Sleep apnea and heart failure: the role of CRT

M. Luzi (Ancona, I)

Effects of Normal Sleep

For the most part, non-rapid eye movement (NREM) sleep, which constitutes approximately 85% of total sleep time, is a state of cardiovascular relaxation. Metabolic rate, sympathetic nervous system activity, heart rate, cardiac output, and systemic vascular resistance fall, whereas vagal activity increases.

Intermittent surges in sympathetic discharge, heart rate, and blood pressure do occur in rapid eye movement (REM) sleep, but in general, REM comprises only 15% of total sleep time, and average blood pressure and heart rate remain below waking levels.
**Definitions of Terms**

**Apnea**
Cessation of airflow for more than 10 seconds

**Hypopnea**
30% reduction in airflow or thoracoabdominal movement as compared to baseline lasting at least 10 seconds, and with a >4% oxygen desaturation

**Apnea-hypopnea index**
The frequency of apneas and hypopneas per hour of sleep; a measure of the severity of sleep apnea

**Sleep apnea syndrome**
At least 10 to 15 apneas and hypopneas per hour of sleep associated with symptoms of sleep apnea, including loud snoring, restless sleep, nocturnal dyspnea, headaches in the morning, and excessive daytime sleepiness

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**Sleep Apnea Diagnosis**

- Sleep Apnea diagnosis is performed using:
  - Polygraphy (PG): detect number of events per hour
  - Polysomnography (PSG): define type of event (apnea hypopnea, obstructive Vs. central). PSG is the reference diagnostic examination
  - PSG = PG + (EEG/EOG/EMG)

- Apnea/Hypopnea Index (AHI) = Number of apneas + hypopneas per hour (sleep)
  - $5 \leq \text{AHI} < 15$ Sleep Apnea mild
  - $15 \leq \text{AHI} < 30$ Sleep Apnea moderate
  - AHI $\geq 30$ Sleep Apnea severe

- Diagnosis of SAS is confirmed for AHI $\geq 5$

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![Image of polysomnography equipment and definitions of terms]
Sleep Apnea: events definition

- **Obstructive Sleep Apnea (OSA):**
  Apnea with respiratory efforts due to collapse of superior airways

- **Central Sleep Apnea (CSA)**
  - Apnea without respiratory efforts (no CNS control on respiration)
  - Cheyne-Stokes Respiration (CSR) is a subset of CSA

- **Mixed**

![American Academy of Sleep Medicine Task Force (Sleep 1999; 22: 667-689)](image)

Obstructive Apnea/Hypopnea

- Airway obstructs
- Airway opens

- Oronasal flow
- Chest movement
- Abdomen movement
- SaO2

Blood oxygen decreases
Central Apnea/Hypopnea

SAO2

Cheyne-Stokes respiration model:

1. Low O2 (High CO2): brain increases breathing depth and rate
2. Due to circulatory delay, no change is felt, breathing depth increases
3. O2 peak reached (CO2 lowers)
4. no stimulus to breathe until the level of CO2 rises again to the “too high” level
5. CO2 rises (O2 lowers)
6. Start again at step 1

Hyperventilation

O2 / CO2

INCREASE BREATHING (decrease CO2)

DECREASE BREATHING (increase CO2)

Mechanical Effects of OSA on Heart Function

Inspiration effort with occluded upper airway

Negative Intrathoracic Pressure

Increased:
- LV transmural pressure
- RV pre-load
- RV distension
- Leftward septum movement during diastole

Impaired LV filling
- Reduced LV pre-load
- Reduced stroke volume

UA = Upper Airway

CSA and HF interaction

- CSA is characterized by repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive
- In HF patients, CSA is believed to result from a combination of:
  - increased CO2 sensitivity
  - prolonged circulation time (Circulatory Delay)

Heart Failure

Circulatory Delay

1 CO2 sensitivity

Altered Ventilatory Control

(CSA)
Prevalence of SDB in HF

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Criteria</th>
<th>Central</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Javaheri et al., 2006</td>
<td>100</td>
<td>AHI ≥ 15/h</td>
<td>49 %</td>
<td>76 %</td>
</tr>
<tr>
<td>Oldenburg et al., 2007</td>
<td>700</td>
<td>AHI &gt; 15/h</td>
<td>53 %</td>
<td>63 %</td>
</tr>
<tr>
<td>Wang et al., 2007</td>
<td>218</td>
<td>AHI &gt; 15/h</td>
<td>46 %</td>
<td>45 %</td>
</tr>
<tr>
<td>Montescano, 2007</td>
<td>139</td>
<td>AHI &gt; 15/h</td>
<td>58 %</td>
<td>89 %</td>
</tr>
<tr>
<td>Vazir et al, 2007</td>
<td>55</td>
<td>AHI &gt; 15/h</td>
<td>53 %</td>
<td>72 %</td>
</tr>
<tr>
<td>Macdonald et al., 2008</td>
<td>108</td>
<td>AHI &gt; 15/h</td>
<td>61 %</td>
<td>51 %</td>
</tr>
<tr>
<td>Yumino et al., 2009</td>
<td>218</td>
<td>AHI &gt; 15/h</td>
<td>46 %</td>
<td>45 %</td>
</tr>
</tbody>
</table>

52 % 63 % 37 %

In some HF patients, OSA and CSA coexist. In such cases, there is a gradual shift from predominantly obstructive apneas at the beginning of the night to predominantly central apneas toward its end.
Under-diagnosis of sleep apnea in patients with heart failure

Study Cohort
N=30,719

SA tested
N=572 (2%)

Not SA tested
N=30,147 (98%)

SA Dx: N=553 (97%)
No SA Dx N=19 (3%)

tested, diagnosed, not treated
N=295
tested, diagnosed, treated
N=258

Javaheri et al. Am J Respir Crit Care Med 2011

Hallmarks of CSA in HF

The pz with sleep apnea are sicker than without
Consequences of Sleep Apnea

Mortality and transplant

Outcome depending on SDB patterns in CHF

NoSDB: AH1<5/hr (N=58)

OSA with AH1 ≥ 5/hr (N=238)

CSA with AH1 ≥ 5/hr (N=98)

Chi-square log-Rank test = 11.9, p=0.003

European Journal of Heart Failure 2012

8 HF pts, median FU 51 months

CSA

No Sleep Apnea

OSA

296 CHF pts, 7 years FU

Undiagnosed HR 2.3 (95%CI 1.3–3.9, P=0.003)

Jilek, Eur J Heart Fail 2011

Prognostic Value of Nocturnal Cheyne-Stokes Respiration in CHF

n = 397 optimally treated patients, LVEF 29±7%, FU 12 months

Table 3 Cox regression results on the predictive value of periodic breathing duration adjusting for clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald y²</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB duration (per 10 min increase)</td>
<td>4.5</td>
<td>0.034</td>
<td>1.03 (1.002–1.057)</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>5.8</td>
<td>0.016</td>
<td>3.0 (1.2–7.1)</td>
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<tr>
<td>NYHA class ≥III</td>
<td>5.4</td>
<td>0.021</td>
<td>2.9 (1.2–7.1)</td>
</tr>
<tr>
<td>LVEDD (per 5 mm increase)</td>
<td>4.8</td>
<td>0.028</td>
<td>1.3 (1.03–1.57)</td>
</tr>
<tr>
<td>Heart rate (per 10 b.p.m. increase)</td>
<td>10.4</td>
<td>0.001</td>
<td>1.6 (1.2–2.0)</td>
</tr>
</tbody>
</table>

PB: periodic breathing; HR: hazard ratio; CI, confidence interval.

Pinna GD et al, Eur J Heart Fail 2009; 11: 264-272
Sleep Apnea associated with increased life threatening arrhythmias in HF

- In patients with HF, CSA and OSA are independently associated with an increased risk for ventricular arrhythmias and appropriate cardioverter-defibrillator therapies

- Increased appropriate therapies (AHI ≥ 15):
  - CSA: by 3.4-fold
  - OSA: by 2.1-fold

POPULATION: 255 CRTD pts
FU: 4 years
Primary Endpoint: event-free survival time period to first appropriate cardioverter-defibrillator therapy
PROTOCOL excluded patients undergoing CPAP

Cardiovascular consequences of Sleep Apnea

- Sudden Death
  - Sleep Apnea increases risk for VT/VF & appropriate ICD therapies by 2-3 fold\(^1,2\)
  - Sleep Apnea increases risk of nocturnal SCD compared to normals (RR: 2.57 vs 0.77)\(^3\)

- Atrial Fibrillation
  - Sleep Apnea is an independent predictor of new onset AF\(^4\), and may be a causative factor in the development of AF\(^5\)
  - Sleep Apnea increases likelihood for AF recurrence post cardioversion (from 42% to 82%)\(^6\)
  - Recurrence decreases after CPAP therapy\(^7\)

1. Bitter, EHJ. 2011
2. Tomaello, Clin Cardiol. 2010
3. Gami, NEJM 2005
4. Gami, JACC 2007
5. Mehra, AJRCCM 1997
6. Gami, Circ 2004
Sleep apnoea as a predictor of mid- and long-term outcome in patients undergoing cardiac resynchronization therapy

Beata Sredniawa*, Radoslaw Lenarczyk, Oskar Kowalski, Patrycja Pruszkowska-Skrzep, Jacek Kowalczyk, Agata Musialik-Lydka, Sylwia Cebula, and Zbigniew Kalarus

**Aims**
To assess the impact of baseline apnoea–hypopnea index (AHI) on mid-term outcome and its change after 6 months of cardiac resynchronization therapy (CRT) on remote outcome.

**Methods and results**
In 71 patients with CRT devices, Holter-derived AHI was assessed before and 6 months after the procedure. Baseline AHI > 20 was considered abnormal. After 6 months of CRT, a 50% decrease of baseline AHI was considered significant and stratified patients into AHI dippers and non-dippers, except those who preserved normal AHI. Prognostic value of baseline AHI and its change were assessed in relation to mortality and major cardiac events (MACE). More patients with an abnormal AHI died during 6 months follow-up (P = 0.02), especially due to sudden cardiac death. MACE-rate was insignificantly higher in abnormal AHI patients. Significantly higher mortality (P = 0.001), especially due to heart failure progression and higher MACE-rate (P < 0.001) during further observation were observed in AHI non-dippers. In multivariate analysis, the absence of AHI reduction was an independent predictor of mortality [hazard ratio (HR) 6.56; P = 0.015] and MACE (HR 6.03, P = 0.002).

**Conclusions**
Abnormal baseline AHI identifies patients prone to death during mid-term observation. Lack of AHI reduction after 6 months of CRT is an independent risk factor of death and MACE during further follow-up.

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Kaplan-Meier curves of cumulative survival after 6 months
AHI dippers vs. AHI non-dippers
Adjusted HR 6.56 (95% CI 5.79–7.33); P = 0.015

[Graph showing Kaplan-Meier curves]
Influence of cardiac resynchronisation therapy on different types of sleep disordered breathing

Olaf Oldenburg, Lothar Faber, Jürgen Vogt, Anja Dorszewski, Florian Szabados, Dieter Horstkotte, Barbara Lamp

Abstract

Aims: This study investigates the influence of cardiac resynchronisation therapy (CRT) on sleep disordered breathing (SDB) in patients with severe heart failure (HF).
Methods and results: Seventy-seven patients with HF (19 females; 62.6 ± 10 years) eligible for CRT were screened for presence, type, and severity of SDB before and after CRT initiation (5.3 ± 3 months) using cardiopulmonary polygraphy, NYHA class, frequency of nocturia, cardiopulmonary exercise, 6-minute walking test results, and echocardiography parameters were obtained at baseline and follow-up.
Central sleep apnoea (CSA) was documented in 36 (47%), obstructive sleep apnoea (OSA) in 26 (34%), and no SDB in 15 (19%) patients. CRT improved clinical and haemodynamic parameters. SDB parameters improved in CSA patients only (apnoea hypopnoea index: 31.2 ± 15.5 to 17.3 ± 13.7/h, p < 0.001; SaO2min: 81.8 ± 6.6 to 84.8 ± 3.3%, p = 0.02; desaturation: 6.5 ± 2.3 to 5.5 ± 0.8%, p = 0.004). Daytime capillary pCO2 was significantly lower in CSA patients compared to those without SDB with a trend towards increase with CRT (35.5 ± 4.2 to 37.9 ± 5.7 mm Hg, no).
After classifying short term clinical and haemodynamic CRT effects, improved SDB parameters in CSA occurred in responders only.
Conclusions: In patients with severe HF eligible for CRT, CSA is common and can be influenced by CRT, this improvement depends on good clinical and haemodynamic response to CRT.
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Changes in apnoea-hypopnoea index (AHI) in patients with central sleep apnoea (CSA) according to their response to cardiac resynchronization therapy (CRT)

(n= 11)  (n= 13)  (n= 12)
Cardiac Resynchronization Therapy and Obstructive Sleep-Related Breathing Disorder in Patients with Congestive Heart Failure

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and PATRICK STROLLO, M.D.†

From the *Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; †Division of Cardiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; §Pulmonary, Allergy and Critical Care Medicine, Pittsburgh, Pennsylvania; and §Epidemiology Data Center, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

Objective: To assess the impact of cardiac resynchronization therapy (CRT) with or without atrial overdrive pacing, on sleep-related breathing disorder (SRBD).

Introduction: CRT may have a positive influence on SRBD in patients who qualify for the therapy. Data are inconclusive in patients with obstructive SRBD.

Methods: Converting patients eligible for CRT underwent a baseline polysomnography (PSG) 2 weeks after implantation during which pacing was withheld. Patients with an apnea hypopnea index (AHI) ≥ 15 but < 50 were enrolled and randomized to atrial overdrive pacing (DDD) versus atrial synchronous pacing (VDD) with biventricular pacing in both arms. Patients underwent two further PSGs 12 weeks apart.

Results: Nineteen men with New York Heart Association class III congestive heart failure participated in the study (age 67.2 ± 7.3, Caucasian 78.9%, ischemic 72.7%). The score on Epworth Sleepiness Scale was 7.3 ± 4.9. Pittsburgh Sleep Quality Index 7.4 ± 3.1, and Minnesota Living with Heart Failure Questionnaire 36.0 ± 21.9. There were no differences between the groups. At baseline, patients exhibited poor sleep efficiency (66.3 ± 16.6%) with nadir oxygen saturation of 63.5 ± 5.2% and moderate to severe SRBD (AHI 21.5 ± 15.3) that was mainly obstructive (central apneas index 3.3 ± 6.7/hour). On both follow-up assessments, there was no improvement in indices of SRBD (sleep efficiency 68.3 ± 17.9%, nadir oxygen saturation 82.8 ± 4.6%, and AHI 24.9 ± 21.8).

Conclusion: In a cohort of elderly male-DHF patients receiving CRT, CRT had no impact on obstructive SRBD burden with or without atrial overdrive pacing. [PACE 2011; 24(5):453-460]

19 pz 8/19 responders to CRT FU 24 weeks

CRT effectiveness on OSA/CSA:
meta analysis

• CRT significantly reduces AHI in CSA but not OSA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Central sleep apnoea (CSA)</td>
<td></td>
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<tr>
<td>Sinha (2004)</td>
<td></td>
<td></td>
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<tr>
<td>Cohen (2005)</td>
<td></td>
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<tr>
<td>Oldenberg (2007)</td>
<td></td>
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<tr>
<td>Lutter (2008)</td>
<td></td>
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<tr>
<td>Ohlin (2010)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
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</tr>
</tbody>
</table>
| Heterogeneity: c2 = 1.42, df = 4 [P = 0.80, F = 0.03] Test for overall effect: Z = 0.03 [P = 0.00001]
| 1.2 Obstructive sleep apnoea (OSA) | | | | |
| Bianchini (2007) | | | | |
| Oldenberg (2007) | | | | |
| Shalaby (2010) | | | | |
| Subtotal (95% CI) | | | | |
| Heterogeneity: c2 = 2.55, df = 2 [P = 0.28] Test for overall effect: Z = 2.14 [P = 0.25]
| 1.3 All types of sleep apnoea (CSA, OSA, Mix) | | | | |
| Matsushita (2007) | | | | |
| Yu (2008) | | | | |
| Subtotal (95% CI) | | | | |
| Heterogeneity: c2 = 0.36, df = 4 [P = 0.83, F = 0.00001] Test for overall effect: Z = 0.49 [P = 0.00001]
| Total (95% CI) | | | | |
| Heterogeneity: c2 = 12.02, df = 9 [P = 0.05, F = 0.20] Test for subgroup differences: Z = 2.47 [P = 0.00001] Test for overall effect: Z = 2.39 [P = 0.00012] Test for subgroup differences: c2 = 0.01, df = 2 [P = 0.98, F = 0.02], 5.7%
These results suggest that the mechanism by which disease severity changes is different for OSA and CSA.

Europace (2011) 13, 1174–1179

<table>
<thead>
<tr>
<th>Study</th>
<th>Predominant type of SA</th>
<th>Baseline (AHI)</th>
<th>CRT (AHI)</th>
<th>CRT + AOP (AHI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luthje et al.11</td>
<td>CSA</td>
<td>37.1 ± 13.4</td>
<td>25.7 ± 17.3</td>
<td>29.7 ± 17.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Shablyy et al.16</td>
<td>OSA</td>
<td>20.3 ± 17.2</td>
<td>31.4 ± 28.1</td>
<td>17.5 ± 28.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

When comparing CRT + AOP with CRT alone, the addition of AOP did not significantly add to the reduction in AHI.
based on the results of this meta-analysis, we can speculate that the possible mechanism by which CRT improves AHI scores in patients with HF and SA, is to increase cardiac output. This reduces pulmonary venous pressure and therefore reduces the tendency towards hyperventilation and hypocapnia, and thus reduces AHI.

Conclusions

• Sleep Apnea is:
  – highly prevalent in HF population
  – associated with increased risk for AF and SCD
  – associated with increased mortality and morbidity in HF

• Sleep Apnea consequences can be reversed by appropriate therapy (i.e. positive air pressure therapies, optimization of pharmacological and electrical therapy in HF pz)

• But we have to better assess the breath disorders to better treat HF patients

1. Shalaby, PACE 2004
Thank you for your attention