Advances in the Treatment of Central Sleep Apnea in Adults

An overview of phrenic nerve stimulation with the remedē System

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Missy Jensen is employed by ZOLL | Respicardia
Agenda

- Central sleep apnea background
  - The remedē System
  - Including remedē in your treatment pathway
  - Talking to patients about remedē
  - After the implant
  - Coding & Reimbursement
Pathophysiology of Central Sleep Apnea

- During sleep, respiration is regulated by the brain whose goal is to maintain a constant blood CO₂.
- To keep CO₂ 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.

Dempsey et al. Physiol Rev 2010; 90:47-112
Orr et al. Respir Med 2017; 22, 43–52
Most patients with CSA have concomitant cardiovascular conditions

**Etiology of Central Sleep Apnea**

- **Heart Failure**, 55%
- **Stroke**, 11%
- **Idiopathic**, 12%
- **AF**, 4%
- **Heart Failure and AF**, 18%

**Heart Failure**

- 70%+ of CSA patients have heart failure and/or reduced left ventricular ejection fraction (LVEF)
- Approximately 75% of HF patients have some form of SDB
- CSA occurs in 30–50% of patients with heart failure with reduced left ventricular ejection fraction (LVEF)

**Atrial Fibrillation**

- 20+% of CSA patients have AF
- CSA occurs in 10-30% of patients with AF
- CSA confers 2- to 3-fold increase in AF risk
- Treatment for CSA associated with improved AF outcomes

Untreated CSA causes life altering levels of fatigue as well as increased health risks for patients with heart failure and atrial fibrillation

CSA is due to a loss of neural drive to breathe during sleep\(^1\)

**Untreated CSA significantly increases health risks for these patients**

- Significantly higher rates of heart failure and atrial fibrillation\(^1,6\)
- 2\(\times\) more likely to have a HF-related readmission within 6 months\(^7\)
- 2\(\times\) the mortality rate in HF patients\(^8\)

**Nighttime sleep disruptions significantly diminish quality of life\(^2,3,4,5\)**

- Severe fatigue
- Excessive daytime sleepiness
- Cognitive impairment
- Depression
- Memory deficits

CSA patients undergo **hundreds** of repeated cycles of oxygen desaturation, arousals and surges in sympathetic drive

2. Dempsey JA. Exp Physiol 2005; 90:13–24,
5. Flemons WW, Tsai W. J Allergy Clin Immunol 1997; 99:S750-S756
## Treatment Options for Central Sleep Apnea

<table>
<thead>
<tr>
<th>Medications</th>
<th>Both studied in short (&lt;3 month) studies with &lt;20 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Theophylline</td>
<td></td>
</tr>
<tr>
<td>• Acetazolamide</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygen Therapy</th>
<th>Small randomized studies show improvement in AHI, but no improvements in arousals or daytime sleepiness</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>CPAP</th>
<th>Most common CSA treatment Improvement in AHI and EF CANPAP showed no improvement in QoL or M&amp;M Stopped early for safety</th>
</tr>
</thead>
</table>

| ASV (Adaptive servo-ventilation) | Largest randomized study in CSA (n=1325) Improvement in AHI No improvement in QoL No difference in M&M, but increased cardiovascular mortality **Black box warning** & Class III recommendation against use in patients with EF <45% |

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  - Including remedē in your treatment pathway
  - Talking to patients about remedē
- After the implant
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The remedē® System brief statement

Indications for Use
The remedē® System is an implantable phrenic nerve stimulator indicated for the treatment of moderate to severe central sleep apnea (CSA) in adult patients.

Contraindications
- The remedē System is contraindicated for the following:
  - Patients with an active infection
  - Patients known to require magnetic resonance imaging (MRI)

Warnings
- Diathermy - Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (collectively referred to as diathermy) on patients implanted with the remedē System.
- Electric Shock - When operating under AC power, the remedē System Programmer must be connected to a grounded power source to avoid risk of electric shock.
- Concomitant Active Implantable Devices - Use remedē System with caution in patients with an active implantable device that may be susceptible to unintended interaction with the remedē system.
- Patients with Evidence of Phrenic Nerve Palsy - Therapy with the remedē System may be ineffective in patients who have evidence of phrenic nerve palsy.
- Pediatric Use - The safety and effectiveness of the remedē® System has not been established for pediatric use.

Precautions
It is recommended that testing for oversensing of remedē stimulation therapy by the concomitant cardiac device occur at the time of implant and prior to initiating remedē System therapy in patients with a concomitantly implanted cardiac device. Use remedē® System therapy with caution in pacemaker-dependent patients without a physiologic escape rhythm. Device interaction may lead to over or undersensing resulting in a loss of pacing. The safety and effectiveness of the remedē System during pregnancy has not been established.

See the Device Manual for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential complications/ adverse events

Adverse Effects
Possible adverse events which may be associated with the use implantation and use of the remedē® system include, but are not limited to, the following: adverse contrast dye reaction such as allergic reaction, pulmonary edema, or worsening renal function, adverse reaction to radiation exposure, thromboembolism, air embolism, bleeding, cardiac perforation including tamponade, hematoma, seroma, local bruising or swelling, hypotension, local wound healing issues at device implant site including wound dehiscence, pocket erosion, extrusion, movement of implanted device, keloid formation, pneumothorax, hemothorax, vascular damage, e.g., venous dissection, perforation, adverse biocompatibility reaction to the implanted system, infection, lead breakage, lead dislodgement, lead not connected or secured appropriately in device header, implantable device malfunction, requirement for more energy to stimulate the nerve or ineffective stimulation, venous occlusion, crosstalk with another implanted device, disrupted sleep, muscle fatigue or discomfort in diaphragm, chest or abdomen from appropriate stimulation, nerve dysfunction, perturbation of blood gases causing hypoxia, hypercapnea and/or hypocapnea, inappropriate sensations, worsening heart failure, respiratory status or overall health, anxiety, arrhythmia, including ventricular fibrillation, death, depression, hypertension, pain, skin irritation or local allergic reaction, thrombus or embolism, potentially leading to pulmonary embolism or stroke.

CAUTION: Rx only. Prior to use, please see the complete “System Implant and Clinician Use Manual” for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator’s Instructions.

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Transvenous phrenic nerve stimulation with the remedē System

- **Fully implantable system** with an indication to treat moderate to severe central sleep apnea in adults; received U.S. FDA PMA approval October 2017

- **Stabilizes breathing** by activating the diaphragm to generate negative pressure in the chest (similar to natural breathing)

- **Turns on automatically at night**, ensuring nightly compliance and adherence over time

- Implanted by cardiac electrophysiologists (EPs)
  - **Pulse generator** implanted below clavicle
  - **Stimulation lead** placed either in left pericardiophrenic or right brachiocephalic vein
  - **Sensing lead** placed in the Azygos vein, helps optimize therapy (optional)

The remedē System therapy uses stimulation pulses to mimic normal breathing.

Neurostimulation characteristics:

- **Stimulation Pulse Amplitude (milliamps):** Range from 0.1 mA to 10 mA.
- **Pulse width (microseconds):** Range from 60 μsec to 300 μsec.
- **Frequency (Hertz):** Range from 10 Hz to 40 Hz.

Abraham WT et al. JACC HF 2015;5:360-369

MedEd2399, REV C
The remedē System therapy activates automatically each night

Therapy is delivered when...

It is within the pre-programmed sleeping hours...

...AND the patient is reclined past the programmed sleeping angle...

...AND the patient is not moving

Example

11:00 pm

Therapy is paused when...

The patient sits up...

...OR the patient moves

Therapy resumes ~ 10 minutes after the patient returns to a reclined position and is once again still
Breathing stabilizes and apnea events are significantly reduced when phrenic nerve simulation is being delivered in this example.\footnote{Costanzo MR, et al., J Card Fail. 2015;21:892-902}
Changes in breathing waveforms with therapy
To demonstrate safety and efficacy and gain FDA approval, Respicardia has evaluated phrenic nerve stimulation for the treatment of CSA in 275+ patients across multiple trials:

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Subjects/Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Study</td>
<td>4 Subjects</td>
</tr>
<tr>
<td>Proof of Concept</td>
<td>10 Subjects</td>
</tr>
<tr>
<td>Lead and Algorithm Development</td>
<td>41 Subjects</td>
</tr>
<tr>
<td>Acute Feasibility (Control Night vs Therapy Night)</td>
<td>16 Subjects</td>
</tr>
<tr>
<td>Chronic Safety Study</td>
<td>8 Implanted Subjects</td>
</tr>
<tr>
<td>Pilot Study - Chronic Feasibility</td>
<td>49 Implanted Subjects</td>
</tr>
<tr>
<td>Pivotal Trial – IDE Study</td>
<td>147 Implanted Subjects</td>
</tr>
</tbody>
</table>

- The pivotal trial is the largest randomized trial thus far in CSA patients to meet its endpoints and show benefit.
- All chronic studies have shown consistent improvements in sleep metrics and quality of life.
In the pivotal RCT, the remedē System demonstrated clinically meaningful improvements in sleep, sleep apnea and quality of life

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Change from baseline</th>
<th>Between group difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% reduction in AHI</td>
<td>51%</td>
<td>11%</td>
<td>41%</td>
</tr>
<tr>
<td>CAI (events/hr)</td>
<td>-25.7 ± 18.0</td>
<td>-2.9 ± 17.7</td>
<td>-22.8 ± 17.8</td>
</tr>
<tr>
<td>Central Apnea Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (events/hr)</td>
<td>-23.9 ± 18.6</td>
<td>1.1 ± 17.6</td>
<td>-25.0 ± 18.1</td>
</tr>
<tr>
<td>Apnea Hypopnea Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ArI (events/hr)</td>
<td>-20.2 ± 18.9</td>
<td>-5.0 ± 18.1</td>
<td>-15.2 ± 18.5</td>
</tr>
<tr>
<td>Arousals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of sleep in REM</td>
<td>1.8 ± 8.2</td>
<td>-0.6 ± 7.8</td>
<td>2.4 ± 7.9</td>
</tr>
<tr>
<td>QOL – PGA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>60%</td>
<td>6%</td>
<td>55%</td>
</tr>
<tr>
<td>% patients w/ marked or moderate improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODI4 (events/hour)</td>
<td>-19.1 ± 18.4</td>
<td>3.6 ± 17.3</td>
<td>-22.7 ± 17.8</td>
</tr>
<tr>
<td>O2 Desaturation 4% below baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL – ESS&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-3.6 ± 5.6</td>
<td>+0.1 ± 4.5</td>
<td>-3.7 ± 5.0</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
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Endpoint Met?

- Yes

91% (CI: 86%,95%) freedom from serious adverse events associated with the implant procedure, device, or the delivered therapy at 12 months

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1. Primary endpoint is the proportion of subjects achieving ≥50% reduction in AHI
2. PGA = Patient global assessment
3. ESS = Epworth Sleepiness Scale, an 8-question assessment used to assess sleepiness
4. For primary endpoint, n=68 for treatment and n=73 for control; for secondary endpoints, n=58 for treatment and n=73 for control

Δ Fisher’s Exact Test.
† Mann-Whitney test for difference in change from baseline between groups.
‡ t-test for difference in change from baseline between groups.
After 24 months of therapy, an in-lab sleep study showed effective and durable results, including sustained apnea-hypopnea index (AHI) improvement and almost no central apneas.

**remedē AHI reduction**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Baseline (n=58)</th>
<th>24 months (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AHI</td>
<td>49*</td>
<td>16*</td>
</tr>
<tr>
<td>Median events/hr</td>
<td>30.1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**Potential reasons for residual events**
1. Obstructive events
2. Incomplete ventilatory capture during therapy adjustment

*Total median AHI does not sum from component medians*
remedē System treatment also resulted in significant improvements in symptoms and quality of life after 6 months of treatment\(^1\)

### Improvement in Epworth Sleepiness Scale

<table>
<thead>
<tr>
<th>Treatment (N=58)</th>
<th>Control (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

ESS Mean Change from Baseline (points) (95% confidence interval)

\(>2.5\) change in ESS is considered clinically meaningful\(^2\)

### Patient Global Assessment

- **Marked or moderate improvement**
- **Mild improvement**
- **No change**
- **Worsened**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (6-months) n=58</th>
<th>Control (6-months) n=72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>60%</td>
<td>6%</td>
</tr>
<tr>
<td>No change/worse</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>14%</td>
<td>61%</td>
</tr>
</tbody>
</table>

### Willingness to repeat

- **95%**

### Demonstrated clinically significant improvement in daytime sleepiness

79\% of patients had an improvement in quality of life with the remedē System

95\% of patients reported they would “elect to have the medical procedure again”

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Sustained Improvement in Arousal Index

Paired at 5 years

- Median change [IQR]: -14 [-22, -2] P<.001
Sustained Improvement in Sleep Architecture

- Shift away from light stage sleep (N1) to more deeper stage sleep (N2 - REM)

Paired at 5 years

N2 – REM ↑14 percentage points

N1 ↓19 percentage points
The remedē® System pivotal trial demonstrated a strong safety profile

- **91% (CI: 86%,95%)** freedom from serious adverse events associated with the implant procedure, the remedē® System, or the delivered therapy at 12 months

- All related serious adverse events resolved **without any long term sequelae**

- **No deaths** related to the procedure, system or therapy

- **97% implant success** rate, including the 42% of subjects that already had a concomitant cardiac device
Agenda

• Central sleep apnea background

• The remedē System

  • Including remedē in your treatment pathway

• Talking to patients about remedē

• After the implant

• Coding & Reimbursement
### Patient Pathway

1. **Potential Patients**
   - Awareness (prevalence & impact of SDB)
   - Pre – Screening
   - Screening/Diagnosis
   - Treatment

2. **Patient Education**

3. **Authorization & Scheduling**

4. **Implant**

5. **Monitoring / Follow Up**
Patient Identification

Which patients benefit from Remedē?
62% of patients in the remedē Pivotal Trial had an EP diagnosis

The remedē System Pivotal Trial

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>Body mass index (kg/m²)</td>
<td>30.8 ± 5.3</td>
<td>31.3 ± 6.6</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>Ejection fraction (%)</td>
<td>40.6 ± 12.8 (n=71)</td>
<td>39.4 ± 12.2 (n=75)</td>
</tr>
<tr>
<td>Ejection Fraction &lt;35%</td>
<td>24% (n=71)</td>
<td>25% (n=75)</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>HFrEF, AF, or Cardiac Device (62%)</td>
<td>66% (n=71)</td>
<td>59% (n=75)</td>
</tr>
</tbody>
</table>

¹ Required the investigator to assign a NYHA Class at the Baseline physical exam. 58% of patients had an EF <= 45%. Mean ± SD for continuous variables/Percent for categorical variables. All nominal p-values ≥ 0.075

The FDA indication for remedē is broad

FDA Indication:

- Moderate to severe CSA in adult patients
  - No requirement to have tried and failed other therapies for CSA
  - No upper limit of Apnea Hypopnea Index (AHI)
  - No upper limit of patient Body Mass Index (BMI)

Contraindications:

- Known requirement for MRI
- Active infection
Appropriate candidates for the remedē System may have events other than central apneas noted during the sleep study.

Patients for remedē therapy should have moderate-to-severe CSA with > 50% of apneas being central.

In the remedē Pivotal Trial, patients had obstructive apneas that made up ≤ 20% of apneas².

Hypopneas may be central or obstructive in nature and do not exclude patients for remedē therapy.
Composition of AHI at baseline for treatment arm subjects in the remedē pivotal trial

Baseline AHI composition of the treatment group by patient, events per hour

Pivotal trial enrollment criteria included:
- Central apnea index (CAI) more than 50% of all apneas
- Obstructive Apnea Index ≤ 20% of the total AHI
Phrenic nerve stimulation in your treatment plan

Patients who should be considered for PNS:

- CSA patients who have tried and cannot tolerate mask-based therapies
- CSA patients with persistently high AHI despite mask therapy
- CSA patients who have heart failure with reduced LVEF (<45

*Have newly diagnosed & treated patients follow-up in sleep clinic to evaluate compliance, tolerance and effectiveness of initial therapies.*
Sample Pathway

- Follow up after PAP initiation
- How will compliance be monitored past the 30-day follow up?
Patient Identification in Sleep Medicine

• Most sleep clinicians identify their first remedē patients within their existing CSA patient population
  • These may be pts not tolerating PAP therapy and/or lost to follow up
    • **PAP compliance software.**
      • From these platforms, you can identify pts having trouble with their masks, Bi-PAPs, ASVs or those not using it.
    • **Encounter reports in EMR/EHR**
      • All major EHR platforms have capability that allow you set up encounter reports without special IT rights/user settings.
    • **Sleep acquisition software.**
      • Search for ASV or BiPAP-(ST) studies
      • Search for CAI/CAHI

*Many of these reports can be set up to run automatically at given time intervals*
Agenda

• Central sleep apnea background

• The remedē System

• Including remedē in your treatment pathway

• Talking to patients about remedē

• After the implant

• Coding & Reimbursement
The following resources are available to help you talk to your patients about remedē

**Patient poster/brochures**: Information to review independently

**Demo remedē device**: Demonstrates the device dimensions and shape

**Patient conversation flip book, FAQ, and therapy card**: Facilitates conversation about remedē

**Patient liaison contact**: Connecting patients to our Patient Liaison to ask questions, attend monthly patient webinars, speak to a current remedē patient, and more!
The remedē® System implant

- Implanted in out-patient cardiac cath lab procedure
- Typical total procedure time ~ 2 hours
- Light/minimal sedation
- Most patients discharged day of procedure
- Post-procedure care similar to cardiac pacemaker implants
  - Limit extreme movement of R arm
  - Wound check ~ 1 week
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## Patient Follow Up Pathway

### Therapy Initiation
- 4-6 weeks after implant
- Device data reviewed
- Patient teaching
- Initial device programming
- Approximately 45 min-1 hour

### Optimization
- 6 weeks after therapy initiation and/or every 6-12 weeks until therapy stable
- Patient subjective assessment
- Device data review
- Programming changes made
- Decision tree for follow-up
- Approximately 30-45 minutes

### Chronic Follow-up
- Every 3-6 months following individualized programming
- Patient subjective assessment
- Device data review
- Minor programming changes
- Decision tree for follow-up
- Approximately 15-20 minutes
Device Activation, Titration and Programming Services

- Procedure codes commonly reported for device interrogation and programming

<table>
<thead>
<tr>
<th>CPT® Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0434T</td>
<td>Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea</td>
</tr>
<tr>
<td>0435T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session</td>
</tr>
<tr>
<td>0436T</td>
<td>during sleep session</td>
</tr>
</tbody>
</table>

Ensure there is a plan for ongoing patient care

Key questions:

- Where will the patient be activated? Titrated?
- Who will the patient follow long-term?
- When will the patient return for sleep studies?

Note: If you are planning to follow your patients through activation and titration, you will be asked to attend to our follow-up visit and programmer training.
Summary

- Central Sleep Apnea contributes to a harmful progressive cycle of hypoxia, arousal and sympathetic activation
- The remedē® System treats patients with CSA and improves
  - Sleep
  - Oxygenation
  - Arousals
  - Quality of life
- Additionally, the remedē® System
  - Restores and stabilizes the normal breathing pattern during sleep
  - Treats patients automatically and continually for assured patient compliance
Discussion

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