Systemic manifestations of Sleep Apnea

Karan Madan
Department of Pulmonary medicine
PGIMER, Chandigarh
Introduction

• Growing epidemic of obesity in an aging population.

• Obstructive sleep apnea (OSA) is increasingly encountered in clinical practice.

• Various systemic manifestations of sleep apnoea have increasingly been recognised.

• Cardiovascular

• Metabolic

• Neurocognitive
Sleep apnea & Cardiovascular disease

• Acute cardiopulmonary stressors consequent to repetitive upper airway collapse.

• Ample biologic plausibility that OSA imparts increased cardiovascular risk, independent of comorbid disease.

• Observational studies have suggested strong associations with multiple disorders, such as systemic hypertension, heart failure, cardiac arrhythmias, and pulmonary hypertension.

• *Effects are cumulative over time.*
Sleep Apnea & Cardiovascular pathophysiology

• *Mechanisms*

• Acute cardiovascular (CV) stressors result from repetitive upper airway closure

• Hypoxemia

• Reoxygenation

• Swings in intrathoracic pressure

• Central nervous system (CNS) arousals

• *Daytime abnormalities in sympathetic nervous system function and heart rate variability*
Sympathetic Neural Mechanisms in Obstructive Sleep Apnea

Virend K. Somers, Mark E. Dyken, Mary P. Clary, and Francois M. Abboud
Departments of Internal Medicine and Neurology and the Cardiovascular Center, University of Iowa College of Medicine, Iowa City, Iowa 52242

- BP, HR, sympathetic nerve activity (SNA), and PSG recorded during wakefulness and sleep in 10 patients with OSA.

- Also obtained after treatment with CPAP in 4 patients.

- Awake SNA also measured in 10 age- and sex matched control subjects and in 5 obese subjects without a history of OSA.
• Peak sympathetic activity (measured over the last 10 s of each apneic event) increased during stage II sleep and during REM sleep (both $P < 0.001$).

• CPAP decreased SNA and BP during sleep ($P < 0.03$).
Hypoxemia

- Stimulation of peripheral arterial chemoreceptors.

- Increased sympathetic efferent traffic during hypoxemic stimulation.

- Demonstrated by direct peripheral intraneural electrode recordings.

- OSA - Exaggerated chemoreflex response to hypoxemic stimulation

- Resulting in acute peripheral vasoconstriction and consequent acute increases in arterial blood pressure (BP).

Reoxygenation

• Promote oxidative stress through formation of reactive oxygen species.

• A cascade that may be associated with heightened inflammation and mitochondrial dysfunction.

Am J Respir Crit Care Med Vol 162. pp 566–570, 2000

Enhanced Release of Superoxide from Polymorphonuclear Neutrophils in Obstructive Sleep Apnea
Impact of Continuous Positive Airway Pressure Therapy

RICHARD SCHULZ, SIAMAK MAHMOUDI, KATJA HATTAR, ULF SIBELIUS, HORST OLSCHEWSKI, KONSTANTIN MAYER, WERNER SEEGER, and FRIEDRICH GRIMMINGER
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Justus-Liebig-University, Gießen, Germany

OSA - “priming” of neutrophils for enhanced respiratory burst.

Might have major impact on the development of cardiovascular disorders

Virtually fully reversed by effective CPAP therapy.
Selective Activation of Inflammatory Pathways by Intermittent Hypoxia in Obstructive Sleep Apnea Syndrome
Silke Ryan, Cormac T. Taylor and Walter T. McNicholas
Circulation 2005;112;2660-2667
IHR (Intermittent hypoxia reoxygenation)

Selective activation of inflammatory over adaptive pathways
In multivariate analysis, CRP levels were independently associated with OSA severity ($F = 6.8$, $P = 0.032$).
• **Role of lung inflation**
  • Under conditions of uninterrupted ventilation, lung inflation plays a role in homeostasis.

• This sympatholysis is incomplete during the apneas and hypopneas characteristic of OSA.

• **Intrathoracic pressure swings**
  • Apneas - Marked reductions in intrathoracic pressure.

• Acute changes in PAP and blood flow and increased afterload.

• Enhanced venous return - Acute leftward septal shift and alterations in transmural cardiac pressures, with impedance of LV filling and increase in myocardial oxygen demand.

CNS Arousals

• Apneas and hypopneas terminate with CNS arousals - Sleep fragmentation and neurocognitive sequelae in OSA.

• Associated with important effects on CV function - Abrupt increases in sympathetic tone, heart rate, and BP.

• Intermediary mechanisms
  • Endothelial dysfunction in OSA - Some studies.

• Role of reduced levels of nitric oxide, in the mediation of vascular disease and BP regulation in OSA.

• Serum endothelin – Levels may be higher in patients with OSA compared with control subjects.

• Glucose intolerance, Coagulation abnormalities.


Cause and effect – Not so easy although

• Shared risk factors—Obesity and advancing age - Primary determinants of SDB, HTN, HF, and PH.

• Renders the disentanglement of the independent effects of OSA on clinical disease challenging.

• Relative paucity of high-level, evidence-based data, such as interventional treatment trials of OSA in the setting of CV disease.

• Much of the above findings - Case–control studies.

• Some have rendered negative associations between OSA and other biomarkers associated with CV risk, including serum levels of BNP and troponin T.
Plasma Brain Natriuretic Peptide in Obstructive Sleep Apnea

Anna Svatikova, BA, Abu S. Shamsuzzaman, MBBS, PhD, Robert Wolk, MD, PhD, Bradley G. Phillips, PharmD, Lyle J. Olson, MD, and Virend K. Somers, MD, PhD


Cardiac Troponin T in Obstructive Sleep Apnea

Apoor S. Gami, Anna Svatikova, Robert Wolk, Eric J. Olson, Carolyn J. Duenwald, Allan S. Jaffe and Virend K. Somers

Chest 2004;125;2097-2100
DOI 10.1378/chest.125.6.2097

Conclusions: Despite the fact that some patients with OSA may experience nocturnal ischemia, this study shows that patients with severe OSA and coexisting CAD do not have nightly episodes of myocardial injury detectable by the current-generation cardiac troponin T assay.

(CHEST 2004; 125:2097–2100)
Sleep apnea & Systemic Hypertension

- Normal individuals – Sleep - Reduced BP compared with wakefulness – “dipping” phenomenon.
- Systolic and diastolic BP may ↓ 10–15%.
- Sleep apnea - Blunts the dipping - Heightened cardiovascular risk.

- Observational studies - Hypertension and OSA often coexist and that subjects with OSA tend to have higher BPs than matched controls.

- Apnea - Acute peripheral vasoconstriction - ↑ in BP during sleep.

- Evidence mounting to support a probable causative role for OSA in diurnal hypertension as well
Prospective Study of the Association Between Sleep-Disordered Breathing and Hypertension

Paul E. Peppard, Ph.D., Terry Young, Ph.D., Mari Palta, Ph.D., and James Skatrud, M.D.

Table 3. Adjusted Odds Ratios for Hypertension at a Follow-up Sleep Study, According to the Apnea-Hypopnea Index at Base Line.*

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 events/hr†</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>0.1–4.9 events/hr</td>
<td>1.66 (1.35–2.03)</td>
<td>1.65 (1.33–2.04)</td>
<td>1.42 (1.14–1.78)</td>
<td>1.42 (1.13–1.78)</td>
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<tr>
<td>5.0–14.9 events/hr</td>
<td>2.74 (1.82–4.12)</td>
<td>2.71 (1.78–4.14)</td>
<td>2.03 (1.29–3.19)</td>
<td>2.03 (1.29–3.17)</td>
</tr>
<tr>
<td>≥15.0 events/hr</td>
<td>4.54 (2.46–8.36)</td>
<td>4.47 (2.37–8.43)</td>
<td>2.89 (1.47–5.69)</td>
<td>2.89 (1.46–5.64)</td>
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<tr>
<td>P for trend‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Effects of CPAP

• CPAP - Acutely attenuates sympathetic drive and nocturnal BP in patients with OSA.

• Data regarding effects on daytime BP - Difficult to interpret.

• Observational studies – Uncontrolled/highly select populations - Improvements in daytime BP control with the use of CPAP.

• Randomized, placebo-controlled studies - Variable results - May be the best indicator of the antihypertensive effects of CPAP

Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial

Justin C T Pepperell, Sharon Ramdasssingh-Dow, Nicky Crosthwaite, Rebecca Mullins, Crispin Jenkinson, John R Stradling, Robert J O Davies

• 118 normotensive men with OSA.

• Randomised parallel trial.

• Therapeutic or subtherapeutic nasal CPAP for 1 month.

• Primary outcome was the change in 24-h mean blood pressure.

Therapeutic CPAP ↓ MAP by 2.5 mm Hg (SE 0.8)
Subtherapeutic nCPAP ↑ by 0.8 mm Hg (0.7)
(difference −3.3 [95% CI −5.3 to −1.3]; p=0.0013, unpaired t test).

Benefit seen in both systolic and diastolic blood pressure

During both sleep and wake.

Benefit was larger in patients with more severe sleep apnoea

Independent of the baseline blood pressure.
• 60 consecutive patients with moderate to severe OSA.

• Randomly assigned to either effective or subtherapeutic nCPAP for 9 weeks on average.

• Nocturnal PSG and continuous NIBP recording for 19 hours was performed before and with treatment.

• Apneas and hypopneas reduced by 95% and 50% in the therapeutic and subtherapeutic groups, respectively.
MAP ↓ by 9.9 ± 11.4 mm Hg with effective nCPAP

No relevant change occurred with subtherapeutic nCPAP ($P<0.01$).

Mean, diastolic, and systolic blood pressures all decreased significantly both at night and during the day.

Predicted to reduce coronary heart disease event risk by 37% and stroke risk by 56%.
The Impact of Continuous Positive Airway Pressure on Blood Pressure in Patients With Obstructive Sleep Apnea Syndrome

Evidence From a Meta-analysis of Placebo-Controlled Randomized Trials

Patrick Haenijens, MD, PhD; Alain Van Meerhaeghe, MD; Antonio Moscariello, MD; Sonia De Weerdt, MD; Kris Poppe, MD, PhD; Alain Dupont, MD, PhD; Brigitte Velkeniers, MD, PhD

Table 1. Design Characteristics of the Trials Included in the Meta-analyses

<table>
<thead>
<tr>
<th>Source*</th>
<th>Site</th>
<th>Study Design</th>
<th>Study Duration, wk</th>
<th>Actively Treated Group</th>
<th>Placebo-Treated Group</th>
<th>Effective CPAP Use, h/Night†</th>
<th>Sample Size‡</th>
<th>Dropout Rate, %</th>
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</thead>
<tbody>
<tr>
<td>Engleman et al, 1996</td>
<td>Edinburgh, Scotland</td>
<td>Crossover</td>
<td>3</td>
<td>CPAP</td>
<td>Sham</td>
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<td>Dimsdale et al, 2000</td>
<td>San Diego, Calif</td>
<td>Parallel</td>
<td>1</td>
<td>CPAP</td>
<td>Sham</td>
<td>...</td>
<td>21/18</td>
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<td>Faccenda et al, 2001</td>
<td>Edinburgh</td>
<td>Crossover</td>
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<td>CPAP</td>
<td>Sham</td>
<td>3.3</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>Barbé et al, 2001</td>
<td>Multicenter study, Spain</td>
<td>Parallel</td>
<td>6</td>
<td>CPAP</td>
<td>Sham</td>
<td>...</td>
<td>29/25</td>
<td>2</td>
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<tr>
<td>Barnes et al, 2002</td>
<td>Heidelberg and Dax Park, Australia</td>
<td>Parallel</td>
<td>8</td>
<td>CPAP</td>
<td>Oral tablet</td>
<td>3.5</td>
<td>25</td>
<td>83</td>
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<tr>
<td>Becker et al, 2003</td>
<td>Marburg, Germany</td>
<td>Parallel</td>
<td>9</td>
<td>CPAP</td>
<td>Sham</td>
<td>5.5</td>
<td>16/16</td>
<td>53</td>
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<tr>
<td>Barnes et al, 2004</td>
<td>Melbourne and Adelaide, Australia</td>
<td>Crossover</td>
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<td>CPAP</td>
<td>Oral tablet</td>
<td>3.3</td>
<td>39</td>
<td>14</td>
</tr>
<tr>
<td>Robinson et al, 2005</td>
<td>Oxford</td>
<td>Crossover</td>
<td>4</td>
<td>CPAP</td>
<td>Sham</td>
<td>4.8</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Norman et al, 2006</td>
<td>San Diego</td>
<td>Parallel</td>
<td>2</td>
<td>CPAP</td>
<td>Sham</td>
<td>6.7</td>
<td>18/15</td>
<td>0</td>
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<tr>
<td>Arias et al, 2006</td>
<td>Madrid, Spain</td>
<td>Crossover</td>
<td>12</td>
<td>CPAP</td>
<td>Sham</td>
<td>6.0</td>
<td>11/10</td>
<td>1</td>
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<tr>
<td>Campos-Rodríguez et al, 2006</td>
<td>Sevilla, Spain</td>
<td>Parallel</td>
<td>4</td>
<td>CPAP</td>
<td>Sham</td>
<td>4.7</td>
<td>68</td>
<td>8</td>
</tr>
</tbody>
</table>
Study | Weighted Mean Difference (95% CI) in Net Change in 24-Hour MBP (in mm Hg) | Weight, % | Weighted Mean Difference (95% CI)
---|---|---|---
Engleman et al, 1996 | | 3.9 | -2.58 (-7.26 to 2.11)
Dimsdale et al, 2000 | | 16.0 | -1.83 (-3.36 to -0.31)
Faccenda et al, 2001 | | 15.4 | -1.00 (-2.60 to 0.60)
Barbé et al, 2001 | | 4.3 | -1.67 (-6.09 to 2.76)
Pepperell et al, 2002 | | 12.6 | -3.30 (-5.30 to -1.30)
Barnes et al, 2002 | | 3.4 | -4.43 (-5.49 to 4.62)
Becker et al, 2003 | | 1.5 | -10.50 (-18.50 to -2.40)
Barnes et al, 2004 | | 18.2 | -0.30 (-1.54 to 0.94)
Robinson et al, 2006 | | 5.8 | -0.74 (-4.40 to 2.90)
Norman et al, 2006 | | 3.9 | -7.00 (-11.66 to 2.34)
Arias et al, 2006 | | 1.7 | -0.45 (-7.82 to 6.94)
Campos-Rodriguez et al, 2006 | | 13.3 | -0.80 (-2.70 to 4.30)
Overall (95% CI) | | **100.0** | **-1.69 (-2.69 to -0.69)**

Tests for Heterogeneity $\chi^2_{11}=18.53$, $P=.07$; $I^2=41\%$
Tests for Overall Effect $z=-3.31$; $P=.001$
**IS THE EVIDENCE ENOUGH??**

- High rate of subject dropout in trials.
- Data from these subjects not included in an ITT analysis.
- Majority of subjects were treated with various antihypertensive medications.
- Most of the trials were limited to normotensive individuals.
- Further research needed on the BP-lowering properties of OSA treatment in hypertensive populations.
Cardiac Arrhythmias and Cardiovascular Mortality

- Observational studies - Association between OSA and various nocturnal arrhythmias.

**Association of Nocturnal Arrhythmias with Sleep-disordered Breathing**

The Sleep Heart Health Study

Reena Mehra, Emelia J. Benjamin, Eyal Shahar, Daniel J. Gottlieb, Rawan Nawabit, H. Lester Kirchner, Jayakumar Sahadevan, and Susan Redline

Departments of Medicine and Pediatrics, Case Western Reserve University, Cleveland, Ohio; Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; and Division of Epidemiology, University of Minnesota, Minneapolis, Minnesota

- Prevalence of arrhythmias compared in two samples of participants.
- Frequency matched on age, sex, race/ethnicity, and BMI.
- 228 subjects with SDB and 338 subjects without SDB.
Individuals with severe SDB have a 2 to 4 fold higher odds of complex arrhythmias than those without even after adjustment for potential confounders.

Similar rates of bradycardias and conduction delays between those with severe OSA and those without significant OSA.

However, Bradyarrhythmias are commonly encountered in OSA.

*Definition of abbreviations: BMI = body mass index; CHD = coronary heart disease; CI = confidence interval.
* Results of logistic regression analysis with SDB as the exposure, n = 228 with SDB and n = 338 without SDB.

Table 3. Adjusted and unadjusted odds ratios relating arrhythmia occurrence and sleep-disordered breathing.


• Bradyarrhythmias may correlate with the severity of disordered breathing.

• Can occur with a structurally normal heart.

• May be attenuated by effective CPAP therapy.
OSA & Atrial fibrillation

- Continuous cardiac monitoring with an atrial defibrillator.
- Nearly 75% of episodes of persistent AF in patients with OSA occurred in the overnight hours (8 P.M.–8 A.M.)
  

- Nocturnal hypoxemia associated with OSA influences the incidence of atrial fibrillation.
  

Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation

Ravi Kanagala, MD; Narayana S. Murali, MD; Paul A. Friedman, MD; Naser M. Ammash, MD; Bernard J. Gersh, MB ChB, DPhil; Karla V. Ballman, PhD; Abu S.M. Shamsuzzaman, MD, PhD; Virend K. Somers, MD, PhD

Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean±SD).

Figure 2. Relationship between oxygen saturation and recurrence of AF in OSA patients. A box-plot comparison of percent fall in nocturnal O₂ saturation (left) and percent of night with O₂ saturations <90% (right) between the untreated OSA patients with recurrence of AF and those without (mean±SD).
• Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without a polysomnographic diagnosis of sleep apnea.

• Appropriate treatment with CPAP in OSA patients is associated with lower recurrence of AF.

• *Are the results conclusive enough?*

• None of these observational data can convincingly implicate OSA as an independent cause of new onset atrial fibrillation.

• Additional longitudinal cohort studies and outcome based interventional trials are needed to characterize the relationship between OSA and atrial arrhythmias.
Ventricular arrhythmias & OSA

Ventricular arrhythmias have been reported in patients with OSA

Causative role for OSA in serious arrhythmias or sudden death not been definitively proven.

Risk of sudden death from cardiac causes in the general population Peaks - 6 a.m. to noon , Nadir - Midnight to 6 a.m.
Study suggests that OSA may influence time of sudden cardiac death.

Does not clearly demonstrate that OSA heightens the risk of sudden death from cardiac causes.
Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study

Jose M Marin, Santiago J Carrizo, Eugenio Vicente, Alvar G N Agusti

<table>
<thead>
<tr>
<th></th>
<th>Healthy men (n=264)</th>
<th>Simple snorers (n=377)</th>
<th>Untreated mild-moderate OSAH (n=403)</th>
<th>Untreated severe OSAH (n=235)</th>
<th>OSAH treated with CPAP (n=372)</th>
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</thead>
<tbody>
<tr>
<td>Non-fatal cardiovascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>12</td>
<td>22</td>
<td>36</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td>Events per 100 person years</td>
<td>0.45</td>
<td>0.58</td>
<td>0.89</td>
<td>2.13*</td>
<td>0.64</td>
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<td>Cardiovascular death</td>
<td></td>
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<td></td>
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<tr>
<td>Number of events</td>
<td>8</td>
<td>13</td>
<td>22</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Events per 100 person years</td>
<td>0.3</td>
<td>0.34</td>
<td>0.55</td>
<td>1.06†</td>
<td>0.35</td>
</tr>
</tbody>
</table>

OSAH = obstructive sleep apnoea-hypopnoea syndrome; CPAP = continuous positive airway pressure. *p < 0.0001 versus healthy men; †p = 0.0012.

Table 2: Incidence of cardiovascular events during the 10-year follow-up in healthy men, snorers, and patients untreated and treated for OSAH

Lancet 2005; 365: 1046–53
Figure 2: Cumulative percentage of individuals with new fatal (A) and non-fatal (B) cardiovascular events in each of the five groups studied.
Study - Among the most persuasive to argue that OSA has detrimental effects on long-term CV outcomes.

**IMPLICATIONS**

Biased by potential and difficult-to-measure influences related to treatment noncompliance

Imbalances in some confounding variables at baseline (such as prevalence of hypertension and glucose intolerance).
OSA & Cerebrovascular disease

• Associations reported primarily in cross-sectional and case-control studies.

• Unclear if OSA is a direct contributor to stroke incidence.

• Comorbidities and risk factors are commonly seen in both diseases.

• INVESTIGATING THE RELATIONSHIP

• Snoring and risk of cardiovascular disease in women.

• Prospective study - Self-reported snoring is an independent risk factor for stroke in women.
• Hypotheses - SDB is associated with an increased prevalence of stroke and also with an increased incidence of stroke.

• For first hypothesis - Cross-sectional analysis of the Wisconsin Sleep Cohort Study (1475 pts).

• For second hypothesis - Longitudinal analysis of the same cohort (1189 pts).

Am J Respir Crit Care Med Vol 172. pp 1447–1451, 2005
### TABLE 2. ADJUSTED ODDS RATIOS FOR THE PREVALENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA–HYPOPNEA INDEX

<table>
<thead>
<tr>
<th>AHI (events/h)</th>
<th>Model 1A</th>
<th>p Value</th>
<th>Model 2A</th>
<th>p Value</th>
<th>Model 3A</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5*</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥ 5 to &lt; 20</td>
<td>0.50 (0.11–2.33)</td>
<td>0.38</td>
<td>0.48 (0.10–2.27)</td>
<td>0.36</td>
<td>0.49 (0.10–2.81)</td>
<td>0.36</td>
</tr>
<tr>
<td>≥ 20</td>
<td>4.33 (1.32–14.24)</td>
<td>0.02</td>
<td>3.87 (1.19–12.63)</td>
<td>0.02</td>
<td>3.83 (1.17–12.56)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; OR = odds ratio.

* This category served as the reference group.

### TABLE 3. ADJUSTED ODDS RATIOS FOR THE INCIDENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA–HYPOPNEA INDEX

<table>
<thead>
<tr>
<th>AHI (events/h)</th>
<th>Model 1B</th>
<th>p Value</th>
<th>Model 2B</th>
<th>p Value</th>
<th>Model 3B</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5*</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥ 5 to &lt; 20</td>
<td>0.40 (0.05–3.18)</td>
<td>0.39</td>
<td>0.35 (0.05–2.69)</td>
<td>0.31</td>
<td>0.29 (0.04–2.36)</td>
<td>0.25</td>
</tr>
<tr>
<td>≥ 20</td>
<td>4.31 (1.31–14.15)</td>
<td>0.02</td>
<td>4.48 (1.31–15.33)</td>
<td>0.02</td>
<td>3.08 (0.74–12.81)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Table 2.

* This category served as the reference group.
Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

H. Klar Yaggi, M.D., M.P.H., John Concato, M.D., M.P.H., Walter N. Kernan, M.D., Judith H. Lichtman, Ph.D., M.P.H., Lawrence M. Brass, M.D., and Vahid Mohsenin, M.D.

Longitudinal data (mean follow-up, 3.4 yr)

More than 1,000 patients with preexisting OSA.

Table 2. Unadjusted and Adjusted Hazard Ratios for the Risk of Stroke or Death from Any Cause.*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.09 (1.06–1.11)</td>
<td>1.08 (1.06–1.11)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.99 (0.62–1.60)</td>
<td>0.78 (0.48–1.28)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (reference group)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>0.96 (0.39–2.38)</td>
<td>0.98 (0.39–2.46)</td>
</tr>
<tr>
<td>Other</td>
<td>0.91 (0.42–1.98)</td>
<td>0.94 (0.43–2.05)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>0.99 (0.97–1.02)</td>
<td>0.99 (0.96–1.02)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.21 (0.90–1.64)</td>
<td>1.46 (0.78–2.98)</td>
</tr>
<tr>
<td>Current consumption of alcohol</td>
<td>1.03 (0.86–1.22)</td>
<td>0.94 (0.75–1.18)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.56 (1.02–2.59)</td>
<td>1.31 (0.76–2.26)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.56 (0.79–3.12)</td>
<td>0.91 (0.45–1.86)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.04 (0.64–1.68)</td>
<td>1.01 (0.61–1.66)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.48 (0.95–2.28)</td>
<td>1.19 (0.75–1.90)</td>
</tr>
<tr>
<td>Obstructive sleep apnea syndrome</td>
<td>2.24 (1.30–3.86)</td>
<td>1.97 (1.12–3.48)</td>
</tr>
</tbody>
</table>

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).*

<table>
<thead>
<tr>
<th>Severity of Syndrome</th>
<th>Stroke or Death</th>
<th>Mean Follow-up Period (yr)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Patients</td>
<td></td>
</tr>
<tr>
<td>AHI ≤3 (reference score)</td>
<td>13</td>
<td>271</td>
<td>3.08</td>
</tr>
<tr>
<td>AHI 4–12</td>
<td>21</td>
<td>258</td>
<td>3.06</td>
</tr>
<tr>
<td>AHI 13–36</td>
<td>20</td>
<td>243</td>
<td>3.09</td>
</tr>
<tr>
<td>AHI &gt;36</td>
<td>34</td>
<td>250</td>
<td>2.78</td>
</tr>
</tbody>
</table>
• Not powered to detect potential differences related to treatment of OSA.

• In contrast to findings in the Marin cohort, there did not appear to be treatment effects in more than half of patients who were either treated with CPAP, lost weight, or underwent upper airway surgery.

• OTHER WAY ROUND – Stroke may itself predispose to sleep-disordered breathing. (Case – control studies).

• *Possible mechanisms* ??
• Disruption of central respiratory control mechanisms.

• Central sleep apnea or brainstem-mediated upper airway reflexes that may cause obstructive apneas or hypopneas.

**Time Course of Sleep-related Breathing Disorders in First-Ever Stroke or Transient Ischemic Attack**

OLGA PARRA, ADRIÁ ARBOIX, SIRAJ BECHICH, LUIS GARCÍA-EROLÉS, JOSEP M. MONTSERRAT, JOSEP ANTONI LOPEZ, EUGENI BALLESTER, JOSEP M. GUERRA, and JUAN JOSE SOPEÑA

Servei de Pneumologia and Neurology, Hospital del Sagrat Cor, Barcelona, Spain; and Institut Clínic de Pneumologia i Cirurgia Toràctica (ICPCT), Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Prospective study - 161 consecutive patients admitted to the stroke unit.

Portable respiratory recording (PRR) study performed within 48–72 h after admission (acute phase), and subsequently after 3 mo (stable phase).

Prevalence of SRBD in patients with first-ever stroke or TIA is higher than expected from the available epidemiological data.

No correlation was found between neurological location and the presence or type of SRBD.

Obstructive events seem to be a condition prior to the neurological disease whereas central events and CSB could be its consequence.
Other mechanisms of increased Stroke risk in OSA

- Effects on atherogenesis and blood vessel function.
- Strong association with atrial fibrillation.
- OSA promotes thrombosis.
- Enhanced platelet aggregation and activation.
- Elevated fibrinogen levels.
- Diminished fibrinolytic activity.
- Doppler measurements – Suggest that apneic events are associated with reduced cerebral blood flow
- Can result in cerebral hypoxia.
- CPAP treatment has been shown to reverse some of these findings.
- Impact of treatment - Yaggi and colleagues - May be limited and needs further evaluation.


OSA & Heart Failure

• HF and OSA - closely linked.

• Strong associations with aging and obesity

• Prevalence of OSA – Approx. 40% in patients with HF referred to a clinical sleep laboratory.
  

• Framingham study - ↑ BMI - Directly correlated with incident HF.

• Effect may be mediated, at least in part, by OSA.

• Incident AF (associated with OSA) - An important risk factor for HF.

• Cascade of physiological responses to repetitive upper airway closure in OSA may exert deleterious effects on cardiac function, particularly in the already compromised heart.
• OSA, HF & CPAP – Why so much noise??

• Despite advances in treatment with drugs, lifestyle modifications, and therapeutic devices - Mortality from HF continues to ↑.

55 patients with CHF and OSA - Randomized to 3 months of CPAP or control (Optimal med. No placebo) groups.

End points were changes in LVEF, overnight urinary NE excretion, blood pressure, and quality of life.

### TABLE 2. ENDPOINT OUTCOME MEASURES

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>CPAP Group</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 21 )</td>
<td>( n = 19 )</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>33.6 ± 2.6</td>
<td>37.6 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>35.1 ± 3.1</td>
<td>42.6 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>1.5 ± 1.4</td>
<td>5.0 ± 1.0†</td>
<td>0.04</td>
</tr>
<tr>
<td>UNE, nmol/mmol creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.3 ± 1.9†</td>
<td>23.5 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>22.9 ± 3.9</td>
<td>13.7 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>1.6 ± 3.7</td>
<td>-9.9 ± 3.6†</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>105 ± 3</td>
<td>99 ± 3</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>99 ± 3</td>
<td>100 ± 2</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>-6 ± 3</td>
<td>1 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>( V_{O_2} ) peak, ml/kg/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.4 ± 0.7</td>
<td>20.3 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>16.3 ± 0.7</td>
<td>20.3 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>-0.2 ± 0.5</td>
<td>0 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.4 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>2.4 ± 0.2</td>
<td>2.3 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>0 ± 0</td>
<td>0.1 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.8 ± 0.9</td>
<td>9.5 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>9.9 ± 1.0</td>
<td>6.9 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>1.1 ± 0.8</td>
<td>-3.1 ± 1.4Δ</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>33.3 ± 1.2</td>
<td>33.6 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>33.5 ± 1.2</td>
<td>33.9 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>0.2 ± 0.3</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>AHl, events per hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>26.6 ± 4.5</td>
<td>25.0 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>18.2 ± 2.8</td>
<td>2.9 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>-8.4 ± 3.6</td>
<td>-21.1 ± 3.8†</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minimum ( \text{Sp}_{O_2} ), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>77.2 ± 3.9</td>
<td>79.6 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>77.2 ± 3.5</td>
<td>91.1 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>( \Delta )</td>
<td>0.0 ± 1.6</td>
<td>11.5 ± 2.7†</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Cardiovascular Effects of Continuous Positive Airway Pressure in Patients with Heart Failure and Obstructive Sleep Apnea

Yasuyuki Kaneko, M.D., John S. Floras, M.D., D.Phil., Kengo Usui, M.D., Ph.D., Julie Plante, M.D., Ruzena Tkacova, M.D., Ph.D., Toshihiko Kubo, M.D., Ph.D., Shin-ichi Ando, M.D., Ph.D., and T. Douglas Bradley, M.D.

- 24 patients with LVEF ≤ 45 % and OSA who were receiving optimal medical treatment for HF underwent PSG.

- On the following morning, their BP, HR and LV dimensions and LVEF were assessed by echocardiography.

- Randomly assigned to receive medical therapy either alone (12 patients) or with the addition of CPAP (12 patients) for 1 month.

### Table 3: Heart Rate and Blood Pressure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Group Receiving Continuous Positive Airway Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Line</td>
<td>1 Mo</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67±4</td>
<td>67±4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128±7</td>
<td>134±8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>60±4</td>
<td>58±3</td>
</tr>
</tbody>
</table>

![Graphs](image)  

**Figure 1.** Individual Values for the Left Ventricular Ejection Fraction in All Patients.  

**Figure 2.** Mean (±SE) Changes in Left Ventricular Dimensions.
Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

• Hypothesis – CPAP would improve the survival rate without heart transplantation of patients who have central sleep apnea and heart failure.

• 258 patients (after medical optimization) with HF (24.5 ± 7.7) and CSA (AHI-40±16).

• Randomly assigned to receive CPAP (128 patients) or no CPAP (130 patients).

• Followed for a mean of two years.

Figure 1. Effect of CPAP on the Frequency of Episodes of Apnea and Hypopnea, Mean and Minimal Nocturnal Oxygen Saturation, and Left Ventricular Ejection Fraction.
Figure 3. Heart-Transplantation–free Survival.
• 26 patients with stable symptomatic CHF and OSA.

• Randomized to nocturnal auto-titrating CPAP or sham CPAP for 6 weeks each in crossover design.

• Co-primary endpoints - Changes in peak VO2 and 6 MWD.

• Secondary endpoints - Changes in LVEF, plasma neurohormonal markers, and QOL measures.

• Mean CPAP and sham CPAP usage – No significant difference.
Findings may relate in part to methodologic limitations, such as the lack of a follow-up PSG to confirm treatment efficacy with autotitrating CPAP.

Currently limited data regarding the impact of OSA treatment on important HF endpoints calls for further interventional trials.

*European Heart Journal (2007) 28, 1221–1227*
OSA & Pulmonary hypertension

THE INFLUENCE OF SHORT PERIODS OF INDUCED ACUTE ANOXIA UPON PULMONARY ARTERY PRESSURES IN MAN

HURLEY L. MOTLEY, ANDRE COURNAND, LARS WERKO, AARON HIMMELSTEIN AND DAVID DRESDALE

From the Department of Medicine, Columbia University and the Chest and Medical Services of the Columbia University Division, Bellevue Hospital, New York, N. Y.

Received for publication May 19, 1947

METHODS. The influence of breathing 10 per cent oxygen in nitrogen has been studied on 5 unanesthetized, conscious white males in a resting basal

<table>
<thead>
<tr>
<th>Pulmonary artery blood pressure, mm. Hg</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>21.9</td>
<td>35.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>6.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Mean</td>
<td>13.1</td>
<td>23.0</td>
</tr>
</tbody>
</table>

Hypoxic pulmonary vasoconstriction

• Critical autoregulatory mechanism important in maintaining an appropriate V/Q relationship.

• Over time - Pulmonary vascular remodeling - May not be reversible.

• Demonstrated in populations with advanced lung disorders.

• OSA pathophysiology - Could also provide a basis for chronic elevations in PAP.

• Precisely defining the role of OSA in the genesis of PH has been difficult for a number of reasons.
Difficulties in establishing association

- Various methods for diagnosis of PH in OSA studies.

- Doppler echocardiography - Varying right heart/PAP thresholds.

- Previous definitions - Systolic PAP > 40 mm Hg and echocardiographic Doppler measurements.

- May be particularly challenging to obtain in obese patients with OSA.

- PH and OSA - Common risk factors—Obesity and aging – Confounding.

- A PASP >40 mm Hg - Found in 6% of otherwise normal individuals > 50 yrs and in 5% of individuals with a BMI > 30 kg/m²

- Finding appropriate control groups - Matched subjects with PH but no OSA – Quite Challenging.
OSA & Pulmonary hypertension

- SDB - Part of the category of respiratory disorders associated with PH. (2009 PAH guidelines).

- Limited epidemiologic data - Numerous case series, comprised primarily of male patients.

- Suggest a prevalence of PH in OSA ranging from 17 to 52%.

- The largest published sample - 220 subjects with OSA - 17% met diagnostic criteria for PH.
  

- Population-based data are currently lacking.
Early studies

• Sleep stage–dependent increases in PAP, with more marked changes occurring during REM sleep.


• Most early clinical studies - Abnormalities in underlying lung function sufficient to induce daytime hypoxemia were required for the development of PH and right heart failure.

• Support - Severity of sleep-disordered breathing, as measured by the AHI, and PAP elevations often failed to correlate.

• Not all studies adequately excluded increases in left atrial pressure as a contributor to the development of daytime increases in PAP.
27 patients with OSAS in whom clinically significant lung or cardiac diseases were excluded.

- 11 OSAS patients (41%) – PAH - (Mean PAP < 26 mm Hg).

- Pts. With PH - More hypoxemic during daytime wakefulness than patients without PH - Could either contribute to or result from PH.

- Hypoxemia in PH patients could not be explained by impairment of lung function, greater body mass, or a higher prevalence of smoking.

- Lung disease is not a prerequisite for PH in OSAS.
Treatment Effects


- Initial reports - Approximate 50% ↓ in PAP in 6 patients with OSA who underwent tracheostomy, some of whom may have had comorbid disease. 


- Very limited data on the effects of CPAP treatment of OSA on PAP
• To investigate whether OSA patients without any other cardiac or lung disease develop PH.

• To assess the effect of CPAP treatment on PA pressure.

• 29 pts – Age 51±10 years with OSA, 12 controls.

• PA pressure before and after 6-month effective treatment with CPAP.

<table>
<thead>
<tr>
<th></th>
<th>OSA patients (n = 29)</th>
<th>Control subjects (n = 12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51 ± 10</td>
<td>53 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34 ± 6</td>
<td>30 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁, % pred.</td>
<td>92 ± 13</td>
<td>91 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % pred.</td>
<td>91 ± 12</td>
<td>88 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>79 ± 4</td>
<td>84 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>PₐO₂, mm Hg</td>
<td>90 ± 10</td>
<td>90 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>PₐCO₂, mm Hg</td>
<td>40 ± 4</td>
<td>39 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>54 ± 19</td>
<td>9 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doppler PₚA, mm Hg</td>
<td>17.2 ± 5.2 (11–30)</td>
<td>12.1 ± 1.9 (8–22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swan-Ganz PₚA, mm Hg</td>
<td>16.9 ± 5.4 (11–33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge pressure, mm Hg</td>
<td>6.8 ± 2.0 (5–11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Anthropometric, lung function, polysomnographic and hemodynamic data in OSA patients with (PH group) and without pulmonary hypertension (non-PH group)

<table>
<thead>
<tr>
<th></th>
<th>PH group (n = 6)</th>
<th>Non-PH group (n = 23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62 ± 4</td>
<td>48 ± 15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>41 ± 7</td>
<td>32 ± 4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>FEV\textsubscript{1}, % pred.</td>
<td>86 ± 15</td>
<td>93 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % pred.</td>
<td>86 ± 16</td>
<td>92 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC, %</td>
<td>76 ± 2</td>
<td>83 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>P\textsubscript{a}O\textsubscript{2}, mm Hg</td>
<td>81 ± 9</td>
<td>92 ± 9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P\textsubscript{a}CO\textsubscript{2}, mm Hg</td>
<td>43 ± 4</td>
<td>40 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>AHJ, events/h</td>
<td>63 ± 18</td>
<td>51 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest \textsubscript{Sp}O\textsubscript{2}, %</td>
<td>60 ± 11</td>
<td>63 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>\textsubscript{Sp}O\textsubscript{2} drops &gt; 4%</td>
<td>280 ± 41</td>
<td>222 ± 109</td>
<td>NS</td>
</tr>
<tr>
<td>Doppler P\textsubscript{PA}, mm Hg</td>
<td>25.6 ± 4.0</td>
<td>14.9 ± 2.2</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean P\textsubscript{PA} before CPAP treatment mm Hg</th>
<th>Mean P\textsubscript{PA} after CPAP treatment mm Hg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA patients (n = 29)</td>
<td>17.2 ± 5.2</td>
<td>13.2 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PH group (n = 6)</td>
<td>25.6 ± 4.0</td>
<td>19.5 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-PH group (n = 23)</td>
<td>14.9 ± 2.2</td>
<td>11.5 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Continuous Positive Airway Pressure Treatment Improves Pulmonary Hemodynamics in Patients with Obstructive Sleep Apnea

DIMITAR SAJKOV, TINGTING WANG, NICHOLAS A. SAUNDERS, ALEXANDRA J. BUNE, and R. DOUGLAS McEVOY

Sleep Disorders Unit and Department of Cardiology, Repatriation General Hospital, Daw Park, Australia; and School of Medicine, Flinders University, Bedford Park, Adelaide, Australia

• 20 patients with OSA (without coexistent pulmonary or cardiac disease) - 4 months of CPAP therapy.

• 5 patients - Met criteria for PH.

• To assess the reversibility of PH - PAP measured by Echo at three levels of fiO₂ (50, 21, and 11%).

• After 4 months of CPAP therapy - PAP (for all patients) ↓- Mean 13.9 mm Hg.

• CPAP may also affect vasoreactivity - PA pressor response to hypoxia was attenuated.

Am J Respir Crit Care Med Vol 165. pp 152–158, 2002
• Randomized cross-over trial of CPAP/sham CPAP -12 weeks -23 patients with OSA.

• 10 patients with PH - More obese, had more ventilatory limitation (reduced FVC), and more severe sleep apnea (by AHI and mean oxygen saturation) than the 13 patients without PH.

• CPAP therapy ↓ PASP in all patients - More so in those with PH at baseline (mean reductions, 8.5 vs. 2.6mmHg).
Baseline differences in obesity and lung function between groups - Preclude the attribution of PH to OSA alone.

First to show, in a placebo-controlled fashion, the positive impact of CPAP therapy on PH in a small group of patients with OSA.

Further research is needed to assess the durability of CPAP therapy on PAP and right heart function

An ever increasing arsenal of pharmacologic treatments for PH
SYNDROME Z – OSA + Metabolic Syndrome (1990’s)

- NCEP ATP III – 5 variables
- HTN, insulin resistance, low serum HDL cholesterol, elevated serum TG’s, and abdominal obesity.
- 3/5 – Metabolic Syndrome.

- Growing experimental and clinical evidence - Independent contribution of OSA toward the development and/or severity of MS.

- MS and its components may have conductive influence on the development of sleep apnea.

- OSA itself may well be a “metabolic disorder” and a component of MS.
OSA, MS & Cardiovascular outcomes – Very scanty Data

- 89 subjects with OSA treated with CPAP.
- 50 % patients had MS at baseline.
- Less CVD events in those with MS than those without MS (Mean period - 22 months).
- CPAP compliance data did not modify the outcome.


- Limitations - Details of pharmacotherapy for metabolic control during the follow-up period were not available.

- Prospective studies with longer follow-up and rigorous characterization of subjects needed to address this issue.
OSA & Glucose Metabolism

- MS – “Insulin resistance syndrome”

- Insulin resistance – DM.

- Any independent contribution of OSA toward insulin resistance and/or glucose homeostasis would have a magnifying effect on the clinical outcomes.

- OSA, MS & Insulin resistance closely linked to obesity.

- Many further implications on the manifestations and sequelae of OSA.
Important to address Obesity as a confounder

- Visceral fat - Metabolically active tissue.

- Large amounts of proinflammatory or vasoactive substances.

- Central obesity is considered to be a very important determinant of MS

- OSA may well modulate the expression of adipose tissue–derived mediators.

- Determine the development of various features in MS as well as cardiovascular diseases.
OSA & Insulin resistance - What is the evidence ??

• Large no. Of studies - Presence and/or severity of OSA are linked to alterations in glucose metabolism independently of the degree of obesity.

• Most - Cross-sectional data, prospective studies very few.

• Additional studies with prospective and/or interventional designs are needed to address causation.

• To establish association - Investigators have explored changes in glucose metabolism after treatment of OSA with CPAP.

• Effects of CPAP treatment on glucose metabolism – Considerable disagreement.
OSA & Neuropsychological Impairment

• Cognitive function and neuropsychological testing - Assessed in numerous studies.

• Differences in sampling and study design.
• Varying characteristics of study populations.
• Most obvious source of variation - Severity of OSA.

• Effect size of cognitive impairment in OSA correlated highly with AHI.
• Severity also influenced the type of cognitive impairment observed.

Other factors affecting assessment

- Daytime CO2 retention and hypoxemia - May play a role in the genesis of cognitive dysfunction independent of sleep apnea.

- Psychological state of subjects, particularly the degree of depression.

- Age and baseline cognitive function of subjects.

- Individuals with high baseline function – Compensatory ability.

- Comparison groups - Published normative data, healthy controls, and other groups like insomniacs, other hypersomnolence disorders, and patients with treated COPD.

- Array of neuropsychological instruments.
• Neuropsychological domains impaired in OSA patients
  • General intellectual function
  • Attention/vigilance/concentration.
  • Memory (working/episodic/procedural) and learning.
  • Executive and motor function.

• Treatment and reversibility
  • Numerous uncontrolled studies show improvement in cognitive function after initiation of CPAP.

• The results of placebo-controlled investigations do not provide unequivocal support for the hypothesis that this change is directly attributable to CPAP.

• Association of depression with OSA.
SUMMARY

• Sleep apnea is a disorder with widespread systemic manifestations.

• Cardiovascular complications have a strong association with sleep apnea.

• Metabolic syndrome and OSA link has increasingly been recognised.

• Neuropsychological manifestations of sleep apnea can affect a number of cognitive domains.

• CPAP has shown to consistently ameliorate sleep disturbances in OSA but systemic effects are not always consistent.

SLEEP APNEA IS MUCH MORE THAN A SLEEP DISORDER.