Sleep apnea and chronic heart failure
An update on practical aspects
(December 2017)

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Comment — Thank you for inviting me to this meeting
1. Presentation & diagnosis of SA in HF patients

2. Mechanisms that potentially link SA and HF
3. Arrhythmias and mortality
4. Effect of treatment of one condition on the severity of the other
5. Conclusion and perspectives

Comment — Sleep apnea is a co-morbidity that might aggravate heart failure. In this 15 min presentation, I will focus on some critical aspects of the link between sleep apnea and heart failure.
Comment — Heart failure patients may not have sleep apnea or may present with obstructive sleep apnea, central sleep apnea, or Cheyne-Stokes respiration. These types of sleep apnea are often associated with one another.
CSA and OSA are prevalent in left ventricular dysfunction

AHI, apnea-hypopnea index

Comment — Heart failure can have any of the following presentations:

- with systolic or diastolic dysfunction, or with a preserved or reduced ejection fraction.
- Sleep apnea is highly prevalent in heart failure patients. The prevalence of each type of apnea, and their severity, are different in each of these categories.
- Please note that the more severe the heart failure is, the more central the sleep apnea is.
Clinical predictors of SA in HF patients
The SchlaHF Registry

N = 6,876 HF patients
46% with moderate-to-severe SA

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Male sex</th>
<th>Age (per 10 years)</th>
<th>BMI (per 5 units)</th>
<th>NYHA III/IV</th>
<th>LVEF (per 5% decrease)</th>
<th>Atrial fibrillation</th>
<th>OR</th>
<th>CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>SA less frequent</td>
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<td></td>
<td></td>
<td>1.90</td>
<td>(1.67;2.17)</td>
<td>&lt;0.001</td>
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<td>SA more frequent</td>
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<td>1.41</td>
<td>(1.34;1.49)</td>
<td>&lt;0.001</td>
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<td></td>
<td>1.29</td>
<td>(1.22;1.36)</td>
<td>&lt;0.001</td>
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<td></td>
<td>1.12</td>
<td>(0.99;1.27)</td>
<td>0.069</td>
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<td></td>
<td>1.10</td>
<td>(1.06;1.14)</td>
<td>&lt;0.001</td>
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<td></td>
<td></td>
<td>1.19</td>
<td>(1.06;1.34)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Arzt et al., JACC HF, 2016, 4, 116-125

NYHA: New York Heart Association; BMI: body mass index; LVEF: left ventricle ejection fraction

Comment — Clinical predictors for at least moderate sleep apnea include male sex, older age, higher BMI, higher NYHA functional classification, more severe impairment of systolic cardiac function, and atrial fibrillation. As you can see, none of these predictors is a good predictor. That’s why patients with heart failure would systematically benefit from undergoing a sleep study.
Differentiation of obstructive and central hypopneas is of diagnostic, prognostic, and therapeutic importance.

**Comment** — A critical fact to point out is the differentiation between central and obstructive events, because they have varying diagnostic, prognostic, and therapeutic consequences. This algorithm helps to differentiate obstructive from central hypopneas. Flattening of the inspiratory airflow curve, arousal position, paradoxical breathing, sleep stages, and the breathing pattern at the end of the hypopnea can each give helpful clues for the classification of hypopnea.
Let’s examine some mechanisms potentially linking sleep apnea and heart failure.
Differing effects of OSA and CSA on *stroke volume* in 40 HF patients

Stroke volume was assessed using photoplethysmography

Yumino et al., AJRCCM, 2013, 187, 433-438

Comment — Hemodynamics. Let’s focus on the differing effects of OSA and CSA on stroke volume.

- During obstructive events, stroke volume **decreased**.
- During central events, it **increased**.
- Similar variations were observed with cardiac output.

Obstructive sleep apnea appeared to have **adverse hemodynamic effects**, whereas central sleep apnea appeared to have little or slightly positive hemodynamic effects in this study.
The overnight change in leg fluid volume was measured before and after polysomnography.

Yumino et al., Circulation, 2010, 121, 1598-1605

Comment — This Canadian group showed that the overnight volume of fluid displacement from the legs to the thorax and the neck may contribute to aggravation of sleep apnea. In this study, heart failure patients were divided into 2 groups: those with obstructive-dominant sleep apnea and those with central-dominant sleep apnea.

• In both groups of patients, the overnight change in leg fluid volume correlated independently with the AHI.
• Moreover, the greater the volume of fluid displacement from the legs to the thorax and the neck, the higher the probability of central-dominant sleep apnea.

This means that the magnitude of overnight rostral fluid movement contributed not only to the severity of sleep apnea, but also to its predominant type.
Comment — There might be interplay between overnight fluid shift and the development of OSA and CSA.
- Overnight fluid shift from the legs to the neck can affect upper airway mechanics and lead to OSA.
- Fluid shift to the lungs can provoke hyperventilation, hypocapnia, and CSA.

PCWP: pulmonary capillary wedge pressure

White and Bradley, J Physiol, 2013, 591.5, 1179-1193
SA might contribute to the development and/or aggravation of HF

Comment — Sleep apnea may contribute to the development and/or aggravation of heart failure.

- Very briefly, the repeated episodes of apnea, hypoxia/reoxygenation, and arousal throughout the night are factors that lead to the pathophysiologic consequences of sleep apnea; all may contribute to worsening heart failure.
- Please note that sleep apnea comorbidities are confounders that are able to produce similar cardiovascular damage. This makes it difficult to discern whether it is the sleep apnea or the confounders that are the root cause of the cardiovascular complications associated with sleep apnea.
Let us now focus on 2 potential severe adverse effects of sleep apnea in heart failure patients – arrhythmias and mortality.

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Atrial fibrillation in HF patients with CSA

May et al., AJRCCM, 2016, 193, 783-791
N = 2,911 older (>65 y) men
Mean follow-up duration: 6 y

<table>
<thead>
<tr>
<th>CAI&lt;5</th>
<th>CAI≥5</th>
<th>No CSA-CSR</th>
<th>CSA-CSR</th>
</tr>
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<tbody>
<tr>
<td>1.00 (reference)</td>
<td>2.58 (1.18-5.66)</td>
<td>1.00 (reference)</td>
<td>2.27 (1.13-4.56)</td>
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<table>
<thead>
<tr>
<th>CAI≥5</th>
<th>CSA-CSR</th>
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<tbody>
<tr>
<td>1.79 (1.16-2.77)</td>
<td>2.23 (1.45-3.41)</td>
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Javaheri et al., AJRCCM, 2016, 193, 561-568

Comment — This slide presents a cohort of patients with CSA and those with CSA and Cheyne-Stokes respiration.

• These patients were associated with an increased risk of atrial fibrillation and incidence of heart failure.

• Conversely, OSA did not predict incidence of atrial fibrillation and was not associated with incidence of heart failure.

Whether CSA is a causative factor for heart failure, or represents an early symptom of HF, is open for speculation.
On the contrary, in this large follow-up study, OSA diagnosis and severity were independently associated with incidence of atrial fibrillation.

Cadby et al., Chest, 2015, 148, 945-952

<table>
<thead>
<tr>
<th>Predictor for incident atrial fibrillation</th>
<th>HR (95% CI)</th>
<th>p</th>
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<tbody>
<tr>
<td>AHI &gt; 5</td>
<td>1.55 (1.21-2.00)</td>
<td>&lt;0.001</td>
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N = 6,841
Follow-up duration: 12 y
### Ventricular arrhythmias in 472 HF patients with SA

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<th>Event-free survival</th>
<th>Time (months)</th>
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<tbody>
<tr>
<td></td>
<td>CSA</td>
<td>OSA</td>
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<tr>
<td><strong>CSA HR 2.15</strong>, 95% CI 1.40-3.30, p&lt;0.001</td>
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<tr>
<td><strong>OSA HR 1.69</strong>, 95% CI 1.64-1.75, p=0.001</td>
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*Bitter et al., Eur Heart J, 2011, 32, 61-74*

**Comment** — Here, heart failure patients were screened for OSA and CSA after implantation of a cardiac resynchronization device with cardioverter-defibrillator. OSA and CSA were associated with an increased independent risk of ventricular arrhythmias. This increased risk was also recently recognized in a European Task Force report.
Mortality
Post-discharge survival plot of acute HF patients
—a prospective study —

Comment — Increased mortality rates were reported in both OSA patients and CSA patients compared to those without sleep apnea in this study that followed patients post-discharge after acute heart failure. In other studies with fewer participants, CSA, but not OSA, was associated with higher mortality in HF patients.
Comment — In this study, heart failure patients were divided into those with ischemic and those with non-ischemic cardiomyopathy.

- In the ischemic group only, mortality was significantly higher in those with sleep apnea than in those without sleep apnea.
- Patients with ischemic heart failure may be more susceptible to the adverse effects of sleep apnea.
SA and HF

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Comment — Let’s now examine the effect of treatment of either condition on the severity of the other
**Optimal HF treatment** and SA severity

Effect of diuretic administration on OSA severity

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<thead>
<tr>
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<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td><strong>AHI (per h)</strong></td>
<td>115</td>
<td>15</td>
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<tr>
<td><strong>75</strong></td>
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<td></td>
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<td><strong>45</strong></td>
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<td><strong>15</strong></td>
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</table>

*Diastolic HF patients*

Effect of β blocker administration on CSA severity

<table>
<thead>
<tr>
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<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td><strong>CSA (per h)</strong></td>
<td>50</td>
<td>0.001</td>
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<tr>
<td><strong>40</strong></td>
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<td><strong>30</strong></td>
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<td><strong>20</strong></td>
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<td><strong>10</strong></td>
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*Systolic HF patients*

Comment — The first step in the management of sleep apnea with concurrent heart failure is optimization of the heart failure treatment.

- Some studies have reported a significant effect of heart failure therapy on sleep apnea severity.
- Administration of diuretic was shown to improve OSA in HF patients with hypervolemia.
- Captopril and beta-blockers reduced CSA.

*References:

Bucca et al., *Chest*, 2007, 132, 440-446

Tamura et al., *Circ J*, 2009, 73, 295-298

Walsh et al., *Br Heart J*, 1995, 73, 237-241*
**CPAP administration** improves left ventricular ejection fraction (LVEF) in HF patients with **OSA**

**Comment** — This is the result of a meta-analysis of RCT studies that showed a significant improvement in LVEF after CPAP treatment in heart failure patients with OSA.
**Effect of OSA treatment on mortality and morbidity in HF patients**

- **Cumulative event-free survival (%)**
  - Untreated OSA
  - Treated OSA
  - \( p = 0.001 \)

*Kasai et al., Chest, 2008, 133, 690-696*

**Comment** — In this non-randomized study including 88 HF patients with OSA, hospitalization-free survival was significantly greater in the 65 CPAP-treated patients than in the 23 untreated patients over 2.1 years. Unfortunately, these results are not conclusive due to the non-randomized nature of the study and its small sample size.
Adaptive servo-ventilation (ASV) for CSA in systolic HF (LVEF<45%): The SERVE study

Cowie et al., NEJM, 2015, 373, 1095-1105

**Comment** — This important study investigated the effects of adaptive servo-ventilation in heart failure patients with reduced ejection fraction below 45% and predominantly CSA.

- The primary endpoint was a composite of these variables. There was no difference between the ASV group and the control group.
- For the endpoints **death from any cause** and **death from cardiovascular cause**, there was an increase in mortality in the ASV-treated group that seemed to occur early.

Therefore, treating patients with ejection fraction <45% with ASV is deleterious. There is currently no explanation in terms of pathophysiology.
Comment — To begin the conclusion of my presentation, I will summarize a recently published European Task force report.
Comment — In heart failure patients, sleep apnea is systematically assessed.

- Optimization of medical heart failure treatment is the first step in the management of sleep apnea.
- The decision tree takes into account the level of ejection fraction (lower or greater than 45%), and the type of dominant sleep apnea (obstructive or central).
- Please note that the first line of treatment recommended, if any, is CPAP administration.
- If ejection fraction is >45% and CSA persists, treatment shifts to ASV administration.
- Conversely, if ejection fraction is less than or equal to 45%, and the AHI decreases below 15, CPAP can be continued.
- If the AHI remains at 15 or greater, it is suggested to discontinue CPAP treatment. If there are minor symptoms, the report suggests to not administer CPAP treatment.
Our understanding of the pathophysiology of the link between sleep apnea and heart failure has improved in the last 2 decades. Studies suggest that sleep apnea and heart failure might have a dangerous association due to the increased risk of arrhythmias and the excessive mortality rates in patients with both conditions. In practice, assessment and treatment of sleep apnea and heart failure require a precise description of the clinical situation and of polysomnographic pattern. Optimization of medical heart failure treatment is the first step in the management of sleep apnea. OSA is thought to contribute to heart failure, and therefore, it should be diagnosed and treated independent of heart failure. The role of adaptive servo-ventilation remains speculative until more data become available. You may have noticed that I did not mention transvenous phrenic nerves stimulation, which is also currently highly speculative.
Thank you