Central Sleep Apnea and Heart Failure

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Director, Clinical Trials Management Organization
Deputy Director, Davis Heart & Lung Research Institute

Central Sleep Apnea is Common in Heart Failure
Pathophysiology of Central Sleep Apnea

- During sleep, respiration is regulated by the brain to maintain a constant blood CO$_2$.
- To keep CO$_2$ regulated, the brain sends signals to the diaphragm via phrenic nerves; these signals control the pattern of breathing.
- In patients with central sleep apnea, the brain develops a respiratory arrhythmia that manifests as an oscillating pattern between hyperventilation and apnea.
- Central sleep apnea is most often associated with cardiovascular disease states, such as heart failure, atrial fibrillation, and stroke.

Deleterious Effects of Central Sleep Apnea

- Increased hypoxia worsens
  - Ischemia
  - Dementia
  - Inflammation
- Reduced sleep efficiency contributes to
  - Insulin resistance
  - Fatigue
  - Poor exercise tolerance
- Increased sympathetic drive causes
  - Atrial and ventricular arrhythmias
  - Decreased cardiac function
  - Increased blood pressure

Dempsey et al. Physiol Rev 2010;90:47-112

Lavie Eur Resp J 2009;33:1467-84.
Stevenson Heart Rhythm 2010;7:1263-70.
Treatment of Central Sleep Apnea

- Multiple therapeutic modalities have been evaluated
  - CPAP / ASV
  - Oxygen
  - Medications

- Unfortunately, none has proven to be safe and effective (and some appear to be harmful, e.g., ASV)

SERVE-HF Trial Results

Cowie M, et al. NEJM 2015
Why Did SERVE-HF Fail?

- The results were a surprise to the investigators
- 3 main theories have surfaced:
  - CSA (in the form of CSR) is a compensatory mechanism
  - Positive pressure delivered by ASV was harmful
  - Intermittent use of the therapy was harmful

Comparison of Normal Inspiration with Mask-Based CSA Therapies

- Normal Breathing
  - Diaphragm *pulls* air into the lungs via negative intrathoracic pressure

- Mask Therapies (ASV, CPAP)
  - Ventilation *pushes* air into the lungs via positive pressure (intrathoracic pressure less negative)
  - Impairs venous return
  - Increases pulmonary vascular resistance
  - Reduces cardiac output
  - May be especially problematic in low EF / low cardiac output heart failure patients
Phrenic Nerve Stimulation for CSA

- Provides TRANSVENOUS UNILATERAL STIMULATION of the phrenic nerve
- Treats patients automatically and continuously THROUGHOUT THE ENTIRE NIGHT and requires no patient adherence
- IMPLANTED BY CARDIOLOGISTS experienced with implantable devices
- Generates NEGATIVE PRESSURE which augments cardiac preload without decreasing cardiac output

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use. AVAILABLE FOR SALE IN THE EU/EEA


Comparison of Phrenic Nerve Stimulation with Normal Inspiration and Mask-Based Therapies

- **Normal Breathing**
  - Diaphragm pulls air into the lungs via negative intrathoracic pressure

- **Mask Therapies (ASV, CPAP)**
  - Ventilation pushes air into the lungs via positive pressure (intrathoracic pressure less negative)

- **Remedé® System**
  - The remedé® System pulls air into the lungs via negative intrathoracic pressure using the same mechanism of action as normal breathing
How is the remedē® System Implanted?

- The remedē® System implant takes place in the EP LABORATORY by cardiologists experienced with CRT
- LIGHT SEDATION is used to keep patients comfortable
- The device is placed UNDER THE SKIN in either the right or left chest
- A STIMULATION LEAD is placed either in the left pericardiophrenic or right brachiocephalic vein
- A second lead to SENSE RESPIRATION is placed in the azygos vein

Effect of Phrenic Nerve Stimulation on CSA

Ponikowski et al. Eur Heart J 2012;33: 889-894
Therapy Safety and Efficacy Confirmed Through a Series of Clinical Development Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Study</td>
<td>4 Subjects</td>
<td>• Established transvenous nerve stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stimulation tolerated well</td>
</tr>
<tr>
<td>Proof of Concept</td>
<td>10 Subjects</td>
<td>• Demonstrated ability to break CSA pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients able to sleep with therapy</td>
</tr>
<tr>
<td>Lead and Algorithm Development</td>
<td>41 Subjects</td>
<td>• Confirmed leads can be place consistently</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stable thresholds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Algorithms optimized</td>
</tr>
<tr>
<td>Acute Feasibility Study</td>
<td>16 Subjects</td>
<td>• Demonstrated improvement in standard indices of sleep apnea control night vs. therapy night</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Central Apnea Index</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oxygen Desaturation</td>
</tr>
<tr>
<td>Chronic Feasibility Experience</td>
<td>7 Implanted Subjects</td>
<td>• Demonstrated safety of chronic implantable system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Subjects still implanted after ~4 years</td>
</tr>
<tr>
<td>Chronic Pilot Study</td>
<td>49 Implanted Subjects</td>
<td>• Statistically significant improvement in sleep indices at 3 &amp; 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Showed clinically meaningful changes in important cardiac physiological markers, quality of life and...</td>
</tr>
</tbody>
</table>

The remedē® System Pilot Study

Clinically Meaningful Improvements in Sleep Parameters

- Decreased CAI improves oxygenation and decreases arousals
- Decreased AHI is associated with decreased in both mortality and ventricular arrhythmias

*All changes are statistically significant at 3 & 6 months by paired student t-test (p<0.0001), n=44

The remedē® System Pilot Study
Clinically Meaningful Improvements in Sleep Parameters

![Graphs showing improvements in sleep parameters over time.]

- Reduced Arousals decreases norepinephrine release and sympathetic drive
- Oxygen Desaturation Index
- Arousal Index
- Sleep Efficiency
- Rapid Eye Movement (REM)

*All changes are statistically significant at 3 & 6 months by paired student t-test (p<0.0001) N=44.


The remedē® System Pivotal Trial
STUDY DESIGN

- Prospective, multi-center, randomized (1:1) controlled trial
- Moderate to severe CSA based on PSG scored by a blinded core laboratory
- PSG inclusion criteria:
  - AHI ≥ 20
  - CAI at least 50% of all apneas with at least 30 central apnea events
  - Obstructive Apnea Index ≤ 20% of the total AHI
- 151 subjects enrolled at 31 centers in the US and Europe
  - All patients underwent system implantation
  - Control group had therapy initiated after the 6 month effectiveness assessment

**The remedē® System Pivotal Trial ENDPOINTS**

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>DESCRIPTION</th>
<th>POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Comparison of the proportion of subjects with ≥50% reduction in AHI between treatment and control</td>
<td>Intention to Treat (ITT)</td>
</tr>
<tr>
<td>(6 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12 months)</td>
<td>Freedom from serious adverse events associated with implant, the remedē system, or delivered therapy</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hierarchical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6 months)</td>
<td>1. Central Apnea Index (CAI)</td>
<td>Per-protocol</td>
</tr>
<tr>
<td></td>
<td>2. Apnea Hypopnea Index (AHI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Arousal Index (ArI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Rapid Eye Movement (REM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Patient Global Assessment (PGA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Oxygen Desaturation Index 4% (ODI4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Epworth Sleepiness Scale (ESS)</td>
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</tbody>
</table>

Costanzo et al. *J Card Fail* 2015

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Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial

*Costanzo et al.*

**Summary**

Background: Central sleep apnoea is a serious breathing disorder associated with poor outcomes. The remedē system (Respicare Inc., Minnetonka, MN, USA) is an implantable device which transvenously stimulates a nerve causing diaphragmatic contraction similar to normal breathing. We evaluated the safety and effectiveness of unilateral neurostimulation in patients with central sleep apnoea.

**Methods**

We recruited patients from 31 hospital-based centres in Germany, Poland, and the USA in this prospective, multicentre, randomised trial. Participants had to have been medically stable for at least 30 days and have received appropriate guideline recommended therapy, be aged at least 18 years, be expected to tolerate study procedures, and willing and able to comply with study requirements. Eligible patients with an apnoea-hypopnoea index (AHI) of at least 20 events per h, tested by a polysomnography, underwent device implantation and were randomly assigned (1:1) by a computer-generated method stratified by site to either stimulation (treatment) or no stimulation (control) for 6 months. The primary effectiveness endpoint in the intention-to-treat population was the comparison of the proportions of patients in the treatment versus control groups achieving a 50% or greater AHI reduction from baseline to 6 months, measured by a full-night polysomnography assessed by masked investigators in a core laboratory. The primary safety endpoint of 12-month freedom from serious adverse events related to the procedure, system, or therapy was evaluated in all patients. This trial is active, but not recruiting, and is registered with ClinicalTrials.gov (NCT01816776).
The remēde® System Pivotal Trial

PATIENT POPULATION

**Intention-to-Treat Population**

**Treatment (n=73)**

**Control (n=78)**

Subjects without results (n=5)
- Unrelated death (n=2)
- Patient exit (n=1)
- Medical issues (n=1)

Per Protocol defined exclusion criteria (n=6)
- Unsuccessful implant (n=2)
- Failed meeting inclusion criteria (n=3)
- Therapy programmed off (n=1)

Without 6 Month PSG results (n=4)
- Device explant (n=3)
- Missed visit (n=1)

**Per-protocol Population**

**Treatment (n=68)**

**Control (n=73)**

Subjects without results (n=5)
- Unrelated death (n=2)
- Patient exit (n=1)
- Lost to follow-up (n=1)

BASELINE DEMOGRAPHICS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT (N=73)</th>
<th>CONTROL (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 12</td>
<td>65 ± 13</td>
</tr>
<tr>
<td>Male gender</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>75.4 ± 12.6</td>
<td>72.9 ± 13.8</td>
</tr>
<tr>
<td>Blood pressure (systolic / diastolic [mmHg])</td>
<td>125.3 ± 18.3 / 74.4 ± 10.5</td>
<td>123.7 ± 17.7 / 75.3 ± 11.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.8 ± 5.3</td>
<td>31.3 ± 6.6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>40.8 ± 12.8</td>
<td>38.4 ± 12.2</td>
</tr>
<tr>
<td>Heart failure¹ (% [NYHA I / II / III / IV])</td>
<td>66% (13 / 44 / 44 / 0%)</td>
<td>62% (25 / 42 / 33 / 0%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>Concomitant cardiac device</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Apnea hypopnea index (events/hr)</td>
<td>48.8 ± 19.3</td>
<td>43.7 ± 16.8</td>
</tr>
<tr>
<td>Central apnea index (events/hr)</td>
<td>30.0 ± 18.0</td>
<td>26.6 ± 16.1</td>
</tr>
<tr>
<td>Oxygen desaturation index 4% (events/hr)</td>
<td>43.2 ± 21.7</td>
<td>37.5 ± 17.5</td>
</tr>
<tr>
<td>Rapid eye movement (%)</td>
<td>10.4 ± 7.2</td>
<td>11.8 ± 7.1</td>
</tr>
<tr>
<td>Arousal index (events/hr)</td>
<td>45.5 ± 17.9</td>
<td>43.6 ± 19.1</td>
</tr>
<tr>
<td>Epworth sleepiness scale (points)</td>
<td>10.2 ± 5.2</td>
<td>9.5 ± 5.8</td>
</tr>
</tbody>
</table>

¹ Required the investigator to assign a NYHA Class at the Baseline physical exam
Mean ± SD for continuous variables/Percent for categorical variables. All nominal p-values ≥ 0.075 except Mixed Apnea Index (p-value 0.029)
### The remedē® System Pivotal Trial

#### BASELINE MEDICATIONS

<table>
<thead>
<tr>
<th>DRUG CLASSIFICATION</th>
<th>TREATMENT (N=73)</th>
<th>CONTROL (N=78)</th>
<th>POOLED (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>67% (49)</td>
<td>65% (51)</td>
<td>66% (100)</td>
</tr>
<tr>
<td>Statin</td>
<td>64% (47)</td>
<td>60% (47)</td>
<td>62% (94)</td>
</tr>
<tr>
<td>ACE-Inhibitor</td>
<td>47% (34)</td>
<td>50% (39)</td>
<td>48% (73)</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>52% (38)</td>
<td>37% (29)</td>
<td>44% (67)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>40% (29)</td>
<td>24% (19)</td>
<td>32% (48)</td>
</tr>
<tr>
<td>Angiotensin Receptor Blocker</td>
<td>19% (14)</td>
<td>18% (14)</td>
<td>19% (28)</td>
</tr>
<tr>
<td>Oral Hypoglycemic</td>
<td>23% (17)</td>
<td>13% (10)</td>
<td>18% (27)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>18% (13)</td>
<td>17% (13)</td>
<td>17% (26)</td>
</tr>
<tr>
<td>Insulin</td>
<td>16% (12)</td>
<td>10% (8)</td>
<td>13% (20)</td>
</tr>
</tbody>
</table>

Percent (n) of subjects using a drug in the classification prior to implant procedure.

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### The remedē® System Pivotal Trial

#### PRIMARY EFFECTIVENESS ENDPOINT

<table>
<thead>
<tr>
<th>PRIMARY EFFECTIVENESS ENDPOINT</th>
<th>BETWEEN GROUP DIFFERENCE</th>
<th>TREATMENT</th>
<th>CONTROL</th>
<th>P-VALUE&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of the proportion of subjects with ≥50% reduction in AHI</td>
<td>41% (25%, 54%)</td>
<td>51% (35/68)</td>
<td>11% (8/73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<sup>1</sup> P-value from 1-sided Fisher’s Exact Test
The remedē® System Pivotal Trial

**87% OF TREATMENT PATIENTS DEMONSTRATED AN AHI IMPROVEMENT**

**PRIMARY SAFETY ENDPOINT**

91% (CI: 85%, 97%) freedom from serious adverse events associated with the implant procedure, the remedē system, or the delivered therapy at 12 months (Kaplan-Meier Estimate)

**IMPLANT METRICS**

- 97% implant success rate
- 3.4% lead revision rate
- 2.7± 0.8 hours average implant time

**No deaths related to the procedure, system or therapy**
The remédé® System Pivotal Trial

SAFETY

Kaplan-Meier Curve of Time to Death (ITT)

Kaplan-Meier Curve of Time to Cardiovascular Death (ITT)

The remédé® System Pivotal Trial
SECONDARY ENDPOINTS HIERARCHICALLY TESTED IN THE PER-PROTOCOL POPULATION

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 Months</th>
<th>Change From Baseline</th>
<th>Between Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>CAI (events/hour)</td>
<td>31.7 ± 18.6</td>
<td>26.2 ± 16.2</td>
<td>6.0 ± 9.2</td>
<td>23.3 ± 17.4</td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>49.7 ± 18.9</td>
<td>43.9 ± 17.3</td>
<td>25.9 ± 20.5</td>
<td>45.0 ± 20.3</td>
</tr>
<tr>
<td>ARI (events/hour)</td>
<td>45.6 ± 18.9</td>
<td>44.0 ± 19.5</td>
<td>25.4 ± 14.3</td>
<td>38.9 ± 19.5</td>
</tr>
<tr>
<td>Percent REM sleep</td>
<td>10.8 ± 6.6</td>
<td>11.8 ± 7.2</td>
<td>12.6 ± 8.7</td>
<td>11.2 ± 7.4</td>
</tr>
<tr>
<td>Moderate / marked PGA improvement</td>
<td>NA</td>
<td>NA</td>
<td>60% (47%, 73%)</td>
<td>6% (2%, 14%)</td>
</tr>
<tr>
<td>ODI4 (events/hour)</td>
<td>43.8 ± 21.5</td>
<td>37.3 ± 18.0</td>
<td>24.7 ± 21.0</td>
<td>40.9 ± 21.3</td>
</tr>
<tr>
<td>ESS</td>
<td>10.7 ± 5.3</td>
<td>9.3 ± 5.7</td>
<td>7.1 ± 4.1</td>
<td>9.4 ± 6.1</td>
</tr>
</tbody>
</table>

Mean ± SD for continuous and % (95% CI) for categorical

Note: The between group difference is the difference in the change from baseline.

Mean ± SD for continuous and % (95% CI) for categorical

Note: The between group difference is the difference in the change from baseline.
Conclusions

- Phrenic nerve stimulation provides **TANGIBLE AND STATISTICALLY SIGNIFICANT** benefits:
  - Treats central sleep apnea as evidenced by a large reduction in apnea hypopnea index
  - Reduces Hypoxia
  - Improves sleep quality
  - Reduces arousals

- **PATIENTS FEEL BETTER** with phrenic nerve stimulation

- The phrenic nerve stimulation system has a **STRONG SAFETY PROFILE**

- The **DATA IS CONSISTENT** among feasibility, pilot, and pivotal studies

- The phrenic nerve stimulation system works continuously and automatically **THROUGHOUT THE ENTIRE NIGHT**