control**
- **6 month follow-up**
- **Stimulation 12 hrs/day**
- **Maximally tolerated stimulation near T3-T5**
- **Stimulation Parameters: Rate = 50 Hz, Pulse width = 0.2 ms**
- **Study Endpoints**
 - **Cardiac remodeling (LV dimensions)**
 - **Exercise tolerance (change in maximal oxygen uptake)**
 - **Biomarker (BNP)**



Selective Stimulation



Stimulation of cardiac parasympathetic fibers

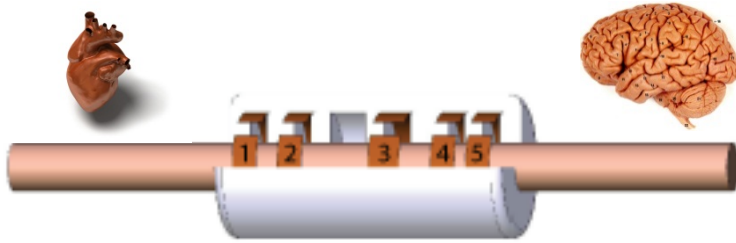
Minimal activation of non-cardiac fibers

Anholt TA, et al. J. Neural Eng 2011.8(3)

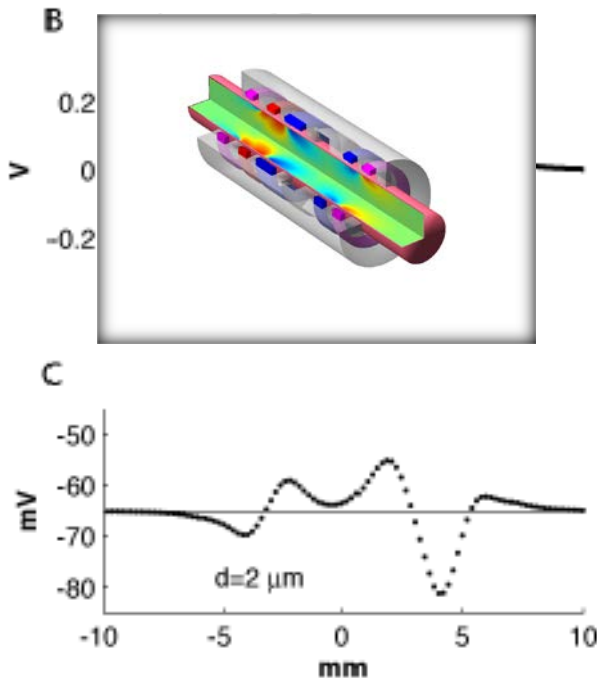
Target Stimulation Dose



Cardiofit Lead



- 5 contacts/rings
- Ring 4: Anode. Narrow for high current density
- Rings 2,3: Cathodes. Wide for low current density
- Rings 1,5: Neutral. Reduce current leakage into surrounding tissue
- Space between rings 2,3 to reduce nerve contact area



Cyberonics VNS Lead



Neuromodulation – Open Questions

Applicable to: VNS – BRS-SCS

Technical Issues

- Ideal current ?
- Ideal frequency ?
- Ideal duty cycle ?
- Ideal location/site of lead implantation? Left or right or both ?
- Timing of delivery during cardiac cycle ?
- Causes for pain and discomfort ? Current leak – anatomy ?
- Percutaneous vs. surgical approaches ?
- Transcutaneous battery charges ?
- Remote activation/stimulation ?
- Dose one size fit all ????



Neuromodulation – Open Questions

Applicable to: VNS – BRS - SCS

Other Clinical Issues

- Organ injury resulting from long-term stimulation ?
- Value on top of background therapy ?
- When to implant during the course of the disease ?
- Confirmation of target engagement during implant ?
- Identification of responders vs. non-responders ?
- Biomarkers for follow-up ?
- Contraindicated populations ? Rhythm abnormalities ?

