Sleep apnea as a risk factor for cardiovascular disease

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Cardiovascular events in OSA

Prospective, controlled cohort study (372 patients with CPAP, 235 without CPAP)

Marin et al. Lancet 2005
Prospective, non-randomised interventional study, 51 patients with stroke and OSA, 18 months follow-up
Abdominal aortic aneurysm & OSA

Cohort study, 127 patients with abdominal aortic aneurysm

Mason et al. AJRCCM 2011
Cardiovascular events in OSA

Incidence of hypertension or cardiovascular events

RCT (357 patients with CPAP vs 366 without CPAP)

Barbe et al. JAMA 2012
David after a holiday in the USA
Mechanisms of vascular damage in OSA

Obstructive sleep apnea

Intrathoracic pressure swings

Recurrent arousals

Intermittent hypoxia

Increased transmural gradients

Sympathetic activation

Oxidative stress, systemic inflammation

Acute blood-pressure rises

Excessive vessel shear stress

Sustained blood-pressure elevation

Endothelial dysfunction

Kohler & Stradling. Nat Rev Cardiol 2010
Increased sympathetic nervous system activity during apnoea.
Acute blood pressure rises

Blood pressure rises with every arousal = repetitive mechanical stress on arterial wall

Camen & Kohler, 2012
Blood pressure variability and CV risk

UK-TIA trial, ASCOT-BPLA

Rothwell et al. Lancet 2010
Sympathetic activity

P=0.004

RCT, N=102, 4 weeks CPAP vs Placebo-CPAP

Kohler et al. ERJ 2008
Sustained blood pressure increase in OSA

Mean arterial pressure (mmHg)

Randomised, controlled study, N=118, 4 weeks of CPAP vs Placebo CPAP

Reduction of diastolic BP of 3.3 mmHg with CPAP

Pepperell et al. Lancet 2002
Increased blood pressure and heart rate

Heart rate (1/min)

Diastolic blood pressure (mmHg)

Reduction of diastolic BP of 6.9 mmHg with CPAP

RCT, n=41, CPAP vs CPAP withdrawal

P<0.001

P<0.01
How does this BP reduction compare?

The effect of CPAP compares to a risk reduction for stroke and myocardial infarction of 34% and 21%, respectively!
Endothelial dysfunction

Baseline vs Post Ischaemia

Flow-mediated dilatation (%)

Baseline, 7 Days, 14 Days

P=0.002  P<0.001

RCT, n=41, CPAP vs CPAP withdrawal

Kohler et al. AJRCCM 2011
Aortic stiffness in OSA

ΔP/PP x 100 = Augmentation index (%)

P=0.001

RCT, N=72 OSAS patients, 4 weeks of CPAP vs Placebo-CPAP

Kohler et al. ERJ 2008
OSA and abdominal aortic atherosclerosis

![Graphs showing differences in maximal aortic thickness and aortic distensibility between OSA patients and control subjects. The graph on the left indicates a significant difference (P < 0.0001) in maximal aortic thickness between the two groups. The graph on the right shows a trend (P < 0.05) in aortic distensibility.](image)
Mason et al. AJRCCM 2011

OSA and abdominal aortic aneurysms

Effect corrected for blood pressure, other CV risk factors and medication
Intermittent hypoxia and blood pressure

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
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<tbody>
<tr>
<td><strong>Baseline (air)</strong></td>
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<tr>
<td><strong>Intermittent hypoxia</strong></td>
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<tr>
<td><strong>Recovery (air)</strong></td>
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</tbody>
</table>

Δ = 4 mmHg

RCT, 10 healthy males, air vs intermittent hypoxia for 4 days

Foster et al. J Physiol 2009
Intermittent hypoxia and blood pressure

12 healthy subjects, intermittent hypoxia for 14 days
Effect of oxygen on blood pressure in OSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP (N=90)</th>
<th>NSO (N=94)</th>
<th>HLSE (N=97)</th>
<th>CPAP vs. HLSE</th>
<th>NSO vs. HLSE</th>
<th>CPAP vs. NSO</th>
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<tbody>
<tr>
<td>24-Hr mean arterial blood pressure</td>
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</tr>
<tr>
<td>Baseline</td>
<td>89.5±8.6</td>
<td>88.6±10.0</td>
<td>87.7±9.3</td>
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<tr>
<td>12 Wk</td>
<td>87.8±8.1</td>
<td>90.2±11.1</td>
<td>89.0±11.2</td>
<td>-2.4 (P=0.04)</td>
<td>0.4 (P=0.71)</td>
<td>-2.8 (P=0.02)</td>
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<tr>
<td>24-Hr mean systolic blood pressure</td>
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<tr>
<td>Baseline</td>
<td>124.7±13.5</td>
<td>125.3±16.9</td>
<td>123.6±14.3</td>
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<td></td>
</tr>
<tr>
<td>12 Wk</td>
<td>123.4±12.8</td>
<td>126.9±16.5</td>
<td>124.7±16.4</td>
<td>-1.9 (P=0.25)</td>
<td>1.2 (P=0.45)</td>
<td>-3.1 (P=0.06)</td>
</tr>
<tr>
<td>24-Hr mean diastolic blood pressure</td>
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</tr>
<tr>
<td>Baseline</td>
<td>72.0±7.7</td>
<td>70.8±8.3</td>
<td>69.6±8.6</td>
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<td>-0.1 (P=0.95)</td>
<td>-2.8 (P=0.006)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The between-group differences are the mean differences at 12 weeks, adjusted for study site, presence or absence of coronary artery disease, and blood pressure as measured at baseline. CPAP denotes continuous positive airway pressure, NSO nocturnal supplemental oxygen, and HLSE healthy lifestyle and sleep education.
Oxidative stress & endothelial dysfunction

- OSA patients before therapy
- OSA patients after therapy

Uncontrolled interventional study, 32 OSA patients, 4 weeks of CPAP

RCT (cross-over), 31 patients with OSA, 12 weeks of CPAP or Placebo-CPAP.
RCT, N=100, OSA patients with comorbidities, 4 weeks of CPAP vs Placebo-CPAP

Kohler et al. Thorax 2009
Inflammation ? Metabolic alterations ?

RCT, 41 OSA patients, CPAP vs CPAP withdrawal for 2 weeks

Kohler & Stradling, J Physiol 2012
Intrathoracic pressure swings

Intrathoracic pressure change increases aortic diameter

Animal model, obstructed airways (simulated obstructive apnoea)
Intrathoracic pressure swings

Experimentally simulated obstructive hypopnoea/apnoea, 20 healthy subjects
Intrathoracic pressure swings

![Graph showing esophageal and mean aortic pressure swings during a Mueller maneuver.](image)

- Experimentally simulated obstructive hypopnoea/apnoea, 10 patients with suspected CAD

Clarenbach et al. J Appl Physiol 2013
Intrathoracic pressure swings

![Graph showing intrathoracic pressure swings](Clarenbach et al. J Appl Physiol 2013)
Marfan’s syndrome and OSA

$r=0.50, p=0.0003$
Cohort study, 44 patients with Marfan’s syndrome

Aortic events in patients with Marfan’s & OSA

P=0.012
Most of the vascular consequences of OSA seem to be due to increased sympathetic nervous system activity. This may be the result of both recurrent arousals and oxidative stress.

There is good evidence from RCTs proving a causal relationship between OSA, vascular dysfunction and hypertension. OSA-induced hypertension ought to translate into increased morbidity and mortality, but this remains to be proven in RCTs.

Whether intrathoracic pressure swings cause cardiovascular disease remains to be proven in controlled trials.
CV events in OSA

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Whether intrathoracic pressure swings cause cardiovascular disease remains to be proven in controlled trials.

There is still no data from RCTs proving a causal relationship between OSA and cardiovascular events!