Neurostimulation for heart failure

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• Autonomic imbalance in HF
• Neuromodulation for heart failure
  – Spinal cord stimulation (SCS)
  – Carotid sinus nerve stimulation
  – Cervical vagal nerve stimulation
  – Intracardiac AV-nodal stimulation
• Unresolved issues in neurostimulation
• On going trials
Parasympathetic and sympathetic innervations of the heart

Europace. 2014;16:109-128

Clin Endocrinol Metab. 1977;6:77.
SPINAL CORD STIMULATION
History of SCS

• Spinal cord stimulation has been used for over 40 years in the management of chronic intractable pain.

• According to the AANS, as many as 50,000 neurostimulators are implanted worldwide every year.

• In our fields
  – Refractory angina, syndrome X, critical leg ischemia, Raynaud’s disease, etc.
In a Canine Postinfarction HF Model

Clinical parameter – BNP

- SCS
- MED
- CTRL

Echocardiographic index

- SCS
- MED
- CTRL

LAD embolization + RV pacing (240 ppm) for 3 weeks

Circulation. 2009;120:286-294
In a porcine model of ischemic HF

**Invasive hemodynamic assessment**

**Figure A**
- LV dP/dt (mmHg/s)
- MI+HF
- 1° SCS 15min
- Recovery
- 2° SCS 15min

Significance:
- *P<0.05 vs. MI+HF
- **P<0.05 vs. Recovery

**Figure B**
- Myocardial oxygen consumption (mL/min/mmHg)
- MI+HF
- 1° SCS 15min

Significance:
- P=0.006

J Cardiovasc Electrophysiol. 2012;23:534-540
SCS for the Treatment of Advanced HF

Abstract. 2000. The 14th HFSA

A.1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>LVEF (%)</th>
<th>LVED mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 y/o male</td>
<td>Ischemic</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>43 y/o male</td>
<td>Ischemic</td>
<td>18</td>
<td>65</td>
</tr>
<tr>
<td>18 y/o female</td>
<td>Non-Ischemic</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>77 y/o male</td>
<td>Ischemic</td>
<td>30</td>
<td>56</td>
</tr>
</tbody>
</table>

A.2. Exercise Duration (Meters)

- Two leads were implanted in each patient (T1-T3 and T9-T12).
- Stimulation frequency of 50 Hz, pulse width 200 msec with bipolar stimulation and output current amplitude set at 90% of initial parasthesias.
- Stimulation was programmed for 2hrs three times a day.
SCS results in a decrease in the TWA magnitude

<table>
<thead>
<tr>
<th>Patient</th>
<th>SCS off</th>
<th>SCS on 2 h</th>
<th>SCS on 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>TWA rep: positive, Valt max: 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>TWA rep: positive, Valt max: 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>TWA rep: positive, Valt max: 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1: after 2 months</td>
<td>TWA rep: positive, Valt max: 6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2: after 2 months</td>
<td>TWA rep: positive, Valt max: 6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3: after 2 months</td>
<td>TWA rep: positive, Valt max: 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- T-wave alternans (TWA) has demonstrated to be a reliable non-invasive test for the stratification of the arrhythmic risk in both ischemic and non-ischemic cardiomyopathy.

- In all the three patients, we observed a significant reduction of TWA amplitude after 2 h stimulation.

- All the tests were classified as negative after 24 h stimulation with the nominal parameters.
Spinal cord stimulation: single-lead placement

- The lead in the posterior epidural space in the mid-thoracic region at approx. T12/L1.
- The impulse generator is usually implanted subcutaneously in the low back or high buttock with tunnelling of the leads down to that region.
CAROTID SINUS NERVE STIMULATION
Baroreceptors

During human HF, this baroreflex is profoundly suppressed and worsens with deterioration of CHF.
Carotid sinus nerve stimulation

Proportion of Subjects That Achieved SBP <140 mm Hg

265 subjects with resistant hypertension


Chronic Baroreceptor Activation Enhances Survival in Dogs With Pacing-Induced HF

Chronic vagus nerve stimulation

NYHA class

IV
n=2
Died

III
n=15
Died

II
n=15

I
n=6
Baseline

3 months
n=19

6 months
n=14
n=5

SNUH

Eur Heart J. 2011;32:847-855
CVRx Neo system
CERVICAL VAGAL NERVE STIMULATION
Parasympathetic system during CHF

- During CHF, the density of cardiac muscarinergic receptors is increased, which is most probably due to an adaptive upregulation secondary to a decreased efferent vagal input.

- The postganglionic vagal nerve transmission seems to be intact in HF.

- Pre- to post-ganglionic parasympathetic efferent neurotransmission via nicotinergic acetylcholine receptors seems to be impaired during CHF.
Mechanisms of action

- Antiarrhythmic effects – ↑Ventricular refractory period, ↑epicardial AP duration, ↓ventricular vulnerability to VF

- Rate slowing effects

- Antifibrotic effects

- Anti-inflammatory effects - ↓HF-associated increases of TNF-a, IL-6, and CRP

- Reverse remodelling
The CardioFit™ System
Echo evaluation after CVS

LV volume index (mL/m²)  LV EF (%)

32 NYHA class II–IV patients [56 ± 11 years, LVEF 23 ± 8%].

Eur Heart J. 2011;32:847-855
INTRACARDIAC AV NODAL VAGAL STIMULATION
Intracardiac AVN vagal stimulation

• 30-40% of patients with CHF eventually will develop AF.

• AF RVR may decrease the degree of LV resynchronization in patients with CRT and may ultimately lead to inappropriate shock delivery in up to 5% of ICD recipients.

• Long-term selective AVN vagal stimulation for ventricular rate control has been developed as potential adjunctive treatment modality for these patients.
Human parasympathetic nerves that control the AV node reside in an epicardial plexus (RIGP), which can be endocardially stimulated at the coronary sinus ostium and/or at the posteroseptal RA.
Effect of AVNVS

50-Hz atrial stimulation

Heart Rhythm. 2009;6:1282-1286
UNSOLVED ISSUES
Inappropriate shock

Neuromodulation devices may have the potential for interfering with implantable cardioverter-defibrillator (ICD).

*Electrocautery devices resulted in oversensing, which led to false detection of ventricular tachyarrhythmia.

M/50
ICD implanted for primary prevention of SCD
Vagal stimulation may facilitate spontaneous premature depolarizations in the atria, shorten the atrial and PV ERP, and increase heterogeneity of refractoriness.

Selectivity of neural stimulation

• The cervical vagal nerve contains efferent and afferent fibers coursing not only to the thoracic but also to or from the abdominal viscera.

• ↑Gastric acid secretion or intestinal motility?
On going trials

- Spinal cord stimulation
  - SCS-HEART (HF patients with ICD, non-random)
  - DEFEAT-HF (HF patients with ICD, on/off)
- Carotid sinus nerve stimulation
  - XR-1 heart failure study (HF patients, device vs. medical)
- Cervical vagal nerve stimulation
  - INOVATE-HF (HF patients, device vs. medical)
- Intracardiac AV nodal vagal stimulation
  - AV node stimulation study (HF patients with CRT-D)
Summaries

• HF is associated with significant perturbances of the autonomic balance with predominant sympathetic activation over the parasympathetic system.

• To therapeutically increase the cardiac parasympathetic tone
  – Spinal cord stimulation
  – Carotid sinus nerve stimulation
  – Cervical vagal nerve stimulation
  – Intracardiac AV nodal vagal stimulation

• However, many issues must be solved. Ongoing clinical trials will address the role and possible benefit.