Sleep apnoea and heart failure

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Disclosure

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Sleep apnoea in heart failure

1. Problems with nomenclature (and perception)
2. Prevalence
3. Diagnosis (in cardiology practice)
4. Pathophysiology
5. PathophysiologicaI and clinical consequences
6. Treatment
... The only peculiarity in the last period of his illness, which lasted eight or nine days, was in the state of the respiration. For several days, his breathing was irregular; it would cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick, and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute, during which there were about thirty acts of respiration”
Sleep apnoea in heart failure
Problems with nomenclature (and perception)

Sleep Physician
Sleep disordered breathing
• obstructive sleep apnoea
• central sleep apnoea
Nomenclature accepted
Prevalent and relevant for M&M and QoL
Target for intervention
How often you investigate whether your HF patient demonstrates sleep disordered breathing (SDB) ?

1. Rarely, SDB are clinically not really relevant

2. If he/she gives me a history of snoring

3. Tend to forget about; typically, when I return from HF meetings

4. I regularly screen for SDB
Sleep apnoea in heart failure
Problems with nomenclature (and perception)

Cardiologist
Prevalent in obese & HTN pts
Snoring problem
Affecting QoL

Breathing abnormality
• Cheyne-Stokes respiration
• During sleep (also at rest)
Nomenclature accepted?
Prevalent and relevant for
M&M and QoL
Target for intervention?

Heart Failure Specialist

Sleep Physician
Sleep disordered breathing
• obstructive sleep apnoea
• central sleep apnoea
Nomenclature accepted
Prevalent and relevant for
M&M and QoL
Target for intervention
Sleep apnoea in heart failure
Problems with nomenclature (and perception)

• **Obstructive sleep apnoea**
  episodes of complete upper airway obstruction; prevalent in non-HF pts;
apnoea and hypoxia & arousals from sleep
CV consequences: hypertension, arrhythmias, myocardial ischaemia

• **Central sleep apnoea**
  temporary withdrawal of central respiratory drive
more specific and prevalent in HF
complex (unclear) pathophysiology; ominous consequences;
emerging target for intervention
Sleep apnoea in heart failure
Problems with nomenclature (and perception)

• Obstructive sleep apnoea
  episodes of complete upper airway apnoea and hypoxia & arousals from sleep
  CV consequences: hypertension, arrhythmias, myocardial ischaemia

• Central sleep apnoea
  temporary withdrawal of central respiratory drive
  complex (unclear) pathophysiology; ominous consequences; emerging target for intervention

Abdominal and chest movement without airflow indicates obstructive apnea
Lack of abdominal and chest movement indicates central apnea
Sleep apnoea in heart failure

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# Prevalence of sleep apnea in patients with HFrEF

<table>
<thead>
<tr>
<th>Country [year] Author</th>
<th>N</th>
<th>AHI ≥ 15/h</th>
<th>CSA</th>
<th>OSA</th>
<th>β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>*USA [2006] Javaheri</td>
<td>100</td>
<td>49%</td>
<td>37%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>USA [2008] MacDonald</td>
<td>108</td>
<td>61%</td>
<td>31%</td>
<td>30%</td>
<td>82%</td>
</tr>
<tr>
<td>*Canada [2007] Wang</td>
<td>287</td>
<td>47%</td>
<td>21%</td>
<td>26%</td>
<td>80%</td>
</tr>
<tr>
<td>*UK [2007] Vazir</td>
<td>55</td>
<td>53%</td>
<td>38%</td>
<td>15%</td>
<td>78%</td>
</tr>
<tr>
<td>Germany [2007] Oldenburg</td>
<td>700</td>
<td>52%</td>
<td>33%</td>
<td>19%</td>
<td>85%</td>
</tr>
<tr>
<td>*Germany [2009] Hagenah</td>
<td>50</td>
<td>64%</td>
<td>44%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>*Germany [2010] Jilek</td>
<td>273</td>
<td>64%</td>
<td>50%</td>
<td>14%</td>
<td>88%</td>
</tr>
<tr>
<td>*Portugal [2010] Ferreira</td>
<td>103</td>
<td>46%</td>
<td>NA</td>
<td>NA</td>
<td>90%</td>
</tr>
<tr>
<td>Total</td>
<td>1676</td>
<td>54%</td>
<td>34%</td>
<td>20%</td>
<td>81%</td>
</tr>
</tbody>
</table>
Sleep-disordered breathing in patients with symptomatic heart failure
A contemporary study of prevalence in and characteristics of 700 patients

Olaf Oldenburg, Barbara Lamp, Lothar Faber, Helmut Teschler, Dieter Horstkotte, Volker Töpfer

- 700 CHF pts, 561 men, age: 65 yrs
- NYHA class – 2.7, LVEF – 28%, peakVO2 – 14.4 ml/kg/min
- Therapy: 95% - ACEi/ARB, 85% - beta-blocker, 90% - diuretics
- Sleep studies with cardiorespiratory polygraphy: nasal air flow, chest and abdominal effort, pulse oximetry, snoring and body position

Prevalence of SDB (% CHF pts)

Severity of SDB (% CHF pts)
Sleep apnoea in heart failure

1. Problems with nomenclature (and perception)
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Sleep disordered breathing in HF
Diagnosis in cardiology practice

• Polysomnography („gold standard”)
  sleep study / sleep laboratory
  portable polysomnograph monitors
  polygraphy / pulse oximetry

• Questionnaires

• Other techniques
  heart rate (blood pressure) variability
  thoracic bioimpedance (pacemakers)
Patients at High Risk for Central Sleep Apnea

✓ Primary risk factors for Central Sleep Apnea
   ✓ Recent heart failure hospitalization
   ✓ Chronic fatigue
   ✓ Nocturia (> 2 per night)
   ✓ Atrial fibrillation
   ✓ Ventricular arrhythmias
   ✓ Witnessed apneas

✓ Additional risk factors (secondary)
   ✓ Male
   ✓ Elderly
   ✓ Lean
   ✓ Decreased exercise tolerance
   ✓ Low ejection fraction
   » Paroxysmal nocturnal dyspnea (PND)
   » Stroke
   » Carotid stenosis
   » Diabetes mellitus
For the cutoff level of AHI >20/h, all patients were correctly classified by the pacemaker (100% specificity and sensitivity).
Sleep apnoea in heart failure

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Pathophysiology of Cheyne-Stokes Respiration in CHF

- J – receptor stimulation ↑
- PCWP ↑
- Fluid Shift
- CHF

Many other factors:
- age, gender, hypoxia, sympathetic tone, peripheral chemoreceptor sensitivity, TLCO etc.
- Impaired feedback control:
  - circulatory delay

Respiratory Control Center

increased central CO₂ – receptor sensitivity

- hyperventilation
- arousals from sleep
- pCO₂ ↓
  - altered apnea threshold
- pCO₂ falls below apnea threshold
- central apnea
- pCO₂ exceeds apnea threshold

airflow

O. Oldenburg, HFA meeting 2011
Cycle of SDB Intertwined with Cycle of Heart Failure

- intrathoracic pressure changes
- arrhythmia (atrial fibrillation)
- myocardial ischemia
- sympathetic activation (arousals)
- inflammation, oxygen radicals
- prolonged circulation time
- hypocapnia below apneic threshold
- dyspnea hyperventilation

Heart failure

Sleep apnea with oxygen desaturations

OSA
CSA

Sleep apnoea in heart failure

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Mechanisms and Clinical Consequences of Untreated Central Sleep Apnea in Heart Failure

Maria Rosa Costanzo, MD, Rami Khayat, MD, Piotr Ponikowski, MD, Ralph Augustini, MD, Christoph Stellbrink, MD, Marcus Mianulli, BS, William T. Abraham, MD

**Apnea-induced hypoxia-reoxygenation**
- Endothelial dysfunction
  - Vasoconstriction, platelet aggregation
  - Thrombosis
- Smooth muscle proliferation
  - Left ventricular hypertrophy
- Altered cardiac contractility, adverse cardiac remodeling

**Inflammation**

**Cardiac myocyte hypertrophy and apoptosis**
- Increased heart failure arrhythmia
- Sodium retention
- RAAS activation
- Increased: Blood pressure, myocardial oxygen demand, blood volume
- Plaque rupture, increased cardiac preload/afterload

**Arousal-induced norepinephrine release**
- PROGRESSION OF HEART FAILURE
CSA Increases Mortality in Heart Failure Patients

- Relationship of increased mortality and CSA constant across all levels of severity of CSA
- Mortality increases with increased AHI in patients with SDB
- Mortality remains high even with optimal current therapies

Javaheri et al. JACC. 2007;49:2028-34
Sleep apnoea in heart failure

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Sleep Apnoea Management in Heart Failure

1. HF management optimization

2. Specific therapies:
   a. non-invasive ventilatory support (CPAP, ASV)
   b. nocturnal O$_2$ / CO$_2$ supplementation
   c. drugs: theophylline, acetazolamide
   d. devices: cardiac pacing (CRT, atrial overdrive pacing), phrenic nerve stimulation,
Positive Airway Pressure Therapies

- **CPAP (Continuous Positive Airway Pressure)**
  - CSA episodes not reduced 100% (30-50%)
  - Requires patient compliance
  - Does not affect M&M
  - May worsen heart failure

- **ASV (Adaptive Servo Ventilation)**
  - CPAP with changes in $\text{O}_2$ pressure to meet patient need
  - Pressure on right side of heart may increase
  - Compliance & tolerance ms
  - In clinical trials
A New Therapeutic Concept

Goal: Restore normal breathing at night

- Phrenic nerve stimulation can be used to modulate diaphragmatic contraction and affect breathing.

- We hypothesized that stimulation of the phrenic nerve during a central event could be used to initiate inspiration or increase inspiratory time, halting or preventing the apnoea.
Elimination of respiratory instability and improvement in oxygenation during unilateral phrenic nerve stimulation in a HF patients with central sleep apnea
The remedē® System Regularizes Breathing During Sleep

The remedē® System:

- Novel neurostimulation device *transvenously implanted* like a cardiac device
- Contracts the diaphragm via *unilateral stimulation* of the phrenic nerve
- Stabilizes carbon dioxide and *restores a normal breathing pattern*
- *Activates automatically* during sleep
remede® System Can Provide Unilateral Stimulation From Two Locations

2 stimulation locations

- Left Pericardiophrenic Vein
- Right Brachiocephalic Vein
Chest X-ray of the remedē® System with CRT-D

[USA] CAUTION: Investigational Device. Federal (or United States) law limits this device to investigational use.
The remedē® System Pilot Study: Key Effects on Sleep Parameters at 3 and 6 Months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline*</th>
<th>3 Months*</th>
<th>6 Months*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea-hypopnea index (AHI), no./hr of sleep</td>
<td>49±15</td>
<td>23±14</td>
<td>23±13</td>
<td>≤ 0.0001†</td>
</tr>
<tr>
<td>Central apnea index (CAI), no./hr of sleep</td>
<td>28±15</td>
<td>5±9</td>
<td>5±7</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Obstructive apnea index (OAI), no./hr of sleep</td>
<td>3±3</td>
<td>4±5</td>
<td>4±5</td>
<td>0.0223‡</td>
</tr>
<tr>
<td>Mixed apnea index (MAI), no./hr of sleep</td>
<td>3±4</td>
<td>0±1</td>
<td>1±2</td>
<td>&lt;0.0002†</td>
</tr>
<tr>
<td>Hypopnea index (HI), no./hr of sleep</td>
<td>15±12</td>
<td>14±9</td>
<td>14±8</td>
<td>0.0179‡</td>
</tr>
<tr>
<td>4% Oxygen desaturation index (ODI4), no./hr of sleep</td>
<td>46±19</td>
<td>22±14</td>
<td>23±13</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Arousal index, no./hr of sleep</td>
<td>36±18</td>
<td>23±11</td>
<td>25±12</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>69±17</td>
<td>77±16</td>
<td>81±13</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Rapid eye movement (REM) sleep, %</td>
<td>11±6</td>
<td>16±8</td>
<td>17±7</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

N = 44 subjects
*All values expressed as mean±SD.
† Repeated measures ANOVA.
‡ Friedman test.
Abraham et al. HFSA 2013
Randomized Controlled Pivotal Trial: Purpose and Endpoints

• Purpose: Evaluate the safety and effectiveness of the therapy delivered by the remedē System in subjects with moderate to severe central sleep apnea (CSA)

1:1 randomization, 147 subjects followed to 12 months, 25 US sites, additional OUS sites

• Primary Endpoints:

  » Effectiveness: Proportion of subjects that achieve a ≥50% reduction in AHI from baseline to 6 months post randomization (Treatment vs Control)

  » Safety: Freedom from serious adverse events (SAEs) associated with the implant procedure, the remedē System, or the delivered therapy at 12 months
Pivotal Trial Design

CSA Patient Pool

Subjects meet study criteria

Subjects implanted and randomized

Subjects followed for safety only

Treatment Group
optimal medical therapy + remedē system therapy

remedē system therapy
6-month post-randomization primary efficacy endpoint

remedē system therapy
12-month post-randomization primary safety endpoint

subject followed every 3 months until PMA approval

Control Group
optimal medical therapy

Optimal medical therapy
6-month post-randomization primary efficacy endpoint

remedē system therapy initiated

remedē system therapy x 6 months
12-month post-randomization primary safety endpoint

Subject followed every 3 months until PMA approval
Sleep apnoea in heart failure - summary

1. Present as OSA or CSA (specific for HF syndrome)
2. Prevalent (affects more than 50% HF pts), but still under-recognized among cardiologists
3. Diagnosis possible in the everyday cardiology practice
4. Ominous pathophysiological and clinical consequences (progression of the disease, increased M&M)
5. Potential therapeutic target in HF