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Treatment of Central and Complex Sleep Apnea

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Conflicts of Interest

• Royalties from UPTODATE as an author and editor
• Received grant monies and was on advisory council for Jazz Pharmaceuticals (2017-2018)
Central Sleep Apnea

Common etiologies:

– Heart failure
– Stroke
– Opioid use
– PAP Emergent
– Idiopathic
Central Sleep Apnea

A diagnosis of **central sleep apnea (CSA)** requires all of the following:

– An apnea hypopnea index > 5
– Central apneas/hypopneas > 50% of the total apneas/hypopneas
– Central apneas or hypopneas ≥ 5 times per hour
– Symptoms of either excessive sleepiness or disrupted sleep
How should this be scored?

1. Obstructive sleep apnea
2. Biot’s breathing pattern
3. Central hypopneas
4. Obstructive hypopneas
5. Cheyne Stokes breathing pattern
How should this be scored?

1. Obstructive sleep apnea
2. Biot’s breathing pattern
3. Central hypopneas
4. Obstructive hypopneas
5. Cheyne Stokes breathing pattern
CSA/CSR in CHF
Cheyne Stokes Breathing and CHF

- CSB is relatively common (33%) in patients with CHF
- **Rule of Thirds**: 1/3 CSA, 1/3 OSA and 1/3 neither
- Associated with increased morbidity and mortality in patient with CHF
- May lead to sleep fragmentation and daytime sleepiness

**Risk factors:**
- Male
- Age > 60
- Higher NYHA class
- Hypocapnia during wakefulness (< 38 mm Hg)
- Atrial fibrillation
- Higher BNP levels
CENTRAL SLEEP APNEA IN HEART FAILURE (HF) PATIENT

- Nasal airflow
- $O_2$ saturation (finger sensor)
- Thoracic effort belt
- Abdominal effort belt

Time (s)

Apnea

Hyperpnea

Apnea-induced hypoxia-reoxygenation

- Endothelial dysfunction
  - Vasoconstriction, platelet aggregation
  - Thrombosis
- Left ventricular hypertrophy

Inflammation

- Smooth muscle proliferation
- Altered cardiac contractility, adverse cardiac remodeling

Cardiac myocyte hypertrophy and apoptosis

Increased heart failure arrhythmia

Sodium retention

RAAS activation

Arousal-induced norepinephrine release

Increased:
- Blood pressure, myocardial oxygen demand, blood volume

Plaque rupture, increased cardiac preload/afterload

PROGRESSION OF HEART FAILURE

Costanzo et al, J Am Coll Cardiol 2015; 65(1):72-84
Clinical Consequences of Central Sleep Apnea
Initial Cheyne Stokes Management in CHF

Maximize Medical Therapy
Other Treatments for CSB in CHF

- **PAP**
  - CPAP may work for some
  - ASV

- **Oxygen**
  - May decrease AHI and improve SpO₂
  - No long term data

- **Transplant**
  - Improves CSR, but may be delayed

- **Phrenic nerve stimulator**
  - Inserted transvenously
Recommendations for tx of sleep-disordered breathing in CHF

• If OSA predominant, CPAP is the mainstay of therapy
  • If CSA persists or emerges (>5/hr) with OSA controlled, ASV trial recommended
• If CSA predominant, CPAP trial to see if AHI<15 can be achieved
  • If not, ASV trial recommended (if EF>45%)
  • Otherwise, optimize heart failure, may consider CPAP plus oxygen or bilevel PAP with BUR
  • ? Phrenic nerve pacing
  • Avoid autotitrating devices
TREATMENT EMERGENT CSA (TECSA)

aka Complex Sleep Apnea
Treatment Emergent CSA (TECSA)

- Predominantly obstructive events on a diagnostic study with persistence or emergence of central events during PAP therapy
- Central events not better explained by another disorder
- Reported prevalence 2%-20%
- Significance and long term outcomes unknown

Baseline: has recurrent events as seen here
CPAP: continues to have similar events at all pressures
Treatment-emergent Sleep Apnea

• Development of CSA during therapy for OSA
  – Unmasking previously-existing CSA
  – Overtitration of CPAP
    • Hering-Breuer reflex
  – More effective ventilation with relief of obstruction
• Can occur with other forms of therapy as well!
  – OAT, UA surgery, tongue retaining device

Therapy Options

- Determine if there is a potential etiology for centrals
- If specific etiology found, may target that initially
- Consider drug trial
  - Reduce arousals
  - Low level evidence
- PAP therapy
  - Best CPAP and re-evaluate; monitor leak
  - ASV
TECSA may go away or start with CPAP therapy

- Prospective study
- Utilized full PSG (no split nights, no HST)
- 675 pts
- Polysomnography
  - Baseline
  - On therapeutic CPAP
  - 3 months after CPAP therapy

Eur Respir J 2011;38:329-37
TECSA may go away or start with CPAP therapy

Eur Respir J 2011;38:329-37
Natural History of TECSA

- Analysis of US telemonitoring device data at week 1 and week 13 after CPAP initiation (133,006 pts)
  - 3.5% of patients with CSA (≥ 5/h)
  - Of those: 55% were transient, 25% persistent and 19.7% emergent
  - More leaks

- Similar results seen in systematic review of literature: (5 studies):
  - 1/3 of patients with TECSA have persistence of TECSA (TPCSA)
    - Have higher CAI
    - May have lower adherence
  - Up to 4% of patients with0ot TECSA can develop delayed TECSA (D-TESCA)

Chest 2017;152(4):751-760
OPIOID INDUCED CSA
Ataxic Breathing Pattern (Biot’s)

- Methadone
- Oxycontin
- Fentanyl patch
- Suboxone
Opioid Related Sleep Disordered Breathing

- Opioid related sleep disordered breathing:
  - Central apneas including Biot’s pattern
  - Prolonged obstructive hypoventilation
  - Obstructive apneas and hypopneas
  - Mixed pattern of sleep disordered breathing
- Most commonly associated with long acting opioids
- Dose dependent relationship with narcotics
- Typically does not resolve spontaneously
- Optimal treatment not clear
  - May respond best to a reduction in dose of opioids
  - ASV treatment data used but not as effective as in CSB
ADAPTIVE SERVOVENTILATION
Adaptive Servoventilation (ASV)

- Non-invasive automated Bilevel Positive Airway Pressure Device
- Aims to stabilize respiratory drive by varying amount of pressure support
- Also called anticyclical ventilation (to patient’s own respiratory drive)
ASV: how does it work?

- Continuously tracks patient’s airflow (3-4 minute window)
- Calculates average weighted minute ventilation (Resmed) or peak flow (Respirronics)
- Device adjusts respiratory parameters to maintain 90% of calculated MV or peak flow
ASV: how does it work?

• EPAP, set or auto-titrating: maintains upper airway patency
• Variable pressure support (PS min, PS max): targets 90%-95% of minute ventilation/peak flow to stabilize ventilatory drive
• Back-up rate: kicks in during central sleep apnea (CSA) events to maintain ventilation and stabilize drive
Airflow
Rib cage
Abdomen
Inspiratory pressure
IPS (cmH₂O)
EPAP
Pressure Support
SaO₂

CHEST 2014; 146 (2): 514 - 523

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ASV devices in the US

• ResMed Ltd:
  – Variable Positive Airway Pressure [VPAP] Adapt,
  – Aircurve 10 ASV

• Phillips Respironics:
  – BiPAP autoSV Advanced
  – Dreamstation BiPAP auto SV

• Description of algorithms : Javaheri, Brown, Randerath. CHEST 2014; 146 (2): 514 - 523
What is the major difference between Resmed and Respironics ASV algorithms?

A. Target minute ventilation vs peak flow
B. Min EPAP pressure
C. Ability to provide “auto” rate
D. Min Pressure support level
What is the major difference between Resmed and Respironics ASV algorithms?

A. Target minute ventilation vs peak flow
B. Min EPAP pressure
C. Ability to provide “auto” rate
D. Min Pressure support level
<table>
<thead>
<tr>
<th></th>
<th><strong>Aircurve 10 ASV (Resmed)</strong></th>
<th><strong>Dreamstation BiPAP auto SV (Respironics)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Target parameter</td>
<td>Average weighted MV (3 min)</td>
<td>Average weighted peak insp. flow (4 min)</td>
</tr>
<tr>
<td>Threshold</td>
<td>90% MV</td>
<td>95% peak flow</td>
</tr>
<tr>
<td>Max Pressure</td>
<td>25 cm of water</td>
<td>30 cm of water</td>
</tr>
<tr>
<td>Min/Max EPAP range</td>
<td>4-15 cm of water</td>
<td>4-25 cm of water</td>
</tr>
<tr>
<td>Min PS</td>
<td>0-6 cm of water</td>
<td>0-5 cm of water</td>
</tr>
<tr>
<td>Max PS</td>
<td>5-20 cm of water</td>
<td>0-26 cm of water</td>
</tr>
<tr>
<td>RR</td>
<td>Auto (15 bpm)</td>
<td>Off, auto or range 4-30 bpm</td>
</tr>
<tr>
<td>Apnea</td>
<td>MV drop ≥75% for ≥10s</td>
<td>Flow drop ≥80%</td>
</tr>
<tr>
<td>Hypopnea</td>
<td>MV drop ≥50% for ≥10s</td>
<td>Flow drop ≥40%</td>
</tr>
<tr>
<td>Rise time</td>
<td>Automatic</td>
<td>Levels 0-3</td>
</tr>
</tbody>
</table>
Indications

• Hypocapnic or eucapnic CSA
  – Treatment emergent CSA (TECSA)
  – CSA in Heart Failure with preserved Ejection Fraction (HFpEF)
  – Opioid related CSA (O-CSA)
Contraindications

- Predominant CSA in Heart Failure with reduced EF < 45%
- Hypoventilation (OHS, NM disease, Restrictive lung dz, chest wall deformities, moderate-severe COPD)
CSA/CSR in CHF

- Initial report of ASV efficacy in 2001
  - 14 subject with chronic heart failure (NYHA III)
  - Predominant CSA on PSG
  - 4 treatment nights

AJRCCM 2001;164(4):614-9
Effect of ASV on AHI in CHF

Weight; Effect size (95% CI)
15.9%; -10.70 (-18.93, -2.47)
13.5%; -2.00 (-12.59, 8.59)
12.6%; -32.70 (-49.81, -15.59)
8.5%; -12.20 (-23.79, -0.61)
15.6%; -12.20 (-17.55, -6.85)
18.7%; -27.40 (-35.93, -18.87)
15.2%; -11.90 (-20.79, -3.01)
100%; -14.64 (-21.03, -8.25)
Effect of ASV on LVEF in CHF

- Pepperell 2003: 9.7%; 0.13 (-0.58, 0.85)
- Fietze 2008: 9.6%; -0.39 (-1.12, 0.33)
- Kasai 2010: 9.3%; 0.83 (0.08, 1.59)
- Koyama 2010: 6.0%; 1.21 (0.14, 2.28)
- Hastings 2010: 6.9%; 0.89 (-0.08, 1.85)
- Koyama 2011: 9.7%; 0.83 (0.11, 1.54)
- Oldenburg 2011: 15.2%; 0.52 (0.15, 0.89)
- Yoshihisa 2011: 12.6%; 0.38 (-0.15, 0.90)
- Haruki 2011: 8.7%; 0.62 (-0.18, 1.42)
- Randerath (in-press): 12.1%; -0.44 (-0.99, 0.12)

Pooled effect: 100%; 0.40 (0.08, 0.71)
SERVE-HF

- Design: International, multicenter, randomized, parallel group, event driven study
- Patients: 1325 patient, LVEF $\leq 45\%$ and NYHA III or IV, or II with one hospitalization for HF in past 24 months; AND predominantly central sleep apnea with AHI $\geq 15$
- Intervention: Randomized to medical management + ASV vs medical management alone (control)
- Primary end point = death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening HF

SERVE-HF results

A Primary End Point

Hazard ratio, 1.13 (95% CI, 0.97–1.31)
P = 0.10

Cumulative Probability of Event

Months since Randomization

No. at Risk
Control 659 463 365 222 136 77
ASV 666 435 341 197 122 52

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SERVE-HF results

B Death from Any Cause

Hazard ratio, 1.28 (95% CI, 1.06–1.55)
P = 0.01

C Death from Cardiovascular Causes

Hazard ratio, 1.34 (95% CI, 1.09–1.65)
P = 0.006

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Control</th>
<th>ASV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since Randomization</td>
<td>659</td>
<td>563</td>
</tr>
<tr>
<td>Control</td>
<td>666</td>
<td>555</td>
</tr>
</tbody>
</table>

Table S3. Average adaptive servo-ventilation device usage over time

<table>
<thead>
<tr>
<th>Proportion of patients with average nightly usage – %</th>
<th>Average usage (h/night)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>16.8</td>
</tr>
<tr>
<td>3 months</td>
<td>21.7</td>
</tr>
<tr>
<td>12 months</td>
<td>29.4</td>
</tr>
<tr>
<td>24 months</td>
<td>31.4</td>
</tr>
<tr>
<td>36 months</td>
<td>40.1</td>
</tr>
<tr>
<td>48 months</td>
<td>38.6</td>
</tr>
<tr>
<td>60 months</td>
<td>33.3</td>
</tr>
<tr>
<td>Total</td>
<td>26.7</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Patients</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>SDB (AHI events/hour)</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>697</td>
</tr>
<tr>
<td>≥ 30</td>
<td>627</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>= II</td>
<td>389</td>
</tr>
<tr>
<td>≥ III</td>
<td>927</td>
</tr>
<tr>
<td>Etiology of HF</td>
<td></td>
</tr>
<tr>
<td>ischemic</td>
<td>756</td>
</tr>
<tr>
<td>other</td>
<td>539</td>
</tr>
<tr>
<td>CSR</td>
<td></td>
</tr>
<tr>
<td>&lt; 20%</td>
<td>237</td>
</tr>
<tr>
<td>20-50%</td>
<td>439</td>
</tr>
<tr>
<td>&gt; 50%</td>
<td>490</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>590</td>
</tr>
<tr>
<td>≥ 70</td>
<td>735</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>male</td>
<td>1198</td>
</tr>
<tr>
<td>female</td>
<td>127</td>
</tr>
<tr>
<td>estimated GFR (ml/min/1.73 m2)</td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>686</td>
</tr>
<tr>
<td>≥ 60</td>
<td>580</td>
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<tr>
<td>Beta blockers</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1223</td>
</tr>
<tr>
<td>no</td>
<td>102</td>
</tr>
<tr>
<td>BMI (median split)</td>
<td></td>
</tr>
<tr>
<td>&lt; 28</td>
<td>648</td>
</tr>
<tr>
<td>≥ 28</td>
<td>660</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>326</td>
</tr>
<tr>
<td>≥ 30</td>
<td>743</td>
</tr>
</tbody>
</table>
SERVE-HF outstanding questions

- Mechanism for increased mortality
- Device effect or class effect?
Could ASV be offsetting benefits of CSR?

- Increased end expiratory lung volumes → better oxygenation
- Deep breathing increases vagal activity and reduces muscle sympathetic nerve activity
- Hyperventilation prevents respiratory acidosis → beneficial to heart muscle
- Respiratory pump assisting cardiac output
- Deep inspiration may overcome airflow limitations associated with airway edema
- Periodic hypoxia may offset HF associated anemia

Thorax 2012 Apr;67(4):357-60
Other potential causes

• ASV led to excess ventilation & respiratory alkalosis → electrolyte disturbances and arrhythmias

• Device effect or class effect?
  – SERVE HF: used older generation device, fixed EPAP, min PS=3
Device effect or class effect?

- Randomized controlled cross-over physiological experiment
- 14 patients with complex sleep apnea, preserved EF, on ASV
- PSG on 4 nights
- Devices: Resmed S7, Resmed S9, Respironics System one, Respironics Dreamstation

AJRCCM 2019, 199(7): Letter

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S7 was 15-40% higher
Since SERVE-HF

• Bad Oeynhausen prospective ASV registry:

• 2004-2013, HFrEF, NYHA $\geq$ II, EF $\leq$ 45%, 550 pts, (224 ASV, 326 controls):
  – No effect on survival,
  – Improved HF symptoms,
  – No effect on exercise, LVEF, BNP or ABG’s
Since SERVE-HF

CAT-HF study:

• 126 hospitalized patients with HF and moderate/severe sleep apnea,

• ASV vs medical therapy alone:
  – no improved CV outcomes at 6 months,
  – subgroup with preserved EF may have benefited (low power)

J AM Coll Cardiol 2017;69(12):1577-1587
ASV for CSA/CSR in CHF

SUMMARY

• Currently contraindicated in predominant CSA in CHF with EF ≤ 45% (especially with EF ≤ 30%)
• Could be used in CSA/CSR with preserved EF
• SERVE-HF results may be device specific
• Awaiting other studies to determine if class effect (ADVENT-HF)
CPAP vs ASV in TECSA

- ASV achieves AHI < 10 at 90 d; better than CPAP (90% vs 64%)
- Compliance, QoL and ESS similar between CPAP and ASV
ASV for TECSA SUMMARY

• TECSA is rare and usually transient
• Long term effects unknown but can lead to symptoms
• Optimizing PAP therapy to control TECSA improves sx
• ASV should be attempted in persistent TECSA (TPCSA) despite CPAP
PAP modalities in Opioid related CSA

- CPAP usually ineffective
- ASV more effective at controlling CAI

PAP modalities in Opioid related CSA

Opioid induced CSA summary

- Reducing dose of opioids/weaning off may reverse CSA
- PAP therapies success for Opioid induced CSA:
  - CPAP: 0-54%
  - BPAP ST: 33-66%
  - ASV: 60-100%
Acetazolamide for CSA

- 2 non-randomized treatment studies reported on the use of acetazolamide for primary CSA
  - 250 mg/day decreased the AHI from $37.2 \pm 23.2$ to $12.8 \pm 10.8$ in 14 patients at 1-month follow-up
  - 1000 mg/day - CAI decreased $54 \pm 29$ to $12 \pm 20$ in 6 patients after 1 week of therapy
- 1 study in CS/CHF
  - Randomized crossover with reduction in AHI
- Considered a low evidence level option
- Side effects: paresthesias, tinnitus, GI symptoms, metabolic acidosis, electrolyte imbalance
Hypnotics for CSA

- **Zolpidem**
  - decreased AHI from $30.0 \pm 18.1$ to $13.5 \pm 13.3$ ($P = 0.0001$) over 9 wks in 20 pts
  - Also has been used in high altitude without much improvement

- **Triazolam**
  - decreased AHI ($P = 0.05$), decreased CAI in 5 pts

- **Low evidence level option**
Gases – Oxygen

- Stabilizes respiratory drive
- CPAP + Oxygen reduces SDB
- Oxygen can help CSB
- Problem:
  - Usually cannot justify payment
  - Not as effective as ASV
  - No long term outcome studies
Transvenous Neurostimulation for Central Sleep Apnoea: a Randomised Controlled Trial
Maria Rosa Costanzo, Piotr Ponikowski, Shahrokh Javaheri, Ralph Augustini, Lee Goldberg, Richard Holcomb, Andrew Kao, Rami N Khayat, Olaf Oldenburg, Christoph Stellbrink, William T Abraham

- Randomized 151 pts
  - ITT 68 treatment group, 73 controls
- 50% reduction in AHI
  - Treatment (58) = 51%
  - Control (73) = 11%
- 91% had no serious AE; 37% reported a nonserious AE which resolved in 36% after reprogramming
Methods

• Prospective, multicenter, randomized controlled trial at 31 hospital-based center (university and non-university hospitals)
• 6 in Germany
• 1 in Poland
• 24 in the USA
• Designed by members of the steering committee and the funder in consultation with the US Food and Drug Administration
Eligibility

- 18 years of age
- Before the baseline assessments, patients had to have been medically stable for at least 30 days
- Have to had guideline recommended therapy appropriate for their clinical condition
- Judged by the investigator to be expected to tolerate study procedures and be willing and able to comply with all study requirements
- PSG AHI of at least 20/hr with at least 50% of events being central apneas, at least 30 total central events, and OAI 20% or lower (AASM scoring)
Methods

• All patients had a study visit 1 month after implantation.
• The system was activated in the treatment group at the 1-month visit, according to a proprietary algorithm that applied a stimulation pattern that enabled full diaphragmatic contraction while the patient continued to sleep. The ranges of pulse stimulation used were 0.1–10.0 mA for 60–300 μs at 10–40 Hz.
• Follow-up visits and assessments done at the 3-month intervals (until trial end) for a physical examination and to check the implanted device.
Study Design

CSA Patient Pool

Subjects meet study criteria

Subjects implanted & randomized 1:1

TREATMENT GROUP
Optimal medical therapy + remedē® System therapy initiation

6 months post-therapy initiation visit
Primary effectiveness endpoint assessment (PSG)

remedē® System therapy initiated

12 months post-therapy initiation visit
Primary safety endpoint

Subjects followed every 3 months until trial closure or PMA Approval

CONTROL GROUP
Optimal medical therapy + inactive remedē® System
Figure S2. Therapy Algorithm

The therapy algorithm used by the remede® System to provide phrenic nerve stimulation during sleep. The system uses time of day, activity level, and body position (upright or recumbent) to determine a potential sleeping state and, therefore, if stimulation should occur. All these parameters are adjustable and can be tailored to each patient's specific sleeping routine.
<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>Age (years)</td>
<td>65 (12)</td>
<td>65 (13)</td>
<td>65 (13)</td>
</tr>
<tr>
<td>Male</td>
<td>63 (86%)</td>
<td>72 (92%)</td>
<td>135 (89%)</td>
</tr>
<tr>
<td>White</td>
<td>70 (96%)</td>
<td>74 (95%)</td>
<td>144 (95%)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>30.8 (5.3)</td>
<td>31.3 (6.6)</td>
<td>31.1 (6.0)</td>
</tr>
<tr>
<td>Neck width (cm)*</td>
<td>42 (5)</td>
<td>43 (5)</td>
<td>42 (5)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>75.4 (12.6)</td>
<td>72.9 (13.8)</td>
<td>74.1 (13.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125.3 (18.3)</td>
<td>123.7 (17.7)</td>
<td>124.5 (17.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74.4 (10.5)</td>
<td>75.3 (11.4)</td>
<td>74.9 (11.0)</td>
</tr>
<tr>
<td>Respiration rate (breaths per min)</td>
<td>17.5 (2.9)</td>
<td>17.3 (2.6)</td>
<td>17.4 (2.7)</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index (events per h)</td>
<td>48.8 (19.3)</td>
<td>43.7 (16.8)</td>
<td>46.2 (18.2)</td>
</tr>
<tr>
<td>Central apnoea index (events per h)</td>
<td>30.0 (18.0)</td>
<td>26.6 (16.1)</td>
<td>28.2 (17.1)</td>
</tr>
<tr>
<td>Obstructive apnoea index (events per h)</td>
<td>2.6 (3.2)</td>
<td>2.3 (2.7)</td>
<td>2.4 (3.0)</td>
</tr>
<tr>
<td>Mixed apnoea index (events per h)</td>
<td>3.1 (4.1)</td>
<td>2.2 (3.3)</td>
<td>2.6 (3.7)</td>
</tr>
<tr>
<td>Hypopnoea index (events per h)</td>
<td>13.1 (11.2)</td>
<td>12.7 (11.6)</td>
<td>12.9 (11.4)</td>
</tr>
<tr>
<td>ODI4 (events per h)</td>
<td>43.2 (21.7)</td>
<td>37.5 (17.5)</td>
<td>40.2 (19.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>32 (44%)</td>
<td>32 (41%)</td>
<td>64 (42%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction†</td>
<td>39.7 (12.1)</td>
<td>39.4 (12.2)</td>
<td>39.6 (12.1)</td>
</tr>
</tbody>
</table>
## Primary Outcome

<table>
<thead>
<tr>
<th>6 months' follow-up</th>
<th>Between-group difference</th>
<th>One-sided p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (N=58)</td>
<td>Control (N=73)</td>
<td></td>
</tr>
</tbody>
</table>

**Primary endpoint**

| Patients with ≥50% reduction in apnoea-hypopnoea index from baseline* | 35 (51%, 39-64)† | 8 (11%, 5-20) | 41% (25-54) | <0.0001‡ |

Register now at [congress.chestnet.org](http://congress.chestnet.org)
Figure S4. Change in AHI for each Subject by Randomized Group and AHI reduction ≥50% versus <50% reduction (ITT with PSG data).

### Treatment SDB Indices

<table>
<thead>
<tr>
<th>Baseline</th>
<th>6 months</th>
<th>Baseline</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>AHI</td>
<td>CAI</td>
<td>CAI</td>
</tr>
<tr>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
<td>Control</td>
</tr>
</tbody>
</table>

- Treatment Group:
  - 50% Reduction (N=35)
  - <50% Reduction (N=26)
  - Baseline 6 Months
  - 6 Months

- Control Group:
  - Baseline 6 Months
  - Baseline 6 Months
  - Baseline 6 Months

Average AHI

Register now at [congress.chestnet.org](http://congress.chestnet.org)
% of pt responses to the pt global assessment
FDA News Release

FDA approves implantable device to treat moderate to severe central sleep apnea

October 6, 2017

The U.S. Food and Drug Administration today approved a new treatment option for patients who have been diagnosed with moderate to severe central sleep apnea. The Resmeda System is an implantable device that stimulates a nerve located in the chest that is responsible for sending signals to the diaphragm to stimulate breathing.

“This implantable device offers patients another treatment option for central sleep apnea,” said Tina Kiang, Ph.D., acting director of the Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices in the FDA’s Center for Devices and Radiological Health. “Patients should speak with their health care providers about the benefits and risks of this new treatment compared to other available treatments.”

Sleep apnea is a disorder that causes individuals to have one or more pauses in breathing or shallow breaths during sleep. Breathing pauses can last from a few seconds to minutes. Central sleep apnea occurs when the brain fails to send signals to the diaphragm to breathe, causing an individual to stop breathing during sleep for a period of 10 seconds or more before restarting again. According to the National Institute of Health’s National Center on Sleep Disorders Research, central sleep apnea can lead to poor sleep quality and may result in serious health issues, including an increased risk for high blood pressure, heart attack, heart failure, stroke, obesity, and diabetes. Common treatment options for moderate to severe sleep apnea include medication, positive airway pressure devices (e.g., continuous positive airway pressure machine), or surgery.
Long-Term Experience with First-Generation Implantable Neurostimulation Device in Central Sleep Apnea Treatment

HENRIK FOX, M.D., THOMAS BITTER, M.D., DIETER HORSTKOTTE, M.D., Fr. D., F.E.S.C., F.A.C.P., OLAF OLDENBURG, M.D., and KLAUS-JÜRGEN GUTLEBEN, M.D.

From the Clinic for Cardiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

Table I.

Patient Demographics and Clinical at Baseline

<table>
<thead>
<tr>
<th></th>
<th>1st Patient</th>
<th>2nd Patient</th>
<th>3rd Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>76</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.5</td>
<td>29.1</td>
<td>33.2</td>
</tr>
<tr>
<td>Heart failure type</td>
<td>HFpEF</td>
<td>HFpEF</td>
<td>HFpEF</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate, beats/min (at rest)</td>
<td>65</td>
<td>55</td>
<td>61</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>60</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>163</td>
<td>158</td>
<td>27.5</td>
</tr>
</tbody>
</table>

Battery life remedē® System

(PACE 2017; 40:498–503)
Conclusions

• Central sleep apnea most commonly seen in CHF, stroke, treatment emergent PAP therapy and opioid use
• Treatment should be targeted at underlying cause if possible (eg tx of CHF, reduction of opioids)
• TECSA may resolve over time
• ASV most effective in HFpEF, TECSA; less effective in OpCSA; should not be used in HFrEF at this time
• Phrenic nerve pacing may be appropriate for some
Thanks to Shirine Allam and Josh Roland for use of some of their slides