Sleep Apnea and Heart Failure

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Sleep Disordered Breathing (SDB) in HFrEF

700 HFrEF patients (LVEF <40%), NYHA II-IV: SDB (AHI >5/h) in 76%: 36% OSA, 40% CSA

<table>
<thead>
<tr>
<th></th>
<th>No SDB (n=169)</th>
<th>OSA (n=253)</th>
<th>CSA (n=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±11</td>
<td>65±10</td>
<td>66±11</td>
</tr>
<tr>
<td>Sex (f)</td>
<td>40%</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26±4</td>
<td>28±5</td>
<td>26±4</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.6±0.5</td>
<td>2.6±0.5</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>28±7</td>
<td>29±3</td>
<td>27±7</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>47±8</td>
<td>51±8</td>
<td>53±9</td>
</tr>
</tbody>
</table>

Sleep Disordered Breathing (SDB) in HFrEF

SDB in HFrEF

CSA
- marker of heart failure severity
- epiphenomen
- compensatory mechanism?
- therapeutic target?

OSA
- independent co-factor contributing to cardiovascular dysfunction
- consequence of congestion?
- therapeutic target?
Central Sleep Apnea (CSA) in Heart Failure

![Graph showing BNP and CSA](image)

- **BNP and CSA**
  - **p<0.0001**

- **PCWP and CSA**
  - \( r = 0.47 \)
  - \( p = 0.006 \)

SDB in HFrEF

- CSA
  - marker of heart failure severity
  - epiphenomenon
  - compensatory mechanism?
  - therapeutic target?

- OSA
  - Independent co-factor contributing to cardiovascular dysfunction
  - consequence of congestion
  - therapeutic target?
Rostral fluid shift: possible contribution to OSA

Kasai T et al. Circulation 2012;126:1495-1510
Why might OSA be relevant for HF?
OSA and HF: lines of evidence

- Pathophysiological concept
- OSA and CV risk factors
- OSA and cardiac structure/function
- OSA and CAD and AF
- OSA and HFrEF
- Effects of CPAP
OSA and HF: lines of evidence

• Pathophysiological concept
• OSA and CV risk factors
• OSA and cardiac structure/function
• OSA and CAD and AF
• OSA and HFrEF
• Effects of CPAP
Mechanisms OSA-CV dysfunction

- Cycles of *intermittent hypoxia and arousals*
  - Sympathetic nervous system activity $\uparrow$
  - Oxidative stress $\uparrow$
  - Systemic inflammation $\uparrow$
- Sleep fragmentation, sleep deprivation
- Intrathoracic pressure swings

Muscle sympathetic nerve activity in OSA

Heart rate recovery and OSA severity

Maeder MT et al. Sleep Med 2008;9:753-61
Simulated apnea (Mueller manoeuvre) and LV strain

OSA and HF: lines of evidence

- Pathophysiological concept
- OSA and CV risk factors
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- OSA and CAD and AF
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- Effects of CPAP
OSA and hypertension

• **Association** well established, problem of «confounding factors» (obesity)

• **Prevalence**↑: AHI 15 h⁻¹: 1.8-fold risk of hypertension compared to AHI 0 h⁻¹

• **Incidence**↑: 1.42 for AHI 0-1-4.9 h⁻¹, 2.03 for AHI 5-14.9 h⁻¹, and 2.89 for AHI ≥15 h⁻¹ versus AHI 0h⁻¹

• **CPAP**: established but small antihypertensive effect

Young T et al. Arch Intern Med 1997;157:1746-52
OSA and diabetes

• **Problem:** confounding factors (obesity)

• **Prevalence**↑: relative risk 2.3 for AHI 15 h\(^{-1}\) compared to AHI<5 h\(^{-1}\)

• **Incidence**↑: relative risk for diagnosis of diabetes within four years: 1.62 for AHI ≥15 h\(^{-1}\) compared to AHI <5h\(^{-1}\)

• **Prevention and treatment** of diabetes by CPAP: unknown

West SD et al. Thorax 2007;62:969-74
OSA and HF: lines of evidence

- Pathophysiological concept
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LV diastolic dysfunction

LV systolic dysfunction

LA dilatation

RV dilatation

RV hypertrophy

Pulmonary hypertension

Coronary artery disease

LV hypertrophy

LA dilatation

Atrial fibrillation

### OSA and cardiac structure and function

<table>
<thead>
<tr>
<th></th>
<th>Effect of OSA</th>
<th>Effect of CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Systolic LV function (s’, strain)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Diastolic LV function (e’)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>LA size</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Pulmonary pressure</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>RV size</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>RV function</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>RA size</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
LV mass index and OSA severity (AHI)

Effect of CPAP on LV function

LV diastolic function

LV systolic function

Butt M et al. Circ HF 2012;5:226-33
Effect of CPAP on the right heart

**Right atrial volume index**

- Graph A shows the change in right atrial volume index (RAVI) over the number of months of CPAP therapy. The index decreases with increasing therapy duration, indicated by asterisks (*) on the graph.

**Right ventricular enddiastolic diastolic diameter**

- Graph B displays the reduction in right ventricular enddiastolic diameter (RVDD) with prolonged CPAP therapy. Similar to the atrial index, the diameter decreases over time, marked by asterisks.

**Right ventricular enddiastolic volume index**

- Graph C illustrates the decrease in right ventricular enddiastolic volume index (RVEDV) across therapy periods. The index also shows a notable decline with extended treatment, signified by asterisks.

*Colish et al. Chest 2012;141:674-81*
OSA and HF: lines of evidence

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• OSA and CAD and AF
• OSA and HFrEF
• Effects of CPAP
OSA and coronary artery disease

Event-free survival

Time (months)

Treated group

Untreated group

P < 0.01

Milleron et al. Eur Heart J 2004;25:728-34
OSA and atrial fibrillation

Prevalence of AF in OSA↑

AF recurrence after PVI↓


OSA and HF: lines of evidence

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### OSA and incident heart failure

<table>
<thead>
<tr>
<th></th>
<th>AHI (Events per Hour)</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>&lt;5.0</td>
<td>5.0 to 14.9</td>
<td>15.0 to 29.9</td>
<td>≥30.0</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>829</td>
<td>644</td>
<td>282</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>No. of heart failure events</td>
<td>44</td>
<td>46</td>
<td>25</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Covariates in model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, race, BMI, smoking</td>
<td>1.00 (Referent)</td>
<td>0.96 (0.63, 1.46)</td>
<td>1.17 (0.71, 1.94)</td>
<td>1.61 (0.95, 2.71)</td>
<td>0.03</td>
</tr>
<tr>
<td>Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus</td>
<td>1.00 (Referent)</td>
<td>0.90 (0.59, 1.38)</td>
<td>1.08 (0.65, 1.80)</td>
<td>1.59 (0.94, 2.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Plus SBP, DBP, use of antihypertensive medications</td>
<td>1.00 (Referent)</td>
<td>0.88 (0.57, 1.35)</td>
<td>1.13 (0.68, 1.89)</td>
<td>1.58 (0.93, 2.66)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Gottlieb DJ et al. Circulation 2010;122:352-60
60 patients with HFrEF (LVEF ≤22%); 43 patients with AHI ≥15/h, 17 patients with AHI <15/h
Effect of CPAP on MSNA in Patients with HFrEF and OSA

17 patients with HFrEF (LVEF <45%) and SDB (AHI >20/h, predominantly OSA), randomized to CPAP for one month (n=8) vs. no CPAP (n=8)

Usui K et al. J Am Coll Cardiol 2005;45:2008-11
NE spillover and prognosis in HFrEF

Kaye DM et al. J Am Coll Cardiol 1995;26:1257-1263
Effect of CPAP on LVEF in HFrEF and OSA

24 patients with HFrEF (LVEF <45%) and OSA (AHI ≥40/h), 55 years, predominantly men, BMI ≥32 kg/m², 100% on ACEI, 50% on BB, randomized to CPAP + optimal medical treatment vs. optimal medical treatment for one month.
Effect of CPAP on LVEF in HFrEF and OSA

164 patients with HFrEF (LVEF <45%), 80% on betablocker:

- No/mild OSA (AHI <15/h; n=113)
- Untreated moderate/severe OSA (AHI ≥15/h; n=37)
- CPAP-treated moderate/severe OSA (n=14)

Moderate/severe OSA: CPAP vs. untreated: trend in favour of CPAP (p=0.07)

88 patients with HFrEF (LVEF <50%) and AHI ≥15/h (predominantly OSA; 60% on betablocker): 65 with CPAP, 23 without CPAP

p=0.03
HR ≈ 2.0

Baseline AHI
45±17/h

Baseline AHI
38±21/h

Kasai T et al. Chest 2008;133:690-6
<table>
<thead>
<tr>
<th>dilated</th>
<th>Size</th>
<th>Non-dilated</th>
</tr>
</thead>
<tbody>
<tr>
<td>eccentric</td>
<td>Remodeling</td>
<td>concentric</td>
</tr>
<tr>
<td>↓↓↓↓</td>
<td>Systolic function</td>
<td>↓</td>
</tr>
<tr>
<td>↓ bis ↓↓↓</td>
<td>Diastolic function</td>
<td>↓ bis ↓↓↓</td>
</tr>
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</table>
**Novel definition ESC 2016**

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms ± signs</td>
<td>Symptoms ± signs</td>
<td>Symptoms ± signs</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LVEF</th>
<th>&lt;40%</th>
<th>40-49%</th>
<th>≥50%</th>
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</table>

<table>
<thead>
<tr>
<th>Additional criteria</th>
<th>-</th>
<th>NP↑ +LVH/LAE</th>
<th>NP↑ +LVH/LAE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>DCM</th>
<th>Small MI + others</th>
<th>HHD + others</th>
</tr>
</thead>
</table>

Ponikowski et al. EHJ 2016 May 20 [epub ahead of print]
«phenotype diversity» in HFpEF

- Ventricular Dysfunction
  - Impaired relaxation
  - Impaired filling
  - Systolic dysfunction

- Atrial dysfunction

- Autonomic dysfunction
  - Chronotropic incompetence

- Vascular dysfunction
  - Vascular stiffening
  - Venticulo-arterial coupling

- Elevated Blood
  - Inadequate BP response to exercise
  - Pulmonary hypertension

- Valvular
  - Dynamic mitral regurgitation

- Lung Disease
  - COPD

- Lung Disease
  - Iron Deficiency
  - Anemia

- Renal Dysfunction
  - Volume Overload

- Aging & Deconditioning

- Obesity & Sarcopenia

- Psychiatric Disorders
  - Depression

- Hypertension
  - Diabetes
  - ROS Production

OSA and HF: lines of evidence

• Pathophysiological concept
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Summary: OSA and Heart Failure

- OSA associated with CV risk factors
- OSA associated with cardiac dysfunction and cardiac diseases associated with HF
- OSA associated with increased sympathetic activation in patient with and without HF
- CPAP therapy with beneficial effects on these features in patients with OSA without HF
- Improvement in LVEF following CPAP in patients with HF and reduced LVEF (very small studies)
- No conclusive data on impact of CPAP therapy on outcomes in patients with HF and reduced LVEF