SLEEP DISORDERED BREATHING

Treatment of obstructive sleep apnoea leads to improved microvascular endothelial function in the systemic circulation

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Thorax 2006;61:491-495. doi: 10.1136/thx.2004.039164

Background: Obstructive sleep apnoea (OSA) is a common and potentially reversible cause of systemic hypertension. The mechanisms whereby OSA leads to hypertension and the effects of treatment on arterial function, however, are not well established. Microvascular arterial endothelial and smooth muscle function was assessed in subjects with OSA before and after treatment with continuous positive airways pressure (CPAP). **Methods:** Ten subjects of mean (SE) age 49 (8) years with at least moderately severe OSA had detailed

forearm vascular reactivity studies before and after 3 months of CPAP treatment. The systemic circulation

was assessed by measuring brachial artery pressure, flow and resistance responses to intra-arterial infusions of acetylcholine (ACh; an endothelium dependent vasodilator), sodium nitroprusside (SNP; an

endothelium independent vasodilator), L-NMMA (a nitric oxide (NO) antagonist), and L-arginine (the

Results: Before CPAP, ACh and SNP infusions increased forearm blood flow in a dose dependent manner

(p<0.01). After CPAP, endothelium dependent dilation to ACh was significantly increased (434 (23)% of

baseline after CPAP v 278 (20)% before CPAP, p<0.001), whereas SNP induced dilation was unchanged.

Resting NO production was higher after CPAP, evidenced by a significantly greater reduction in basal flow

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Received 13 December 2004 Accepted 17 January 2006 Published Online First 14 March 2006

by L-NMMA (p = 0.05). L-Arginine reversed the effect of L-NMMA in all cases. **Conclusion:** In patients with OSA, treatment with CPAP improves baseline endothelial NO release and stimulates endothelium dependent vasorelaxation in the systemic circulation. This is a potential mechanism for improving systemic and vascular function in patients with OSA treated with CPAP.

bstructive sleep apnoea (OSA) is a common disease associated with a significantly increased risk of systemic hypertension.^{1 2} Moderate to severe OSA, with an apnoea hypopnoea index (AHI) of >15/hour, affects 4% of middle aged women and 9% of middle aged men.³ About 50% of individuals with OSA have systemic hypertension.⁴ OSA is characterised by repetitive airway occlusion resulting in cyclical surges of hypoxia which may occur hundreds of times a night. In addition, OSA is associated with heart failure,⁵ stroke,^{6 7} and coronary artery disease.^{8 9} The mechanisms that explain the relationship between OSA and daytime systemic hypertension and the ways to reduce OSA related vascular risk are unknown.¹⁰

substrate for NO).

Endothelial dysfunction, a key early event in hypertension and atherosclerosis, has been implicated as a possible mechanism linking the acute cyclical vascular stresses during sleep in OSA and the increased prevalence of chronic vascular diseases. We therefore hypothesised that nocturnal continuous positive airway pressure (CPAP), which alleviates airway obstruction, might improve systemic endothelial function.

METHODS

Subjects

Consecutive consenting patients with newly diagnosed untreated moderate to severe OSA (AHI >15/hour) were enrolled from the Royal Prince Alfred Sleep Disorders Clinic, Sydney, Australia. Exclusion criteria included cigarette smoking, systemic hypertension, bleeding disorders, needle phobias, any regular vasoactive or antioxidant medications, and previous failed attempts at CPAP therapy. Twelve subjects met these inclusion criteria and underwent baseline (pre-CPAP) forearm vascular reactivity studies. Of these, two were unable to tolerate CPAP therapy and therefore 10 were invited to complete the second study. In all cases the study procedures were uncomplicated.

Institutional ethics committee approval was obtained for this study and written informed consent obtained from all subjects.

CPAP treatment

The subjects were autotitrated and treated with an automated CPAP device (Autoset T, ResMed, Sydney, Australia). CPAP compliance was monitored nightly throughout the study, with adequate compliance prospectively defined as being a mean of 5 hours usage per night with a reduction of obstructive episodes to AHI <5 for 3 months.

Measurements

During the vascular studies, ECG, heart rate and arterial blood pressure were measured continuously (Hewlett Packard, USA). Forearm blood flow was measured by strain gauge plethysmography (EC, Hokanson), in which stretch of a mercury in Silastic strain gauge correlates to increase in the volume of the forearm which is proportional to forearm blood flow.¹¹ Cholesterol was measured by an automated enzymatic analyser (Hitachi 917, Japan; Roche Diagnostics, USA).

Abbreviations: ACh, acetylcholine; AHI, apnoea hypopnoea index;

BMI, body mass index; CPAP, continuous positive airway pressure; L-NMMA, N^G-monomethyl-L-arginine; NO, nitric oxide; OSA, obstructive sleep apnoea; SNP, sodium nitroprusside

Study protocol

All subjects fasted from midnight before the experimental procedure and were studied in the morning in the supine position. The room was kept quiet and at a constant temperature $(22-24^{\circ}C)$. A 20 G arterial line (Arrow RA-04120, Germany) was inserted by the Seldinger technique into the brachial artery of the non-dominant arm of each subject under sterile conditions with local anaesthetic. Blood was drawn for analysis and the cannula was connected to heparinised saline 1000 units in 500 ml (Baxter) at an infusion rate of 60 ml/hour. The subjects were then rested for 30 minutes before initial baseline measurements.

The vasoactive drugs infused were acetylcholine (ACh; a vasodilator that stimulates the release of nitric oxide (NO) and other dilator substances from the endothelium), sodium nitroprusside (SNP; an endothelium independent vasodilator), L-monomethylarginine (L-NMMA; a competitive antagonist of NO synthesis), and L-arginine (the physiological substrate for NO synthesis). Subjects were randomly assigned to either ACh or SNP as the first drug infusion.

Serial infusions were made into the brachial circulation via the arterial line in the following sequence using a syringe pump (Terumo STC-521, Tokyo, Japan): (1) a 4 minute control infusion (0.9% saline); (2) two consecutive 4 minutes of either 2 and 20 μ g/min ACh or SNP; 1 and 2.5 μ g/min; (3) a repeat control infusion; (4) two 4 minute infusions of the drug *not* infused in step 2, either ACh or SNP; (5) a repeat control infusion; (6) a 4 minute infusion of L-NMMA (4 mg/ min); (7) L-NMMA 4 mg/min with ACh 20 μ g/min; and (8) a 4 minute infusion of L-arginine (10 mg/min) (fig 1). All measurements were made with the subject awake. Forearm blood flow is expressed as a percentage of the control forearm blood flow uring the baseline infusion of saline. Forearm blood flow in the contralateral arm was also measured throughout to exclude effects from external stimuli.

Analysis of data

All analyses were conducted by observers blinded to the subject identity and whether the study was conducted before or after CPAP treatment. Forearm blood flow was expressed as ml/min per 100 ml forearm volume. Changes in blood flow were reported as percentage change from baseline.

The results are expressed as mean (SE). Differences in resistance vessel dilation to drug infusions were determined by two way ANOVA with repeated measures (SPSS version 9). Differences between subject characteristics before and after CPAP were determined by paired Student's *t* tests. A two sided p value of ≤ 0.05 was considered statistically significant.

RESULTS

All 10 subjects were healthy non-smokers of mean (SE) age 49 (8) years. Nine of the subjects were men. The female subject was post-menopausal. All subjects had at least

haracteristic	Pre-CPAP	Post-CPAP	
Age (years)	49 (8)	49 (8)	
AHI (/hour)	39 (15-104)	4.4 (2.1-6.1)*	
BMI (kg/m²)	31 (24-41)	31 (25-41)	
Systolic BP (mm Hg)	122 (11)	125 (13)	
Diastolic BP (mm Hg)	80 (6)	76 (12)	
Total cholesterol (mmol/l)	4.9 (0.9)	4.6 (0.9)	

moderate OSA with an AHI of 39/hour (range 15–104). The subjects were not on any regular medications and did not start any medications during the study.

Baseline study (pre-CPAP)

Before CPAP, systemic blood pressure was 122/80 mm Hg (SE 11/6). The body mass index (BMI) was in the obese range: 31 kg/m² (range 24–41), as is frequently seen in the OSA population. Total cholesterol, LDL, and HDL were all within normal limits. Between study visits there were no significant changes in resting blood pressure or heart rate, BMI, or the lipid profile of the subjects (table 1).

In response to ACh there was a dose dependent increase in brachial artery flows compared with the baseline value (p<0.01). There was also a dose dependent increase in flow to SNP (p<0.01). By contrast, there was no significant change in flow to L-NMMA. Co-infusion of L-NMMA partially inhibited the increase in forearm blood flow with ACh (p<0.01, fig 1).

Post-CPAP study

AHI was reduced to 4.4/hour (range 2.1-6.1) on successful CPAP (p<0.01). Baseline forearm blood flow was not significantly changed, nor was the arterial blood pressure (125/76 mm Hg (SE 13/12).

In response to ACh there was a significantly *greater* increase in flow compared with pre-CPAP (434 (23)% v 278 (20)%, p<0.001; table 2). This CPAP related increase was observed with both low and high dose ACh. By contrast, SNP responses were similar to pre-CPAP values (fig 1). After CPAP, L-NMMA induced vasoconstriction and a greater reduction in the brachial artery flow compared with pre-CPAP values (p = 0.05; fig 2). Co-infusion of L-NMMA reduced the high dose ACh related increase in forearm blood flow, although the flow remained greater than the pre-CPAP co-infusion flow values (p<0.001). L-Arginine reversed the L-NMMA related constriction, consistent with an inhibitory effect of L-NMMA on the NO pathway (fig 2).

There was no correlation between severity of noctural hypoxaemia (r = 0.18, p = 0.62), AHI (r = 0.61, p = 0.062), or



Figure 1 Infusion protocol for all studies. The order of ACh and SNP infusions were randomised. Infusion rates for all substances were 1 ml/min. BL, baseline blood flow measurements with infusion of 1 ml/min 0.9% saline; S, 0.9% saline infusion; ACh, acetylcholine; SNP, sodium mitroprusside; L-NMMA, N^G-monomethyl-L-arginine.

	ACh low	ACh high	SNP low	SNP high	L-NMMA high	ACh/L-NMMA	L-Arg
Before CPAP							
Subject 1	167	209	624	1250	164	149	80
Subject 2	132	296	281	357	67	60	57
Subject 3	362	474	372	650	95	431	159
Subject 4	141	156	149	222	113	124	138
Subject 5	167	572	376	476	94	420	128
Subject 6	135	168	151	214	114	137	135
Subject 7	122	183	224	285	63	174	135
Subject 8	300	442	264	354	62	372	161
Subject 9	87	163	134	194	67	106	125
Subject 10	106	163	88	101	78	104	111
After CPAP							
Subject 1	122	289	188	368	62	159	176
Subject 2	228	369	249	340	94	227	146
Subject 3	508	764	403	538	82	470	167
Subject 4	495	504	336	561	103	138	130
Subject 5	190	661	472	571	103	520	147
Subject 6	130	267	291	393	66	59	61
Subject 7	131	253	382	523	80	183	122
Subject 8	248	411	153	337	70	278	136
Subject 9	206	412	153	293	70	273	137
Subject 10	105	410	207	260	67	459	131

CPAP compliance (r = 0.71, p = 0.85) and the magnitude of the change in vascular function with treatment. This finding is, however, consistent with the small size of the study.

DISCUSSION

OSA is a major and underdiagnosed risk factor for hypertension and its complications.12 In this study we found that CPAP, an effective treatment for OSA, significantly improves microvascular function in the systemic circulation of OSA subjects. Specifically, CPAP treatment of OSA enhanced endothelial NO release in the forearm microcirculation (as evidenced by enhanced L-NMMA related vasoconstriction) and improved stimulated endothelium dependent vasodilatation (as shown by greater ACh vasodilator responses). This improvement in vasodilatation after ACh was only partially inhibited by co-infusion of L-NMMA, indicating that not only NO endothelium dependent pathways but also non-NO pathways were enhanced. These significant changes in vascular reactivity were observed after only 3 months of effective CPAP treatment. By contrast, the responses to the endothelium independent dilator SNP did not differ before

and after CPAP treatment, consistent with improved endothelial but not smooth muscle vasodilator function.

It has previously been shown that subjects with OSA have impaired systemic endothelial function compared with control subjects. Carlson *et al*¹² found impairment of the ACh response in normotensive and hypertensive OSA subjects compared with those without OSA loosely matched for age, sex and weight. In this study impairment in the SNP response was also reported in the hypertensive OSA subjects. However, Kato *et al*¹³ recently compared the vascular responses in eight subjects with OSA with a tightly matched control group on no medications and found that ACh responses were impaired but there was no difference in the SNP response.

Several mechanisms have been proposed to explain the reduction in endothelial responsiveness in patients with OSA. Animal studies have shown that intermittent hypoxia plays a key role in the development of persistent daytime endothelial dysfunction. Sprague-Dawley rats exposed to intermittent hypoxia have less in vivo responsiveness to increasing doses of ACh than control rats. There is also significantly greater vasoconstriction to L-NAME (an NO antagonist) in



Figure 2 Forearm blood flow responses before and after CPAP showing significantly enhanced responses to ACh alone or ACh with L-NMMA after CPAP than before (p<0.001). SNP responses were unchanged with CPAP treatment. The vasoconstrictor response to L-NMMA was significantly greater after CPAP than before (p=0.05), consistent with an enhanced release of nitric oxide from the vascular endothelium.

intermittently hypoxic rats, suggesting impairment of basal NO production.¹⁴ Human studies have also pointed to hypoxia as a possible cause of endothelial impairment; abnormal vascular responses have been observed in OSA patients exposed to acute isocapnic hypoxia.¹⁵

Possible mechanisms of hypoxia induced impairment of endothelial function might include direct damage to the endothelium or altered biosynthesis of NO from L-arginine, which is an oxygen dependent process.¹⁶ Such hypoxia induced endothelial impairment may occur in isolation or it may be additive to other acute effects of apnoea such as cyclical surges of blood pressure.

Our data have shown (for the first time to our knowledge) that microvascular endothelial vasodilator dysfunction in subjects with OSA is reversible with appropriate long term treatment; indeed, basal and stimulated endothelial vasodilator release are significantly enhanced. Previous studies have shown that CPAP might reduce the acute physiological effects of apnoeas in OSA, including cyclical hypoxia, surges in blood pressure and sympathetic nerve activity,^{17–19} but have not addressed longer term effects on vascular physiology. Imadojemu *et al*²⁰ found an improvement in forearm vasoreactivity in response to a limited non-invasive reactivity study after 2 weeks of CPAP therapy.

Consistent with our findings are the results from two studies on the effect of CPAP on plasma levels of NO derivatives in subjects with OSA. Ip *et al*²¹ reported reduced serum nitrite and nitrate levels in subjects with moderate to severe OSA compared with matched controls, which returned to normal levels after one night of CPAP treatment. Schulz *et al*²² also found increased serum NO derivatives in subjects with OSA after short term CPAP treatment, and this increase in NO derivatives was maintained at long term follow up. CPAP treatment also improves hypertension control, both at night and during the day,²³ by an average of 10 mm Hg (systolic, mean and diastolic), which may in part be explained by the improvement in microvascular endothelial vascular function.²⁴

Although most studies of endothelial function in OSA have concentrated on the microvasculature—the level of the systemic circulation considered most relevant in the pathogenesis of hypertension²⁵—other groups have recently reported studies of endothelial function in peripheral conduit vessels such as the brachial artery. Both Kraiczi *et al*²⁶ and Ip *et al*²⁷ have found impaired flow mediated dilation (FMD) in OSA subjects consistent with a predisposition to atherosclerosis; Ip *et al* also reported a beneficial effect of CPAP on FMD (although no mechanistic data regarding the role of NO were available).

One of the limitations of our study is its relatively small size due to the invasive nature of the protocol and the restrictions of our enrolment criteria. The study was not therefore able to find a correlation with the severity of OSA and the degree of endothelial impairment. Furthermore, we elected not to perform these invasive studies on a control group of normal subjects without OSA in whom forearm vascular responses to ACh, SNP, and L-NMMA have been extensively published previously with consistent results.^{13 25 28}

Kato *et al* found a similar dose dependent increase in forearm blood flow in untreated OSA patients in response to brachial artery infusions of ACh and SNP, with the increase in endothelium dependent vasodilatation to ACh blunted compared with normal controls, indicating impaired microvascular endothelial function.¹³ For our study, each patient was their own control for the vascular responses after CPAP and no difference was found in the characteristics of the subjects before and after CPAP.

Finally, we elected to study normotensive rather than hypertensive subjects with OSA. This was to allow study of

the underlying vascular mechanisms in the absence of any confounding effects of antihypertensive medications, many of which are known to influence endothelial function per se²⁹ even several half-lives after discontinuation.³⁰ Furthermore, as CPAP is known to reduce blood pressure in hypertensive OSA subjects,²⁴ we also wished to avoid the possible confounding effects of blood pressure lowering itself on systemic endothelial and smooth muscle dependent vascular reactivity.

In conclusion, treatment of OSA with CPAP improves systemic vascular endothelial function. OSA has been implicated in the pathogenesis of hypertension, cardiovascular disease, heart failure, and stroke, all of which are associated with impaired endothelial responses. CPAP treatment may therefore provide an opportunity to reduce the vascular risk attributable to OSA; long term end point studies will be needed to address this important possibility.

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Dr Lattimore is supported by a Cardiac Society of Australia and New Zealand Research Scholarship. This work was supported in part by a grant-in-aid from the National Heart Foundation of Australia.

A/Prof Ian Wilcox is a minor shareholder in ResMed, Australia.

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LUNG ALERT

Tumour necrosis factor α in refractory asthma: new insight

A Berry MA, Hargadon B, Shelley M, *et al.* Evidence of a role of tumour necrosis factor α in refractory asthma. N Engl J Med 2006;**354**:697–708

The authors showed that monocytes from 10 patients with refractory asthma expressed significantly higher levels of TNF- α receptor 1, TNF- α converting enzyme, and membrane bound TNF- α than monocytes from 10 normal controls or from 10 patients with mild to moderate asthma.

They also investigated the effect of 10 weeks of treatment with etanercept, a soluble TNF- α receptor antagonist, on 10 patients with refractory asthma in a randomised, double blind, placebo controlled, crossover study. Compared with placebo, etanercept significantly reduced peripheral blood monocyte expression of membrane bound TNF- α , increased the concentration of methacholine required to decrease forced expiratory volume in 1 second (FEV₁) by 20%, and improved asthma quality of life scores. Furthermore, treatment significantly improved post bronchodilator FEV₁ and decreased the total symptoms score and mean sputum histamine concentration. There was no significant difference between groups in any of the other airway inflammatory markers studied (exhaled nitric oxide concentrations, sputum eosinophilic cationic protein, interleukin 8, or cysteinyl leukotriene concentrations).

The study concluded that the TNF- α axis is upregulated in peripheral blood monocytes of patients with refractory asthma. Although not powered to detect effects on airway inflammatory markers, the significant reduction in sputum histamine but not in other markers suggests that the effect of etanercept is primarily directly on smooth muscle and mast cells. Further investigations are needed to confirm this.

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