A Deadly Combination: Central Sleep Apnea & Heart Failure

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Disclosures

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• Medtronic: research grant, fellowship support, speaking honoraria
• Abbott/St. Jude Medical: research grant
• Bristol-Meyers-Squibb: research grant
Overview

• Defining Central Sleep Apnea (CSA)
• Diagnosing Central Sleep Apnea
• Deadly Combination of Central Sleep Apnea and Heart Failure
• Device based therapy: remede® system
  – Pivotal Trial Results
• Discussion

Central Sleep Apnea

• A central apnea is a >10 second pause in ventilation with NO associated respiratory effort
• It results from an intermittent neural drive to breathe resulting in a periodic breathing pattern
• Patients with heart failure, atrial fibrillation and stroke are at increased risk for development of central sleep apnea (CSA)
Central Sleep Apnea Comorbidities

- Many patients with central sleep apnea have concomitant cardiovascular disease

T. Douglas Bradley and John S. Floras
Circulation. 2003;107:1822-1826
Central Apnea

↓PaO₂, ↑PaCO₂

↓PaCO₂

Hyperventilation

↓Myocardial O₂ supply

Lung Inflant Receptors

Pulmonary Edema

Lung Stretch Receptors

LV Filling Pressure

LV Afterload

Myocardial O₂ Demand

Vasoconstriction

THR

T: Douglas Bradley and John S. Floras
Circulation. 2003;107:1822-1826
Central Apnea

Hyperventilation

↓PaCO2

↓Myocardial O2 supply

↓PaO2 ↑PaCO2

Chemoreceptors

↓Myocardial Edema

Lung Stretch Receptors

LV Failure Cardiac Output LV Filling Pressure

Vasoconstriction ↑ BP

T. Douglas Bradley and John S. Floras
Circulation. 2003;107:1822-1826
## Screening for Central Sleep Apnea

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4.33 (2.5-7.52)</td>
</tr>
<tr>
<td>Awake PCO2 &lt; 38mmHg</td>
<td>4.33 (2.5-7.52)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>4.08 (1.74-9.57)</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>2.37 (1.35-4.15)</td>
</tr>
</tbody>
</table>

• It is unclear if there are symptoms specific to CSA

• In contrast to patients with obstructive sleep apnea (OSA), patients with CSA are unlikely to snore, exhibit daytime somnolence or be obese.

**Author:** Aweith - (CC BY-SA 4.0)
Diagnosis of Central Sleep Apnea

Clinical Suspicion

Home Sleep Study

Polysomnogram (PSG)

Diagnosis of Central Sleep Apnea

Clinical Suspicion

Polysomnogram (PSG)
Diagnosis of Central Sleep Apnea

Clinical Suspicion

Home Sleep Study

Sleep Study Interpretation

- Apnea-Hypopnea Index (AHI): Overall number of apneas and hypopneas per hour of sleep
  - Apnea is defined as >10 second pause in respiration
  - Hypopnea is a decrease but not complete cessation of ventilation to less than 50% of normal, with associated fall in oxygen saturation or arousal
- Oxygen Desaturation Index (ODI4):
  - Apnea/hypopneas with an associated oxyhemoglobin desaturation greater than 4% are associated with cardiovascular disease independent of confounding variables
Sleep Study Interpretation

• Apnea-Hypopnea Index (AHI): Overall number of apneas and hypopneas per hour of sleep

  Central Apnea Index (CAI):
  • Number of central apneas per hour
  • Central sleep apnea is diagnosed when the number of central events > obstructive events

• Oxygen Desaturation Index (ODI4):
  – Apnea/hypopneas with an associated oxyhemoglobin desaturation greater than 4% are associated with cardiovascular disease independent of confounding variables

Polysomnogram of Heart Failure Patient with Central Sleep Apnea

Journal of the American College of Cardiology, ISSN: 1558-3597, Vol: 65, Issue: 1, Page: 72-84 Publication Year: 2015 - (CC BY-NC-ND 4.0)
The Central Sleep Apnea Cycle

Effects of Central Sleep Apnea & Heart Failure are Intertwined
Readmissions and Mortality in Heart Failure Patients with CSA

- Over 25% of hospitalized heart failure patients with central sleep apnea had 2 or more readmissions within 6 months
- Central sleep apnea is an independent predictor of mortality

Two strategies to treat central sleep apnoea in heart failure.

Treatments:
- Continuous positive airway pressure (CPAP)
- Adaptive servo-ventilation

See the following Journal article for more information:
John S. Floras Eur Heart J 2012;33:810-812
Sleep Apnea & Heart Failure: Guidelines

• The results of the SERVE-HF trial indicate harm from ASV therapy for CSA – increase in all cause mortality and cardiovascular mortality

Transvenous phrenic nerve stimulation for the treatment of central sleep apnea in heart failure
Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure

See Figure 1 - in the following Journal article for more information:
European Heart Journal, Volume 33, Issue 7, 1 April 2012, Pages 889–894
Published: 19 August 2011  Article history

Elimination of respiratory instability and improvement in oxygenation during unilateral phrenic nerve stimulation in a heart failure patient with central sleep apnoea.

Transvenous phrenic nerve stimulation for the treatment of central sleep apnea in heart failure

- Elimination of respiratory instability and improvement in
Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea

- The remedē System consists of an implantable pulse generator, an implantable stimulation leads, and an external system programmer.

The device is implanted in the right pectoral area. The right subclavian approach was used to place the stimulation lead (A) in the left pericardiophrenic vein and to place the sensing lead (B) in the azygos vein.
Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea

The device is implanted in the right pectoral area. The right subclavian approach was used to place the stimulation lead (A) in the left pericardiophrenic vein and to place the sensing lead (B) in the azygos vein.

JACC: Heart Failure May 2015, 3 (5) 360-369
Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial

Mario Rosa Castorino, Piotr Ponikowski, Shahrokhi Javaheri, Ralph Augusti, Lee Goldberg, Richard Holcomb, Andrew Koo, Rami N Khayat, Olaf Oldenburg, Christoph Stellbrink, William T Abraham, for the remedi System Pivotal Trial Study Group

- Prospective, multi-center, randomized controlled trial
- AHI > 20 events/hour with at least 50% central events
- 151 eligible patients randomized (1:1) to treatment or control groups at time of implant
  - Control - device implantation but stimulation off for 6 months, then therapy turned on
  - Treatment – device implantation but stimulation programmed on at 1 month post implant
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=73)</th>
<th>Control (n=78)</th>
<th>Pooled (n=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>65 (12)</td>
<td>65 (13)</td>
<td>65 (13)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>63 (86%)</td>
<td>72 (92%)</td>
<td>135 (89%)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>70 (96%)</td>
<td>74 (95%)</td>
<td>144 (95%)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>30.8 (5.2)</td>
<td>31.3 (6.6)</td>
<td>31.1 (6.0)</td>
</tr>
<tr>
<td><strong>Neck width (cm)</strong></td>
<td>42 (5)</td>
<td>43 (5)</td>
<td>42 (5)</td>
</tr>
<tr>
<td><strong>Heart rate (beats per min)</strong></td>
<td>75.4 (12.6)</td>
<td>72.9 (13.8)</td>
<td>74.1 (13.3)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>125.3 (18.3)</td>
<td>121.3 (17.7)</td>
<td>124.5 (17.9)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td>74.4 (10.5)</td>
<td>73.3 (11.4)</td>
<td>74.0 (11.0)</td>
</tr>
<tr>
<td><strong>Respiration rate (breaths per min)</strong></td>
<td>17.5 (2.9)</td>
<td>17.3 (2.6)</td>
<td>17.4 (2.7)</td>
</tr>
<tr>
<td><strong>Apolo- Aropna index (events per h)</strong></td>
<td>4.8 (1.9)</td>
<td>4.7 (1.6)</td>
<td>4.6 (1.2)</td>
</tr>
<tr>
<td><strong>Central apnena index (events per h)</strong></td>
<td>30.0 (18.0)</td>
<td>26.6 (15.1)</td>
<td>28.2 (17.1)</td>
</tr>
<tr>
<td><strong>Obstructive apnoea index (events per h)</strong></td>
<td>2.6 (3.2)</td>
<td>2.3 (2.7)</td>
<td>2.4 (3.0)</td>
</tr>
<tr>
<td><strong>Mixed apnoea index (events per h)</strong></td>
<td>3.1 (4.1)</td>
<td>2.2 (3.3)</td>
<td>2.6 (3.7)</td>
</tr>
<tr>
<td><strong>Hypopnoea index (events per h)</strong></td>
<td>13.4 (11.2)</td>
<td>12.7 (11.6)</td>
<td>12.9 (11.4)</td>
</tr>
<tr>
<td><strong>OSA (events per h)</strong></td>
<td>43.2 (21.7)</td>
<td>37.5 (17.5)</td>
<td>40.2 (19.8)</td>
</tr>
</tbody>
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Lancet. 2016 Sep 3;388(10048):974-82
## Baseline Characteristics

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<td>17.4 (2.7)</td>
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</tbody>
</table>

### Obstructive apnoea index (events per h)
- Treatment: 2.6 (3.2)
- Control: 2.3 (2.7)
- Pooled: 2.4 (3.0)

### Mixed apnoea index (events per h)
- Treatment: 3.1 (4.1)
- Control: 2.2 (3.3)
- Pooled: 2.6 (3.7)

### Hypopnoea index (events per h)
- Treatment: 13.1 (11.2)
- Control: 12.7 (11.6)
- Pooled: 12.9 (11.4)

### ODI4 (events per h)
- Treatment: 432.2 (21.7)
- Control: 375 (27.5)
- Pooled: 402 (19.8)

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## Baseline Characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment (n=73)</th>
<th>Control (n=78)</th>
<th>Pooled (n=151)</th>
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</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>32 (44%)</td>
<td>32 (41%)</td>
<td>64 (42%)</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction</strong></td>
<td>39.7 (12.1)</td>
<td>39.4 (12.2)</td>
<td>39.5 (12.1)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>48 (66%)</td>
<td>48 (62%)</td>
<td>96 (64%)</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6/48 (13%)</td>
<td>12/48 (25%)</td>
<td>18/96 (19%)</td>
</tr>
<tr>
<td>II</td>
<td>21/48 (44%)</td>
<td>20/48 (42%)</td>
<td>41/96 (43%)</td>
</tr>
<tr>
<td>III</td>
<td>21/48 (44%)</td>
<td>16/48 (33%)</td>
<td>37/96 (39%)</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>40 (55%)</td>
<td>44 (56%)</td>
<td>84 (56%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>53 (73%)</td>
<td>60 (77%)</td>
<td>133 (75%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>27 (37%)</td>
<td>19 (24%)</td>
<td>46 (30%)</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>6 (8%)</td>
<td>6 (8%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td>17 (23%)</td>
<td>21 (27%)</td>
<td>38 (25%)</td>
</tr>
<tr>
<td><strong>Concomitant cardiac devices</strong></td>
<td>31 (42%)</td>
<td>33 (42%)</td>
<td>64 (42%)</td>
</tr>
<tr>
<td><strong>Implantable cardioverter-defibrillator</strong></td>
<td>19/31 (61%)</td>
<td>14/33 (42%)</td>
<td>33/64 (52%)</td>
</tr>
<tr>
<td><strong>CRT-D</strong></td>
<td>9/31 (29%)</td>
<td>11/33 (33%)</td>
<td>20/64 (31%)</td>
</tr>
<tr>
<td><strong>Non-CRT pacemaker</strong></td>
<td>2/31 (6%)</td>
<td>8/23 (24%)</td>
<td>10/64 (16%)</td>
</tr>
<tr>
<td><strong>CRT-P</strong></td>
<td>1/31 (3%)</td>
<td>0</td>
<td>1/64 (2%)</td>
</tr>
</tbody>
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Lancet. 2016 Sep 3;388(10048):974-82
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Change 6 months</th>
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</thead>
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<tr>
<td>Atrial fibrillation</td>
<td>32 (44%)</td>
<td>32 (41%)</td>
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</tr>
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<td>N</td>
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</tbody>
</table>

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Percent Change in AHI at 6 months

Lancet. 2016 Sep 3;388(10048):974-82
Primary Endpoint Met:

- The proportion of subjects achieving ≥50% reduction in AHI for the Treatment group was 51% compared to 11% for the Control group, resulting in a difference between groups of 41% in favor of the Treatment group (p<.0001)
- 87% of patients in the Treatment Group had a reduction in AHI at 6 months

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Safety and Feasibility

<table>
<thead>
<tr>
<th>Safety and Feasibility</th>
<th>Implant Metrics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 97% implant success rate</td>
<td>• 3.4% lead revision rate</td>
</tr>
<tr>
<td>• 3.4% lead revision rate</td>
<td>• 2.7 +/- 0.8 hours ave. implant time</td>
</tr>
<tr>
<td>• 2.7 +/- 0.8 hours ave. implant time</td>
<td>• No deaths related to procedure or therapy</td>
</tr>
</tbody>
</table>

Table 3: Serious adverse events associated with procedure, device, or therapy at 12 months' follow-up

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Improvements in Quality of Life

- **Patient Global Assessment:**
  - 79% of Patients with Improved QoL
  - 99% Marked or Moderate Improvement
  - 14% Mild Improvement
  - 7% No Change
  - 6% Worsened

- **Epworth Sleepiness Scale:**
  - Reduction of 3.6 Points with Treatment
  - Treatment (N=58) vs Control (N=73)
  - Improvement from Baseline

Lancet. 2016 Sep;388(10048):974-82
Sleep Improvements Sustained Over Time

Heart Failure Patients Demonstrate Similar Benefit in Sleep and Quality of Life

- Post-hoc analysis showed between Group improvements
  - **Sleep metrics** *(Ap<0.0001)*
    - Apnea Hypopnea Index (AHI)
    - Central Apnea Index (CAI)
    - Oxygen Desaturation Index (ODI)
    - Arousal Index
  - **Epworth Sleepiness Scale**
    - 3.2 ± 4.9 point improvement between groups *(p<0.001)*
  - **Patient Global Assessment**
    - 57% vs 9% *(p<0.0001; Figure)*
Post-hoc Heart Failure Analysis Demonstrates Improvements in Heart Failure Specific Metrics

- Minnesota Living with Heart Failure improved by 6.3±17.0 points (baseline to 12 months; p=0.044; n=32)
- Improvement in left ventricular ejection fraction and remodeling

Summary

- Central sleep apnea (CSA) is caused by an intermittent neural drive to breathe resulting in a periodic breathing pattern. It is prevalent in 30-50% of heart failure patients as well as patients with atrial fibrillation and stroke.
- Central sleep apnea is an independent predictor of mortality and heart failure rehospitalization.
- In the Pivotal trial of the remede® system, 87% of patients in the Treatment Group had a reduction in AHI at 6 months, with 29% experiencing marked improvement and 31% experiencing moderate improvement in AHI. Results were sustained over 18 months and beyond.
- In the Patient Global Assessment, 79% of patients receiving treatment reported improved quality of life.
- The remede system can be implanted safely in about 2.7 hours.
Summary

• A post hoc analysis of the subgroup of heart failure patients in the Pivotal trial indicated that heart failure patients responded well to remed system therapy including:
  – Improved sleep metrics and decreased sleepiness
  – Improvement in MLWHFQ, LVEF, & LV remodeling
  – Decrease in time to first heart failure hospitalization