Continuous positive airway pressure improves vascular function in obstructive sleep apnea hypopnea syndrome: a randomized controlled trial

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Abstract

Background
The obstructive sleep apnea/hypopnea syndrome (OSAHS) is associated with hypertension and increased cardiovascular risk, particularly when accompanied by marked nocturnal hypoxemia. The mechanisms of these associations are unclear. We hypothesised that OSAHS combined with severe nocturnal hypoxemia causes impaired vascular function that can be reversed by continuous positive airways pressure (CPAP) therapy.

Methods and Results
We compared vascular function in two groups of patients with OSAHS: 27 with more than twenty 4% desaturations/hr (desaturator group) and 19 with no 4% and less than five 3% desaturations/hr (non-desaturator group). In a randomized double-blind placebo controlled crossover trial, the effect of 6-weeks CPAP therapy on vascular function was determined in the desaturator group. In all studies, vascular function was assessed invasively by forearm venous occlusion plethysmography during intra-arterial infusion of endothelium-dependent (acetylcholine, 5-20 µg/min, and substance P, 2-8 pmol/min) and independent (sodium nitroprusside, 2-8 µg/min) vasodilators.

Compared to the non-desaturator group, patients with OSAHS and desaturations had reduced vasodilatation to all agonists ($P \leq 0.007$ for all). The apnea/hypopnea index and desaturation frequency were inversely related to peak vasodilatation with acetylcholine ($r=-0.44$, $P=0.002$ and $r=-0.43$, $P=0.003$) and sodium nitroprusside ($r=-0.42$, $P=0.009$ and $r=-0.37$, $P=0.02$). In comparison to placebo, CPAP therapy improved forearm blood flow to all vasodilators ($P \leq 0.01$).

Conclusions
Patients with OSAHS and frequent nocturnal desaturations have impaired endothelial-dependent and endothelial-independent vasodilatation that is proportional to hypoxemia and is improved by
CPAP therapy. Impaired vascular function establishes an underlying mechanism for the adverse cardiovascular consequences of OSAHS.

**Keywords:** CPAP, OSAHS, Endothelium, Blood Flow, Randomised Controlled Trial
The obstructive sleep apnea/hypopnea syndrome (OSAHS) is caused by upper airways obstruction during sleep leading to hypopnea or apnea events. This leads to a symptom complex characterised by sleepiness and impaired cognitive function in conjunction with loud snoring(1). The arousals at the terminations of apneas and hypopneas are associated with transient rises in blood pressure (2). Obstructive sleep apnea is associated with sustained hypertension in animal models(3), and in clinical epidemiological(4) and interventional(5;6) studies. The elevation of blood pressure is most marked in those with more severe sleep related hypoxemia. Recent evidence indicates that OSAHS is associated with an increased risk of cardiovascular (6) and cerebrovascular disease(7,8).

The mechanism of the association between OSAHS, hypertension and cardiovascular disease is unclear. OSAHS is associated with increased sympathetic tone both in association with arousals from sleep(9) and during daytime wakefulness(10;11). This could also be associated with activation of the renin-angiotensin-aldosterone system(12), alteration of baroceptor control(9), oxidative stress,(13), increased inflammatory responses(14) and increased hypercoagulability(15).

Altered endothelial and vascular function may be the important link between OSAHS and cardiovascular disease. Current contradictory evidence reports, either no effect(16), impaired endothelium-dependent vasodilatation (17), impaired endothelium-independent vasodilatation(18) or even vasoconstriction(16). These findings are limited because of small group sizes (n=8-10 per group), lack of correlation with nocturnal hypoxemia, and variable use of control groups.
The aims of this study were to determine whether endothelial function is altered in patients with OSAHS and whether potential alterations in endothelial function correlate with the degree of sleep-related hypoxemia. Finally, we sought to establish the reversibility of any alterations in vascular function by using a double blind randomized placebo controlled cross-over trial of CPAP therapy.
Methods

Subjects

Fifty-one patients with obstructive sleep apnea/hypopnea syndrome, (OSAHS), Epworth Sleepiness Score > 10, aged 34-62 years old participated in this study. Patients with clinical evidence of atherosclerotic vascular disease, asthma, respiratory failure, or an inter-current illness were excluded from the study. OSAHS was diagnosed on the basis of symptoms, an Epworth Sleepiness Score[^19] >10 and an apnea/hypopnea index (AHI) of greater than 15/hr on overnight polysomnography. Patients were stratified as desaturators (2 major symptoms of OSAHS, AHI>15, >20 of 4% desaturations/hr or non-desaturators (2 major symptoms of OSAHS, AHI>15, < 5 of 3% desaturations/hr and no 4% desaturations/hr).

Study design

Study 1: Comparison of baseline vascular function in desaturators versus non-desaturators

All patients with OSAHS (n=51) attended for a screening visit that included a clinical history, physical examination and polysomnography. Desaturators and non-desaturators were identified a priori according to the polysomnographic findings from an in-patient sleep study, and all were invited to attend for a vascular assessment: 27 desaturators and 19 non-desaturators completed the study protocol (Figure 1).

Study 2: Randomized placebo controlled trial of CPAP in desaturators

Patients with OSAHS and significant nocturnal desaturation (n=27) had in-hospital CPAP autotitration using a ResMed Spirit [ResMed, Poway, Ca]. The next morning, they were randomized in a double-blind crossover study to receive 6 weeks of continuous positive airways pressure...
(CPAP), at the fixed pressure determined from the CPAP titration, and 6 weeks of sham CPAP with a one-week washout period between treatment periods. Patients underwent a repeat vascular assessment at the end of both treatment phases (Figure 1). Patients and researchers were blinded to the randomized treatment allocation.

**Vascular assessment**

All patients abstained from alcohol for 24 hours and from food, tobacco and caffeine-containing drinks for at least 4 hours before each vascular study. Studies were carried out in a quiet, temperature controlled room maintained at 22-24°C with subjects lying supine.

Patients underwent brachial artery cannulation with a 27-standard wire gauge steel needle under controlled conditions. Following a 30 min baseline saline infusion, acetylcholine at 5, 10 and 20 µg/min (endothelium-dependent vasodilator; Clinalfa AG, Switzerland), substance P at 2, 4 and 8 pmol/min (endothelium-dependent vasodilator; Clinalfa AG) and sodium nitroprusside at 2, 4 and 8 µg/min (endothelium-independent vasodilator; David Bull Laboratories, UK) were infused for 6 min at each dose. The three vasodilators were separated by 20 min saline infusions and given in a randomised order although this order was kept constant on each visit for each individual subject.

Forearm blood flow was measured in the infused and non-infused arms by venous occlusion plethysmography using mercury-in-silastic strain gauges as described previously (19). Supine heart rate and blood pressure in the non-infused arm were monitored at intervals throughout each study using a semi-automated non-invasive oscillometric sphygmomanometer.

**Data analysis and statistics**
Plethysmographic data were determined as described previously (11). All data were analysed finalized and locked by researchers blind to treatment type before treatment codes were assigned to the data set. Continuous variables are reported as mean ± SEM. Statistical analyses were performed with GraphPad Prism (Graph Pad Software) using analysis of variance (ANOVA) with repeated measures and two-tailed Student’s \( t \)-test where appropriate.
Results

Study 1: Desaturators versus non-desaturators

Desaturators had greater apnea-hypopnea indices (AHI) than non-desaturators (63±5 versus 21±1, P<0.0001). The patient groups were otherwise well matched except for body mass index, where the desaturators were more obese (37±1 versus 30±1 m²/kg, P=0.0003). There were no differences in resting heart rate, blood pressure or baseline forearm blood flow between desaturators and non-desaturators (Table 1).

Acetylcholine, substance P and sodium nitroprusside caused a dose-dependent increase in forearm blood flow in all patients (P<0.001). The increase in blood flow was blunted in desaturators compared to non-desaturators (Figure 2) for each vasodilator: acetylcholine (P<0.001), substance P (P=0.007) and sodium nitroprusside (P<0.001). Maximal vasodilatation was negatively correlated with AHI (Figure 3A-C) and desaturation frequency (Figure 3D-F).

As the desaturators were heavier than the non-desaturators, a post hoc analysis was performed in which the 5 heaviest desaturators and 4 lightest non-desaturators were excluded – these deletions were made without knowledge of patients’ vascular function. Whilst the resulting groups (22 desaturators, 15 non-desaturators) had similar body mass indices ±SEM (34.2 ±1.1 and 31.4 ±0.9 kg/m²; p=ns), vasodilatation remained impaired in the desaturators compared to the non-desaturators: acetylcholine (p=0.0002), substance P (p=0.009) and sodium nitroprusside (p=0.005).

Study 2: Randomized placebo controlled trial

Treatment with CPAP or sham CPAP for 6 weeks did not affect resting heart rate, blood pressure or baseline forearm blood flow (Table 2). On an intention to treat basis, the compliance for the CPAP
limb of the study was 4.49 ± 0.4 h, and the compliance for the sham CPAP limb of the study was 3.08±0.48 h (p=0.015 two tailed t-test).

Intra-brachial infusions of acetylcholine, substance P and sodium nitroprusside caused dose-dependent increases in forearm blood flow at each visit (P<0.001), that was unaffected by sham CPAP (data not shown). In comparison to results after sham CPAP, treatment with CPAP for 6 weeks improved forearm blood flow to all vasodilators (Figure 4): acetylcholine (P=0.002), substance P (P=0.01) and sodium nitroprusside (P=0.003).
Discussion

We have demonstrated that patients with OSAHS have markedly impaired vascular function that is proportional to the degree of hypoxemia. Using a rigorous double-blind randomised placebo controlled crossover trial, we have further demonstrated that CPAP therapy resulted in a clear improvement in vascular function in patients with OSAHS. Together these important and novel findings suggest that vascular dysfunction is related to disease severity in OSAHS, and that effective treatment with CPAP can improve vascular function and consequently reduce the associated cardiovascular complications.

Vascular dysfunction in OSAHS

Our findings add to the evidence base that OSAHS is associated with vascular dysfunction and disease. Our study represents the largest investigation of vascular function in patients with OSAHS. The study population is ~3-fold larger than previous studies({15}, {16}, {17}) and we have incorporated the use of two distinct endothelium-dependent vasodilators. We have found a marked impairment in endothelium-dependent and –independent vascular reactivity in patients with OSAHS. Given the associations with hypoxemia, our findings also suggest that severity of OSAHS directly affects vascular reactivity with greater impairment in more severely desaturating patients (Figure. 3).

Animal models have suggested that hypoxia ({21}), cyclical hypoxia and reoxygenation ({22}) can have detrimental vascular effects, existing evidence ({23}) suggests that vascular dysfunction can be induced by hypoxia in susceptible individuals. We therefore speculate that the adverse vascular effects of OSAHS are mediated through nocturnal hypoxemia.

Effect of CPAP on vascular dysfunction in OSAHS
Previous studies into the effect of treatment in OSAHS on vascular function have been either observational (\cite{24}, \cite{25}, \cite{26}) or without a placebo control (\cite{24}, \cite{27}, \cite{25}). We have conducted a double blind randomized placebo controlled crossover trial that maximizes the study power whilst minimizing the potential for treatment bias. Our findings provide robust evidence that OSAHS related dysfunction of vasomotor tone is reversible with CPAP within 6 weeks of initiating therapy. This provides a potential explanation for, our own (\cite{5}) and others (\cite{6}) observations that CPAP lowers blood pressure most in severely desaturating patients with OSAHS.

In a subgroup of patients with OSAHS and hypertension blood pressure does not fall appropriately during sleep (“non-dippers”).\(\cite{28}\). This may lead to increased left ventricular mass(\cite{29}) and an increased risk for cardiovascular events(\cite{30}). These patients have most to gain from CPAP use, by avoiding the vascular dysfunction associated with OSAHS, mediated through repetitive hypoxemia.

**Mechanism of vascular dysfunction**

Impaired endothelium-dependent and -independent function in the forearm vascular bed is associated with an increased risk of acute cardiovascular events, including cardiac death(\cite{31}). We initially hypothesized that endothelial-dependent mechanisms alone were responsible for vasomotor dysfunction in the OSAHS. However, our findings suggest that both endothelium-dependent and -independent mechanisms are impaired. It is unclear whether the observed impairment is mediated primarily by the endothelium or is a result of vascular smooth muscle dysfunction.

Reduced nitric oxide bioavailability (\cite{32}) in the presence of increased systemic vascular oxidative stress (\cite{33}) is an attractive hypothesis. Here, increased consumption of nitric oxide, whether it is endogenously derived from endothelial nitric oxide synthase or from an exogenous source, such as sodium nitroprusside, would explain the observed impairment to both endothelial dependent and
independent vasodilators. The endothelium is a major target of oxidative stress, which plays an important role in the pathophysiology of cardiovascular disease. In OSAHS, recurrent episodes of hypoxemia followed by re-oxygenation may trigger oxidative stress and endothelial damage. Urinary 8-isoprostane concentrations are elevated in patients with moderate-severe OSAHS suggesting that the syndrome is associated with systemic oxidative stress (\cite{34}). Furthermore, 8-isoprostane levels correlate with the duration of nocturnal hypoxia, and fall following treatment with CPAP. However, the occurrence and role of oxidative stress in OSAHS is controversial (\cite{13}, \cite{33,35}, \cite{36}) and measuring systemic oxidative stress is notoriously difficult.

Alternative explanations for the pattern of vascular impairment should also be considered. Compared to wakefulness, heart rate, blood pressure and sympathetic nerve traffic to the vasculature decrease progressively throughout sleep (\cite{29,37}). In contrast, sympathetic activity and blood pressure increase during arousals. Thus the autonomic nervous system and its response to sleep and arousals may play a key role to the mechanism of vascular dysfunction in OSAHS. Sleep disordered breathing and hypoxia may contribute to the elevation of Endothelin-1 concentrations in patients with OSAHS induced hypertension (\cite{12,23,38}).

**Study Limitations**

A limitation to the study included the absence of a normal control group. It would not have been feasible to find weight matched healthy volunteers who did not have some degree of irregular breathing during sleep. Obesity and insulin resistance are associated with vascular dysfunction (\cite{39}), and this could be partly responsible for our observed differences. We took the pragmatic approach of using a non-desaturating OSAHS group as a control.

We did not include non-desaturators in the treatment trial, and therefore cannot comment on the potential benefits to vascular function of therapy in these patients. We focused on the desaturating
group in this trial as our objective was to determine whether any vascular function abnormality was reversible and we decided *a priori* that changes with CPAP were most likely to be demonstrated in the more hypoxemic group.

We acknowledge the inevitable BMI mismatch that resulted from consecutively recruiting desaturating and non-desaturating patients. However, our post hoc analysis matching for BMI (Figure 5) and by post hoc multivariate analysis strongly suggest that weight was not a factor in the difference in vascular responses between the groups.

There was no statistically significant carryover effect but also no measurements were made until 7 weeks after crossover – 1 week washout plus 6 weeks treatment – and the known effects of CPAP wear off within a few days.

There is no perfect placebo for CPAP. CPAP improves patency of the upper airway and is the treatment of choice for patients with OSAHS by pneumatically splinting open the upper airway. Sham CPAP, using a similar device altered to deliver a sub-therapeutic airway pressure, is arguably the best placebo,\(^6\). However, sham CPAP use was significantly lower than actual CPAP and this suggests that patients received positive re-enforcement from the benefits of actual CPAP use. The clear difference in vascular function after active rather than sham CPAP is robust evidence of abnormal function in OSAHS that is reversible with effective treatment.

**Conclusions**

Patients with OSAHS and frequent nocturnal desaturations have markedly impaired endothelial-dependent and -independent vasodilatation. In these patients, treatment with CPAP for 6 weeks resulted in marked improvements in vascular function. These findings suggest that disease severity is an important modulator of vascular function, and that CPAP treatment may play an important role...
in reducing the cardiovascular complications associated with nocturnal apneas.
Acknowledgements

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Table 1. Baseline characteristics of desaturating and non-desaturating Obstructive Sleep Apnoea Hypopnoea Syndrome patients

<table>
<thead>
<tr>
<th></th>
<th>Desaturators</th>
<th>Non-desaturators</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=27[ND2]</td>
<td>n=19</td>
<td>P value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 (2)</td>
<td>50 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>26/1</td>
<td>18/1</td>
<td>*0.065</td>
</tr>
<tr>
<td>AHI</td>
<td>63 (5)</td>
<td>20 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>6</td>
<td>7</td>
<td>*0.28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>0</td>
<td>*0.40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>4</td>
<td>*0.70</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8</td>
<td>6</td>
<td>*0.89</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>115 (5)</td>
<td>91 (3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index (m²/kg)</td>
<td>37 (1)</td>
<td>30 (1)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1</td>
<td>2</td>
<td>*0.82</td>
</tr>
<tr>
<td>Statin</td>
<td>2</td>
<td>2</td>
<td>*0.71</td>
</tr>
<tr>
<td>β-blocker</td>
<td>3</td>
<td>2</td>
<td>*0.95</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>0</td>
<td>0</td>
<td>*0.0</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64.7 (12)</td>
<td>72 (3.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>143.2 (3.3)</td>
<td>143.4 (4.64)</td>
<td>0.97</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.4 (2.02)</td>
<td>81.4 (2.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Infused FBF (mL/100 mL tissue/min)</td>
<td>3.9 (0.5)</td>
<td>3.4 (0.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Non-infused FBF (mL/100 mL tissue/min)</td>
<td>3.5 (0.4)</td>
<td>3.2 (0.2)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Values are presented as number or mean (SEM)

FBF = forearm blood flow

* = Chi Squared Applied

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### Table 2. Haemodynamic variables in patients at baseline and following 6 weeks of CPAP or sham CPAP treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Sham</th>
<th>CPAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>64.7 (1.2)</td>
<td>65.5 (2.6)</td>
<td>63.9 (2.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>143.2 (3.3)</td>
<td>144.8 (3.7)</td>
<td>141 (3.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.4 (2.02)</td>
<td>82.3 (1.7)</td>
<td>82.3 (1.9)</td>
<td>0.84</td>
</tr>
<tr>
<td>Infused FBF (mL/100 mL tissue/min)</td>
<td>3.4 (0.2)</td>
<td>3.4 (0.2)</td>
<td>3.5 (0.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Non-infused FBF (mL/100 mL tissue/min)</td>
<td>3.2 (0.2)</td>
<td>3.5 (0.2)</td>
<td>3.1 (0.2)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Values are reported as mean (SEM), two-tailed paired t-test; FBF = forearm blood flow;
Figure 1.
Figure 2. Infused (solid line) and non-infused (dashed line) forearm blood flow in desaturating (●) and non-desaturating (○) patients with OSAHS during intra-brachial infusion of acetylcholine, substance P, and sodium nitroprusside: for all dose responses in the infused arm P<0.001. For desaturating (●) versus non-desaturating patients (○; ANOVA); acetylcholine (P<0.001), substance P (P=0.007) and sodium nitroprusside (P<0.001).

(NB: expressed as mean and 95% CI)
Figure 3. Peak vasodilatation following infusion of substance P, acetylcholine and sodium nitroprusside was negatively correlated with both apnoea/hypopnea index (Figure 3A-C) and desaturation frequency (Figure 3D-F).
Figure 4. Infused (solid line) and non-infused (dashed line) forearm blood flow in patients following 6 weeks treatment with sham (●) and CPAP (○) during intra-brachial infusion of acetylcholine, substance P, and sodium nitroprusside: for all dose responses in the infused arm P<0.001. For sham (●) versus CPAP (○, ANOVA); acetylcholine (P=0.002), substance P (P=0.01) and sodium nitroprusside (P=0.003).

(NB: expressed as mean and 95% CI)
Figure 5 Post Hoc Weight Matched Analysis

Figure. 5 Infused (solid line) and non-infused (dashed line) forearm blood flow in desaturating (●) and non-desaturating (○) OSAHS patients during intra-brachial infusion of acetylcholine, substance P, and sodium nitroprusside: for all dose responses in the infused arm P<0.001. For desaturating (●) versus non-desaturating (○, ANOVA); acetylcholine (p=0.0002), substance P (p=0.009) and sodium nitroprusside (p=0.005).

(NB: expressed as mean and 95% CI)
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