Autonomic manipulation with implantable devices: Preclinical studies with spinal cord stimulation in canine heart failure.

2011 Korea Circulation Symposium
December 2, 2011

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Disclosures and Funding

- Medtronic, Inc. - Research Support
- Indiana Institute for Medical Research
- Department of Veteran Affairs
- Herman C Krannert Endowment
- Charles E Fisch Research Endowment
- Indiana Clinical & Translational Science Institute
Neuromodulation with spinal cord stimulation

- Implantable systems for spinal cord stimulation (SCS) are a U.S. FDA-approved therapy for the treatment of chronic pain syndromes

The system consists of a stimulation lead(s) placed in the spinal epidural space connected to a stimulation device placed in the abdomen (or elsewhere)
Neuromodulation with spinal cord stimulation

- SCS is also used in Europe to treat patients with cardiac angina refractory to medical or revascularization therapies.

Prior Studies with **Acute** SCS in Normal Canines

- In **normal** canines, Zipes and coworkers demonstrated that **acute** modulation of autonomic tone with thoracic spinal cord stimulation (SCS) **reduced** heart rate and blood pressure, and increased intracardiac electrical conduction times.
- Vagal ligation eliminated this effect.
- Sympathetic ligation did not abolish this effect.

Prior Studies with Acute SCS in Experimental Heart Failure

In a canine post-infarction heart failure model, Issa and coworkers demonstrated that acute modulation of autonomic tone with thoracic spinal cord stimulation (SCS) reduced susceptibility to ischemic ventricular arrhythmias, presumably via a sympatholytic mechanism.

Prior Studies with Chronic SCS in Experimental Heart Failure

• A ten-week treatment with SCS significantly improved cardiac contractile function and heart failure parameters and reduced arrhythmic incidence in canines with heart failure

• In this study, SCS showed greater efficacy than combined therapy with carvedilol and ramipril or medications alone at improving ventricular function and reducing arrhythmia incidence.

(Circulation. 2009;120:286-294.)
Prior Studies with SCS: Heart rate effects

* p < 0.01 compared to other groups
† p < 0.01 compared to SCS and SCS+MEDS
‡ p < 0.05 compared to SCS and SCS+MEDS

(Circulation. 2009;120:286-294.)
Prior Studies with SCS: Ventricular arrhythmias

During acute infarct
0 - 2 wk after infarct
0 - 2 Wk Neuromod
2 - 5 Wk Neuromod
5 - 10 Wk Neuromod

Spontaneous ventricular arrhythmias

* P<0.05 vs CTRL

(Circulation. 2009;120:286-294.)
Prior Studies with SCS: Ejection Fraction

(Circulation. 2009;120:286-294.)

- BSLN
- After HF
- 2 Wk Neuromod
- 5 Wk Neuromod
- 10 Wk Neuromod

* P<0.05 vs CTRL
Question addressed in latest study

What are the optimal characteristics of spinal cord stimulation that yield the maximal therapeutic benefits in our canine heart failure model?
Hypothesis

The beneficial effects of spinal cord stimulation in a canine heart failure model will be dependent upon:

1) the spinal cord stimulation site
2) intensity of stimulation.
* Data: HR, BP, Wt, ECG, Echocardiogram, Serum, Arrhythmias

ICD detections ALWAYS ON

ICD therapies ON for procedures
Treatment Groups

SCS 90T1  - spinal cord stimulation (T1, 90% MT, 2hrs TID)
SCS 90T4  - spinal cord stimulation (T4, 90% MT, 2hrs TID)
SCS 60T4  - spinal cord stimulation (T4, 60% MT, 2hrs TID)
SCS 30T4  - spinal cord stimulation (T4, 30% MT, 2hrs TID)
SCS 90T8  - spinal cord stimulation (T8, 90% MT, 2hrs TID)
CTRL     - no therapies

Note: All SCS groups had SCS ON for 5 weeks, followed by a five week washout period. MT = motor threshold.
Methods - SCS Implantation

SCS lead placed in epidural space > advanced to midline T1, T4, or T8 spinal segment

SCS pulse generator implanted in right lumbar parasternal area

SCS applied at variable motor threshold, 50 Hz frequency, for 2 hrs TID for 5 weeks

SCS ON daily from 8AM-10AM, 4PM-6PM, and 12PM-2AM
Results - Ambulatory Heart Rate

* p < 0.05 from control

- Baseline
- After HF Induction
- After 5 Wk Neuromod
- After 5 Wk Washout

Ambulatory Heart Rate (bpm)
Results - Ejection Fraction

Ejection Fraction (%)

- Baseline
- After HF Induction
- After 5 Wk Neuromod
- After 5 Wk Washout

* P<0.05 vs CTRL
Results - Spontaneous Ventricular Arrhythmias

* P < 0.05 from control

Spontaneous ventricular arrhythmias (total #)

- During MI
- 0-2 wk After MI
- 0-5 Wk Neuromod
- 0-5 Wk Washout

Graph showing the number of spontaneous ventricular arrhythmias at different time points and conditions, with significant differences indicated by * (P < 0.05 from control).
Summary and Conclusions

The response to SCS was dependent upon site and intensity of stimulation.

SCS at T1-90%, T4-90%, and T4-60% caused improvement in LV function that was sustained five weeks after cessation of therapy.

SCS at T1-90%, T4-90%, and T4-60% reduced spontaneous ventricular arrhythmias, but this effect was not sustained five weeks after cessation of therapy.
Insights into Mechanism of SCS Action

Suppression of Arrhythmias

Investigated function and expression of the transient outward potassium current ($I_{to}$) in post-mortem tissues from failing and SCS-treated canine hearts

- $\rightarrow$ Membrane electrical changes
- $\rightarrow$ Ion channel expression
SCS Returns I\textsubscript{to} Current Density to Normal Levels

**A**

- Normal
- HF Control
- HF w Spinal Stim
- HF w Beta Blocker

**B**

- Voltage vs Normal
- HF Control
- HF Spinal Stim
- HF Beta Blocker

I\textsubscript{to} density (pA/pF) vs Voltage (mV)

- 5 pA/pF
- 30 ms
Insights into Mechanism of SCS Action

Recovery of left ventricular function

Investigated myocardial nerve innervation in post-mortem tissues from failing and SCS-treated canine hearts

- Sympathetic nerve innervation
- Growth-associated protein staining
Cardiac nerve staining
GAP43 staining (nerve growth marker)

HF untreated (decreased)  HF SCS-treated (increased)
Global Conclusions from Preclinical Studies

- SCS causes the following effects in heart failure:
  - Decreases incidence of ventricular arrhythmias
  - Improves left ventricular function better than standard medications
  - Has site- and intensity-dependent effects
  - Causes myocardial nerve sprouting
  - Remodels cellular ionic currents
  - Human SCS trials are now underway
DEFEAT-HF®

• First human study to assess safety and efficacy of SCS in human heart failure patients
• Will assess SCS effects on cardiac function and arrhythmias
• Ongoing in USA and Europe
• Goal is 240 patients
• Approximately 20 patients enrolled to date
• Sponsored by Medtronic, Inc.
Acknowledgements

Krannert Institute of Cardiology
Christopher Corr, MS
Jason Garlie, MD
Elizabeth Lopshire, BS
Upasana Jarori, BS
Nhila Jagadeesan, BS
Richard Shelton, MD
Saurabh Malhotra, MD
Douglas P. Zipes, MD

Medtronic, Inc.
Xiaohong Zhou, MD
Thomas Mullen, PhD
Abstract: Autonomic manipulation with spinal cord stimulation (SCS) has been routinely applied to treat chronic pain syndromes and angina. In preclinical studies, our laboratory set out to determine the effects of chronic SCS on suppression of ventricular tachyarrhythmias (VT) and LV remodeling in experimental heart failure (HF). We used a previously-validated canine post-infarction heart failure model for these studies. Briefly, canines underwent ICD implantation followed by percutaneous foam embolization of the LAD to induce MI. After recovery, high rate pacing was applied for three weeks to induce HF, and then animals were randomized to receive SCS or no therapy (CTRL) for 5-10 weeks. In the first study, the SCS-treated animals had fewer VT events and improved LV ejection fraction as compared to controls. A follow-up study demonstrated that SCS alone was more efficacious on the above endpoints that standard medical therapy (beta-blockade + ACE-inhibitor). A subsequent study demonstrated this effect was dependent on the spinal site and intensity of SCS. An ongoing study is examining the neural substrates of this phenomenon. These preclinical studies have spawned an early human trial to assess the safety and feasibility of SCS in human HF patients.