Sleep Apnea: Types, Mechanisms and Clinical Cardiovascular Consequences
A Frequent Condition, but Easily Missed

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Definitions

Apnea       Cessation of airflow ≥10 seconds (missing 2 breaths)

Hypopnea    Decrease in airflow ≥10 seconds
Apnea: Cessation of airflow $\geq 10$ seconds

2 phenotypes: OSA and CSA
Sleep and Genioglossus Muscle
OA, Hypopnea and Snoring

Normal Airway

Obstructed Airway
AHI is the metric to define the presence and the severity of sleep apnea as a disorder

- **AHI**: number of events per hour of sleep
- **NI**: less than 5
- **Mild sleep apnea**: 5, <15
- **Moderate sleep apnea**: 15, < 30
- **Severe sleep apnea**: ≥30
  
  (HSAT)
Risk Factors for OSA

1. Obesity: Most important risk factor for OSA

   Neck fat (within the throat)

   Neck size
   17 in males
   16 in females

   35% of US population are obese
## Current Prevalence of OSA in USA population

<table>
<thead>
<tr>
<th>(Age, years)</th>
<th>2007-2010 Peppard/Young Am J Epidemiol, 2013</th>
<th>2015</th>
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</thead>
<tbody>
<tr>
<td><strong>Men (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI &gt; 5/hr (30-70)</td>
<td>34</td>
<td>?</td>
</tr>
<tr>
<td>AHI &gt; 15/hr (30-70)</td>
<td>13</td>
<td></td>
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<td><strong>Women (%)</strong></td>
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</tr>
<tr>
<td>AHI &gt; 15/hr (30-70)</td>
<td>6</td>
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</tbody>
</table>
34% in males and 17% in females

\[ 34\% + 17\% = \frac{51}{2} = 25\% \]

25% of 300,000,000 = 75,000,000
diagnosed sleep apnea

undiagnosed sleep apnea in general population

…..Only the “tip” has received medical attention

Few millions diagnosed sleep apnea

“undiagnosed” sleep apnea in general population
OSA a Major Public Health Issue

Cardio-metabolic consequences of OSA

- HTN
- Resistant HTN
- Pulmonary HTN
- CAD
- CHF, HFrEF and HFpEF
- A. Fib
- TIA
- Stroke
- Sudden death
- Metabolic dysregulation-Insulin Resist/DM

Huge Health Cost
Prevalence of OSA in CV Population vs. Community Based

<table>
<thead>
<tr>
<th>Condition</th>
<th>% OSA</th>
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</thead>
<tbody>
<tr>
<td>HTN</td>
<td>22-30%</td>
</tr>
<tr>
<td>Resist. HTN</td>
<td>64-70%</td>
</tr>
<tr>
<td>CAD ACS</td>
<td>40-65%</td>
</tr>
<tr>
<td>CHF</td>
<td>12-38%</td>
</tr>
<tr>
<td>Atrial Fib</td>
<td>43-49%</td>
</tr>
<tr>
<td>General population</td>
<td>13%</td>
</tr>
</tbody>
</table>

Wisconsin Sleep Study 2013

Drager, L. Am J Cardiol. 2010
Pedrosa, RP. Hypertension. 2011
Zhao LP. J Clin Sleep Med. 2014
Gami AS. Circulation. 2004

Bitter, T. Dtsch Arztebl Int. 2009
Javaheri, S. Int J Cardiol. 2006
Oldenburg, O. Eur J Heart Fail. 2007
Overnight pathophysiological consequences of OSA

Arousal:

↑ HR/BP

Apnea

Hypoxia-reoxygenation

Negative swings in juxta-cardiac Pressure
OSA

↑ HR/BP

PCO₂

Hypoxia-reoxygenation

Negative swings in juxta-cardiac Pressure
Recurrent episodes OSA (AHI=80/hr)
Biological pathways mediating CV complications of sleep apnea
Javaheri, Principles and Practice of Sleep Medicine, 2016

Cycles of sleep apnea and recovery

\( \downarrow \text{PO}_2/\uparrow \text{PCO}_2 \) \( \uparrow \text{PO}_2/\downarrow \text{PCO}_2 \)

- Low oxygen delivery to organs (\( \downarrow \text{O}_2 \) delivery) → Organ dysfunction
- Oxidative stress and inflammation
- Hypoxic and hypercapnic pulmonary vasoconstriction → Right ventricular afterload
- Sympathetic activation → Blood pressure increase, arrhythmias, myocyte toxicity
- Parasympathetic withdrawal → Heart rate increase
- Transmural pressure of all cardiac chambers (aorta, pulmonary capillary hydrostatic pressure)
  - R and L ventricular afterload
  - Arrhythmias (atrial)
  - Aortic dilatation
  - Increased lung H2O
CVD Comorbidities with OSA and Impact of Therapy with CPAP

- Resistant HTN
- A. Fib
- HF
- Mortality and SCD
Mean change in 24-h BP from 4 RCTs in Resistant HTN

- The pooled estimate shows a favorable reduction of BP with CPAP treatment in patients with resistant hypertension and OSA.
- The effect sizes are larger than those previously reported in patients with OSA without resistant hypertension.

**J Hypertens 2014 32:2341–2350**
Prevalence of secondary causes associated with resistant hypertension.

- OSA: 64.0%
- Primary Hypertension: 34.4%
- Primary Aldosteronism: 5.6%
- Renal Artery Stenosis: 2.4%
- Oral Contraceptives: 1.6%
- Renal Parenchymal Disease: 1.6%
- Thyroid Disease: 0.8%

Pedrosa et al. Hypertension. 2011
OSA as a cause and recurrence of A Fib

Negative swings in intrathoracic/juxtacardiac pressure
UAO \uparrow \text{transmural Pr}

of all cardiac chambers

Implications for A. fib and increased ventricular afterload
OSA is arrhythmogenic

1. Hypoxia

2. Acidosis

3. Increased sympathetic activity

4. Increased negative intrathoracic pressure resulting in activation of mechano receptors and ion channels

5. Upregulation of oxidative stress and inflammatory cascades
OSA and Recurrent Atrial Fibrillation

Kanagala et al., Circulation, 2003
CPAP decreases recurrence of post-ablation A Fib in OSA (Qureshi et al, Am J Cardiol, 2015)

N= 1247 OSA
CPAP= 698
No CPAP= 549
CPAP decreased recurrence rate by 44%, RR=.56 CI= .47, .68 p<.001

Heterogeneity Tau = 0.0  Chi² = 5.91, df = 7 (p = 0.55), I² = 0%
Test for overall effect Z = 6.00 (p <0.001)
Obesity begets A Fib
The link between OSA and AF

OSA
Hypoxia
Acidosis
ANS dysregulation
Atrial mechanoreceptor stimulation

Obesity

Atrial fibrillation
Heart failure comorbid with OSA

Study Cohort
N=30,719

SA tested
N=572 (2%)

SA Dx: N=553 (97%)

tested, diagnosed, not treated
N=295

tested, diagnosed, treated
N=258

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

No SA Dx N=19 (3%)

Javaheri et al. Am J Respir Crit Care Med 2011
Heart failure comorbid with OSA

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Javaheri et al. Am J Respir Crit Care Med 2011
Kaplan-Meier Survival Curves, Adjusted by Age, Gender, and Charlson Comorbidity Index, 2004-2005

Percent of Cohort Alive

Hazard ratio = .33 (95% CI = .21-.51), P <.0001

Baseline 1 2 3 4 5 6 7 8
Quarters after HF diagnosis

258 HF patients
Tested, diagnosed with sleep apnea, and treated

30,065 HF patients
Not tested and not treated for sleep apnea

258 HF patients
Tested, diagnosed with sleep apnea, and treated

30,065 HF patients
Not tested and not treated for sleep apnea
## 2 y hospitalizations, all cause mortality and mortality

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<tr>
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<th>Clinically suspected tested, diagnosed treated</th>
<th>Clinically suspected not tested not treated</th>
</tr>
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<tbody>
<tr>
<td>Patients, No (%)</td>
<td>258 (100)</td>
<td>630 (100)</td>
</tr>
<tr>
<td>Mortality, No (%)</td>
<td>20 (7.8)</td>
<td>185 (29.4)</td>
</tr>
<tr>
<td>Patients hospitalized, No (%)</td>
<td>192 (74)</td>
<td>570 (91)</td>
</tr>
<tr>
<td>Medicare payment per patient</td>
<td>42859 $</td>
<td>63747 $</td>
</tr>
<tr>
<td>Difference per patient</td>
<td>21000 $</td>
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Medicare savings

If 630 patients were all tested, diagnosed and treated with CPAP:

Cost of 2 sleep studies  1300 $
Cost of CPAP device  1200 $
Cost per patient  2500 $
Cost for 630 patients  1,6 million $
Actual cost difference for 630 patients  13,200000 $
2 y Medicare savings for 630 patients  12 million $
Probability of survival over 18 year f/u period (n=1522)

HR for all-cause mortality: 3.8 (95% CI = 1.6-9.0)
HR for CV mortality: 5.2 (CI = 1.4-19.2)

All-cause mortality with untreated SDB,
(sample excludes 126 CPAP users ) (Young, Sleep, 2008)
Day-Night Pattern of SCD

Gami, Howard, Olson, Somers NEJM 2005
HCSB breathing and CSA in HF
Treatment of CSA

Optimization of cardiac dysfunction

- Cardiac Transplantation
- Medications
- Phrenic Nerve Stimulation
- Positive Airway Pressure Devices
  - CPAP
  - Bilevel
  - ASV

- Nasal Oxygen
- Theophylline
- Acetazolamide
Transplant-free survival in SHF patients according to effect of CPAP on CSA (Artz, Circ, 2007)

- **CPAP responders**, AHI = 6.5
  - n = 57, β blocker, 81%

- **Control**, AHI = 36
  - n=130
  - β blocker, 78%

* vs. control: HR=0.36, p=0.040
Transplant-free survival in the control group and according to effect of CPAP on CSA

CPAP responders, n = 57
AHI at 3 months < 15/hr, mean=6.5

Control, n = 110
AHI at 3 months ≥ 15/hr, mean=36

CPAP non-responders, n = 43
AHI at 3 months ≥ 15/hr, mean=35

*versus control: HR=0.36, p=0.040
Changes in inspiratory pressure support during Hunter-Cheyne-Stokes breathing

- Airflow
- Rib cage
- Abdomen
- Inspiratory pressure
- IPS (cmH2O)
- EPAP
- Pressure Support
- SaO2
Study Name | Sleep Apnea | Sites | NO | Intervention | Primary Endpoints
---|---|---|---|---|---
SERVE-HF | CSA | Europe | 1325 | ASV vs conservative treatment | Morbidity and Mortality
ADVENT-HF | CSA OSA | Multinational | 860 | ASV vs conservative treatment | Morbidity and Mortality
Remede system | CSA | Multinational | 173 | PNS vs. optimal therapy | AHI reduction of 50% with PNS
Stimulation Location

- Right Phrenic Nerve
- Left Phrenic Nerve

Stimulation Sites:
- Right Brachiocephalic Vein
- Left Pericardiophrenic or Left Brachiocephalic Vein

Diaphragm
Left Pericardiophrenic Vein

Cardima Catheter in Left Pericardiophrenic Vein

Augostini et al. Heart Rhythm Society 2011
Therapy Terminates CSA

Ponikowski et al. 2011 Eur Heart J doi:10.1093/eurheartj/ehr298
“Don’t ever go to sleep. Too many people die there.”

— Mark Twain