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
CHF Parasympathetic Withdrawal & Sympathetic Overdrive

Increased HR and NE

NO Dys-Regulation

Excess Cytokine Release

Myocardial Energetics

LV Function

Pro-Arrhythmic
Electrical Stimulation
Vague Nerve, Baroreflex, Spinal Chord

HR Reduction
Modulate NOS
Myocardial Energetics
Anti-Arrhythmic
Anti-Inflammatory
Contractility
Vagus Nerve Stimulation

Stimulator

Vagus Nerve Electrode

Intracranial Electrode
Rheos$^\text{TM}$
Electrical Activation Carotid Baroreflex System
Spinal Cord Stimulation
Implantation in Epidural Space
VNS

ACh

Activation of $\alpha$-7nACh Receptors

Inhibit HMGB1

High Mobility Group Box-1

Macrophage Release of Cytokines

Activation of M3 Receptors

Increase Expression & Phospho Cx43

Reduce Ventricular Arrhythmias

Activate M2 Receptors

Reduce HR (Reduce Speed of Depolarization)

Reduce MVO$_2$

Reduce Release of Cytokines

Improve Mitochondria Function & Biogenesis

Improve LV Function & Attenuate Adverse LV Remodeling

Prevent SCD

Normalize NOS

Increase eNOS

Decrease iNOS

Decrease nNOS

Increase eNOS

Decrease iNOS

Decrease nNOS

Increase expression & Phospho Cx43
Protein Expression of TNFα
(densitometric units)

Protein Expression of IL-6
(densitometric units)

TNFα Plasma Levels (pg/ml)

IL-6 Plasma Levels (pg/ml)

p<0.05 vs. NL

p<0.05 vs. HF
Expression of Nitric Oxide Synthases in LV Tissue

**eNOS Protein in LV Tissue (du)**
- NL: 80
- HF: 60
- HF+VNS: 70

*p<0.05 vs. HF*

**iNOS Protein in LV Tissue (du)**
- NL: 10
- HF: 15
- HF+VNS: 20

*p<0.05 vs. NL* and *p<0.05 vs. HF*

**nNOS Protein in LV Tissue (du)**
- NL: 10
- HF: 50
- HF+VNS: 30

*p<0.05 vs. NL* and *p<0.05 vs. HF*
∆ LV Systolic Indexes Treatment Effect

Control (n = 6)

BAT (n = 8)

All p-values <0.05

Sabbah et al, Circulation Heart Failure, 2011
Percent of Dogs Induced into VT or VF

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

PRE  3M  6M  6W Post

Wang...Sabbah et al, Circulation 2008
Fluoroscopic Image of Implant in Epidural Space

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

Electrodes 1 and 3: Cathodes, 50%
Electrodes 6 and 8: Anodes, 50%

Note: Midline Electrode Location T3-T5
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

LV End-Diastolic Volume (ml)

Control Group 1

Group 1

Group 2

LV End-Systolic Volume (ml)

Control Group 1

Group 1

Group 2

LV Ejection Fraction (%)

Control Group 1

Group 1

Group 2
Clinical Experience
Pilot Study
32 patients implanted as part of a European Safety/Feasibility Trial
Exercise Capacity – 6 min Walk

- 6 Minute Walk Distance (m)
- P-values are versus paired baseline

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 ≤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 Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure

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

6 months follow-up NYHA III, EF ≤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 ± 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

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?