Effect of supplemental oxygen on blood pressure in OSA: a randomised, CPAP withdrawal trial

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At a glance commentary:
Scientific knowledge on the subject:
Obstructive sleep apnea (OSA) is associated with systemic hypertension. In animal and human experimental models, intermittent hypoxia has been shown to cause diurnal blood pressure elevations. Previous trials assessing the effects of supplemental oxygen on blood pressure in OSA have had methodological limitations and therefore have not adequately addressed the role of intermittent hypoxia in daytime blood pressure elevations in OSA.
What this study adds to the field:
In this study, following CPAP withdrawal, supplemental oxygen virtually abolished the rise in morning blood pressure seen with supplemental air, over fourteen days. Thus, intermittent

hypoxia, which supplemental oxygen ameliorated, is likely to be the dominant cause of increased morning blood pressure in OSA. This is the first study to demonstrate the importance of intermittent hypoxia as the dominant cause of morning blood pressure increases in patients with OSA. It potentially has important implications for patients with OSA who have resistant hypertension and who cannot tolerate CPAP, the standard treatment for OSA. As such, further work is required to assess if the effects of supplemental oxygen on blood pressure following CPAP withdrawal translate into a therapeutic benefit for patients.

"This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org”

Abstract

Rationale

Obstructive sleep apnea (OSA) is associated with systemic hypertension. Either overnight intermittent hypoxia, or the recurrent arousals that occur in OSA, could cause the daytime increases in blood pressure (BP).

Objectives

To establish the role of intermittent hypoxia in the increased morning BP in patients with OSA.

Methods

Randomised, double-blinded, cross-over trial assessing the effects of overnight supplemental oxygen versus air (sham) on morning BP, following continuous positive airway pressure (CPAP) withdrawal in patients with moderate to severe OSA. The primary outcome was the change in home morning BP following CPAP withdrawal for 14 nights, oxygen versus air. Secondary outcomes included oxygen desaturation index (ODI), apnea hypopnea index (AHI), subjective (Epworth sleepiness score) and objective (Oxford sleep resistance test) sleepiness.

Measurements and main results

Supplemental oxygen virtually abolished the BP rise following CPAP withdrawal and, compared to air, significantly reduced the rise in mean systolic BP (-6.6mmHg; 95% confidence interval or CI -11.3 to -1.9; p=0.008), mean diastolic BP (-4.6mmHg; 95% CI -7.8 to -1.5; p=0.006), and median ODI (-23.8/h; interquartile range -31.0, -16.3; p<0.001),

following CPAP withdrawal. There was no significant difference, oxygen versus air, in AHI, subjective or objective sleepiness.

Conclusions

Supplemental oxygen virtually abolished the rise in morning BP during CPAP withdrawal. Supplemental oxygen substantially reduced intermittent hypoxia, but had a minimal effect on markers of arousal (including AHI), subjective or objective sleepiness. Therefore intermittent hypoxia, and not recurrent arousals, appears to be the dominant cause of daytime increases in BP in OSA.

Abstract word count: 247

Key words: Sleep apnea, obstructive; blood pressure; intermittent hypoxia.

Introduction

Obstructive sleep apnea (OSA) is associated with significant cardiovascular disease (1, 2), particularly with elevated daytime blood pressure (BP) and hypertension (3, 4). CPAP has been shown to improve important markers of cardiovascular health; improving BP (5-7)– particularly in those with resistant hypertension (7) – and improving endothelial function (8). The potential underlying roles of intermittent hypoxia, versus sleep fragmentation, in the development of hypertension in OSA are not fully understood, and an improvement in this understanding may help to develop new treatments to reduce cardiovascular risk in OSA.

Hypertension is a key risk factor for cardiovascular disease (9). OSA causes both acute rises in BP overnight (10), and daytime elevations in BP (3). Acute rises in BP overnight are known to be due to arousals and not the intermittent hypoxia (11, 12). However, the mechanisms underlying daytime elevations in BP are not fully understood. Experimental exposure to intermittent hypoxia increases awake blood pressure in rodents (13), and in healthy human subjects (14). In addition, canine models of OSA produce more marked daytime blood pressure elevations than sleep fragmentation in the same dogs, suggesting that either intermittent hypoxia or another non-arousal mediated mechanism, are responsible (15). However, we have previously argued that these experiments do not accurately model the intermittent hypoxia of OSA, and that sympathetic activation from arousals may be a more important cause of daytime BP elevations in OSA (16).

Supplemental oxygen therapy can abolish intermittent hypoxia in OSA (17), and therefore, if intermittent hypoxia is the dominant cause of daytime increased BP rather than recurrent arousals, it should lower daytime BP in OSA. Two previous randomised controlled trials showed no effect of supplement oxygen on BP in OSA (18, 19). However, both had

limitations; the flow rates of oxygen used were low at 2-3l/min, patients with the most severe OSA and the most severe hypoxemia were excluded, and the average usage of supplemental oxygen was modest. Due to these limitations, these trials have not definitely established whether intermittent hypoxia or recurrent arousals are the dominant cause of daytime BP rises in OSA.

CPAP withdrawal is a useful experimental model of OSA (20). The return of OSA during two weeks of CPAP withdrawal leads to a large rise in morning BP (approximately 9.0mmHg systolic and 5.4mmHg diastolic) (21). We hypothesised that if intermittent hypoxia is important in daytime BP elevations in OSA, then supplemental oxygen would attenuate the rise in BP seen during CPAP withdrawal, compared to supplemental air (sham).

Some of the results of these studies have been previously reported in the form of abstracts (22, 23).

Methods

The Supplemental Oxygen during CPAP withdrawal (SOX) trial was a single, tertiary centre, double blind, cross-over trial with randomised treatment order. It was prospectively registered (ISRCTN 17987510) and approved by the South Central Oxford B Research Ethics Committee (REC Reference 15/SC/0007).

Patients and screening

Patients had an original diagnosis of moderate-to-severe OSA and had been treated with CPAP for >1 year with an average CPAP usage of >4h/night. Following written informed consent, patients underwent screening which involved: three nights of overnight pulse

oximetry (Konica Minolta 300i, Japan) on CPAP, followed by four nights of overnight pulse oximetry without their CPAP. Full inclusion and exclusion criteria are reported in the supplementary material *(pages 3-4)*; briefly, eligible patients had adequate control of OSA on CPAP with a nocturnal oxygen desaturation index ≥4% ($ODI_{\geq 4\%}$) of <10 and showed return of OSA off CPAP with an $ODI_{\geq 4\%}$ of >20 on at least 1 out of 4 nights off CPAP. Following screening, eligible patients resumed their normal CPAP for at least two weeks before attending for randomisation.

Randomisation, intervention, and blinding

Figure 1 summarises the trial visits and procedures. Briefly, patients were randomised at visit 1 to receive overnight supplemental oxygen or air (using a real or sham concentrator, respectively) at a rate of 5 l/min via either nasal cannulae or fitted face mask, instead of their CPAP for 2 weeks. Following that, after a 2-week washout period back on CPAP, at visit 3, patients crossed over to receive supplemental air or oxygen for another 2 weeks, again instead of their CPAP. A high flow rate of oxygen was chosen because in a previous RCT a flow rate of 3l/min oxygen showed only modest reductions in intermittent hypoxia in patients with severe OSA (18).

Treatment order was randomised 1:1 using permuted blocks of 6 to either oxygen-air or air-oxygen, via online randomisation software (Sealed Envelope, London, UK). Patients and researchers carrying out outcome assessments and data analyses were blinded to the study allocation, i.e. oxygen or sham (air) arm. Oxygen and sham concentrators (NewLife Elite, AirSep, Buffalo, USA) were identical in appearance and were labelled A (oxygen) or B (air) by an unblinded researcher not involved in outcome assessment or day-to-day trial management.

Procedures

Full details of the study procedures can be found in the supplementary material *(pages 4-8)*. Patients recorded their BP in triplicate at home for five days before and on the 14 days of each treatment arm. In addition, office BP was recorded in triplicate at all four study visits. During each treatment arm, patients recorded overnight pulse oximetry on nights 1-13 and performed home respiratory polygraphy (Stowood Scientific Instruments, Beckley, UK) on night 14. To assess daytime sleepiness, the Epworth sleepiness score (ESS) and maintenance of wakefulness test equivalent, the Oxford Sleep Resistance (OSLER) test (see *Supplementary material page 6)*, was recorded at each trial visit. On night 14 of each treatment arm, patients collected overnight urine for urinary metadrenaline and normetadrenaline measurements. At each trial visit, serum was collected to measure high sensitivity CRP (hsCRP). Venous base excess – as an integrated measure of carbon dioxide levels (24) – was measured at all visits for the last 12 patients.

Outcome measures

The primary outcome measure was the difference in the change of home morning BP from baseline to follow-up at two weeks, between the oxygen and the air arms (*supplementary material pages 4-5)*. Triplicate home early morning BPs were averaged over the three days prior to each visit. Secondary outcome measures were the absolute, or change in: home morning heart rate, office BP and heart rate, overnight urinary normetadrenaline and metadrenaline (metabolites of sympathetic hormones noradrenaline and adrenaline respectively), ESS, OSLER test, overnight pulse oximetry parameters, and the Apnea Hypopnea Index (AHI), oxygen versus air. Pulse oximetry parameters were averaged from nights 8-13 of each arm. Pulse oximetry parameters were: the $ODI_{\geq 4\%}$, percentage time with

oxygen saturations <90%, mean overnight heart rate, and heart rate rises (HRR) index (as a surrogate marker of 'arousals' at the brain stem level, so-called 'autonomic' arousals) (25). Home respiratory polygraphy was recorded on night 14 of each treatment arm *(supplementary material page 5)* to calculate the AHI. There was no oxygen desaturation requirement in our hypopnea definition, as this would have introduced an obvious bias between the treatment arms. The relative change in venous base excess and serum hsCRP were included as exploratory outcomes.

Statistics

In a meta-analysis of previous CPAP withdrawal trials, sham CPAP led to a +9.7mmHg (standard deviation, SD, 14) rise in home morning systolic BP when compared to continued CPAP (19). Thus, we calculated that the number of participants required in order not to miss a 6mmHg difference in home morning systolic BP (approximately two thirds the size of the BP rise seen between sham CPAP and continued CPAP) was 24, in a cross-over design using a paired t-test, assuming a SD of the change of 10mmHg (approximately two-thirds of the size of the SD in BP change between sham CPAP and continued CPAP), for a power of 80%, and a significance level of <0.05. In previous parallel withdrawal trials, there were very low drop-out rates of ~1% (21). Therefore, to allow for increased drop-outs due to the more arduous cross-over design, a sample size of 30 was initially proposed. Due to a significantly higher actual drop-out rate, with nine of the first 23 patients dropping out (39%), the protocol was amended part way through the trial to allow increased recruitment to 50 patients, allowing for this higher drop-out rate and still providing 24 complete datasets for analysis.

Outcome measures were assessed for normality. Normally distributed data are expressed as mean ± SD and non-normally distributed data as median (first quartile, third quartile). Where normally distributed, the primary and secondary outcome measures were assessed using paired t-tests, and when not normally distributed, using Wilcoxon rank tests. Statistical analyses were conducted using SPSS (Version 20, IBM, Armonk, NY, USA).

Results

Patients were recruited from June 2015 until June 2017, when enough complete datasets were available. Details of screening, randomisation, and withdrawals are shown in the CONSORT diagram in *Figure 2*. Twenty patients received treatment order oxygen-air and 18 patients received treatment order air-oxygen. After receiving the first trial intervention, there were seven patients who withdrew consent whilst receiving supplemental air, five patients who withdrew consent whilst receiving supplemental oxygen, and one patient who withdrew consent during the washout period whilst on CPAP due to an unrelated illness.

Baseline characteristics

The baseline characteristics are shown in *Table 1* for all 25 patients who completed the trial and for each order of treatment. Patients allocated to the treatment order air-oxygen had by chance a lower median ODI during pre-trial screening of 26.7/hour (25.2, 34.3), compared to those allocated to the oxygen-air (median 42.7/hour (30.5, 54.3). Otherwise the two treatment orders were well matched.

Concentrator usage

The mean operation hours of the concentrators during the treatment arms were 7.2 ± 1.0h/night, and 7.4 ± 0.8h/night for oxygen and air respectively.

Morning blood pressure

Supplemental oxygen abolished the usual rise in home BP caused by 2 weeks of CPAP withdrawal (21). Compared to the supplemental air (sham) arm, the effect size for oxygen was -6.6 mmHg systolic (95% confidence interval or CI -11.3 to -1.9, p=0.008) and -4.6mmHg diastolic (95% CI -7.8 to -1.5, p=0.006) (*Table 2* and *Figure 3*). Adjustments for treatment order and potential modifiers essentially did not alter these relationships *(supplementary material page 8-9*).

There was a significant effect of supplemental oxygen compared to air on office BP changes, recorded later in the morning, as shown in *Table 3*. There was no significant effect of supplemental oxygen compared to air on either home or office morning heart rate (*Table 2* and *Table 3*, respectively).

Overnight pulse oximetry and respiratory polygraphy

As expected, supplemental oxygen significantly and markedly attenuated measures of intermittent hypoxia, with a median reduction in ODI of -23.8/h (p<0.001; IQR -31.0, -16.3), and an absolute median reduction of the percentage time with oxygen saturations <90% of -9.8% (p<0.001; IQR -16.7, -4.3), compared to air. There was a small significant reduction in the heart rate rises index (a measure of autonomic arousals), with a median reduction of -3.7/h (p=0.006; IQR -9.1, -0.8), oxygen versus air. The small reduction in median AHI of -3.6/h (p=0.98; IQR -10.2, +10.1), oxygen versus air, was not statistically significant.

Daytime sleepiness and sympathetic activation

There were no significant differences in the change of either subjective or objective sleepiness, oxygen versus air. There were no significant differences in the change in mean overnight urinary volume or overnight urinary creatinine concentration, oxygen versus air. The small reduction in mean overnight urinary normetadrenaline levels of -12.8nmol/µmol (p=0.25; 95% CI -35.3 to +9.6) oxygen versus air, was not statistically significant. There was no significant difference in overnight urinary metadrenaline or normetadrenaline production, oxygen versus air, whether correcting either for the rate of urinary production or urinary creatinine levels *(Supplementary material page 14 and Supplementary Table 3)*.

hsCRP and venous blood gasses

Changes in hsCRP and venous base excess were exploratory outcomes. There were no significant differences in the change in hsCRP levels, oxygen versus air. Mean venous base excess from baseline to follow-up increased by +3.1mmol/l (p<0.001; 95% CI +1.8 to +4.4), oxygen versus air.

Discussion

Supplemental oxygen virtually abolished the rise in morning BP during CPAP withdrawal, compared with air. This suggests that intermittent hypoxia is responsible for the increased morning blood pressure in OSA. As expected, supplemental oxygen markedly attenuated intermittent hypoxia, whilst having only a small effect on heart rate rises and the AHI, surrogate markers of arousal. This suggests that intermittent hypoxia, rather than arousals, is responsible for the increased morning BP in OSA. The partial reduction in overnight urinary normetadrenaline was not significant and it is thus not clear in patients with OSA

whether overnight intermittent hypoxia increases morning BP via changes in sympathetic activity or via another mechanism. Unexpectedly, venous base excess was significantly increased with supplemental oxygen therapy and needs to be monitored in patients with OSA given such therapy.

The effects of supplemental oxygen during CPAP withdrawal on BP contrast with the findings of a previous RCT (19). Gottlieb *et al.* found no effect of supplemental oxygen on BP during 12-weeks of therapy in OSA patients, compared with control. However, Gottlieb *et al.* used a low flow rate of 2l/min supplemental oxygen delivered by nasal cannulae, monitoring ambulatory BP using an intermittent method that itself causes arousals and elevations in nocturnal BP (26); furthermore they excluded patients with the most severe OSA or hypoxia (those with either an AHI>50 or with >10% time with oxygen saturations <85%). In our study we used a higher flow rate of 5l/min supplemental oxygen, monitored morning awake BP, and did not exclude patients based on OSA or hypoxia severity. The exclusion of patients with severe OSA in previous studies is a key difference, as a previous meta-analysis has shown that greater severity of returning OSA during CPAP withdrawal leads to larger increases in morning blood pressure (21). We also used a more powerful cross-over CPAP withdrawal design, including patients with moderate to severe OSA with known previous response to CPAP, rather than treatment naïve patients. In addition, the mean usage of oxygen was lower in the Gottlieb study, at 4.8h/night compared to 7.2h/night in our study. It is likely that these methodological issues explain the differences in our findings. Gottlieb *et al.* also examined the effects of oxygen over a longer time period of 12 weeks rather than two weeks. Although it is possible that the effect of supplemental oxygen on BP may decrease over time we did not observe any decrease in the attenuating effect of

supplemental oxygen on BP over two weeks (see *Supplementary Table 2* and *Supplementary Figures 1 &2*).

As has been the case previously (17), supplemental oxygen did substantially reduce intermittent hypoxia in the SOX trial, which makes it likely to be responsible for the changes in BP. The reductions in overnight heart rate rises and the AHI (surrogates of arousal) that we observed were small, and therefore very unlikely to be a significant alternative explanation for the virtual abolition of BP rises observed with supplemental oxygen during CPAP withdrawal.

Fletcher and colleagues conducted elegant experiments in rodents showing that intermittent hypoxia leads to diurnal BP rises (13); furthermore, these diurnal BP rises were shown to be dependent on the carotid body, the adrenal medulla, peripheral sympathetic nervous system, and the renin-angiotensin system (13, 27). Intermittent hypoxia also increases daytime BP and muscle sympathetic nerve activity in healthy volunteers (14). These experiments suggest that intermittent hypoxia, sensed by the carotid chemoreceptors, leads to increased daytime BP by increased sympathetic activity. In the SOX trial overnight urinary normetadrenaline levels, used as a marker of sympathetic activity, were only slightly reduced and this change was not statistically significant. This is perhaps not a surprising result as supplemental oxygen had little effect on the AHI or heart rate rises, so arousal mediated sympathetic activity was presumably unaffected by supplemental oxygen. Previously supplemental oxygen has been shown to decrease daytime, but not night-time, noradrenaline levels in OSA patients (18). It is therefore still possible that reductions in daytime sympathetic activity underlie attenuated BP rises during CPAP withdrawal, but this is uncertain.

Whilst supplemental oxygen markedly attenuated the rise in BP with CPAP withdrawal, it had no effect on the rise in morning heart rate. If supplemental oxygen attenuates BP rises by attenuating sympathetic activation, similar attenuation in heart rate rises might have been expected. However, baroreceptor-mediated vagal activation from the rise in the BP might have prevented significant rises in heart rate in the air arm (28). In addition, the mechanisms by which intermittent hypoxia/sympathetic activation lead to BP rises and heart rate rises are different. In animal models intermittent hypoxia-mediated BP rises were dependent on the renin-angiotensin system (27), and diurnal heart rate increases were not observed with intermittent hypoxia (29). Vagal tone is also important in determining heart rate and there is evidence of altered sympathetic/vagal balance with reductions in vagal modulation in OSA (30), which could be mediated by other mechanisms.

In the SOX trial, supplemental oxygen also had no effect on either objective or subjective sleepiness. Similarly, supplemental oxygen in OSA has previously been shown not to effect daytime sleepiness (31). Arousal-mediated sleep fragmentation therefore seems likely to cause daytime sleepiness in OSA, rather than intermittent hypoxia. Supplemental oxygen also had no effect on nocturia suggesting hypoxia is not a driver of this consequence of OSA.

Previous studies have shown that supplemental oxygen could increase the size of myocardial injury, potentially by increasing oxidative stress, when given to normoxic patients following myocardial infarction (32). We have not measured oxidative stress in this study but did not see any downstream changes in systemic inflammation, measured by hsCRP. This potential deleterious effect of supplemental oxygen is not directly related to our primary outcome in this physiological mechanistic study but would need consideration in future research studies assessing any therapeutic effects of supplemental oxygen.

Supplemental oxygen caused significant increases in venous base excess, compared to oxygen. Venous bicarbonate was used as an integrated marker of hypercapnia (24). The longer-term safety of oxygen therapy in OSA therefore needs careful consideration as, although hypercapnia was not particularly marked in this study, oxygen has the potential to worsen/lead to hypercapnic respiratory failure in some individuals, particularly those with OSA/obesity hypoventilation overlap (33).

There was a higher drop-out rate in this trial compared to previous withdrawal trials (26% vs 1%) (21). This is probably explained by the longer duration and cross-over design of the SOX trial. Patients who withdrew after randomisation were more obese and had more severe OSA *(Supplementary Table 1)* and there were slightly more patients who withdrew whilst receiving supplemental air than when receiving supplemental oxygen (7 versus 5, NS). However, adjustments for treatment order and baseline characteristics essentially did not alter the primary outcome *(Supplementary material pages 8-9*). Although a higher drop-out rate would have been of concern in a clinical trial of therapy, this is of less importance in a physiological mechanistic study.

BP was only recorded in the early and later morning, and the effect of oxygen therapy on 24-hour BP profile is not known. Morning BP was chosen as an outcome as OSA is associated with a "non-dipping" pattern in BP which is an important risk factor for cardiovascular disease (34). Standard 24-hour BP monitoring techniques have limitations and have been shown to cause arousals from sleep and thus raise BP (26). Changes in office BP, which was measured later than the home measurement (at approximately 10am), were of similar magnitude to changes in home BP. This suggests the BP rise is not isolated to a very brief period after waking.

Conclusions

Supplemental oxygen virtually abolished the rise in morning BP during two weeks of CPAP withdrawal. Supplemental oxygen markedly attenuated intermittent hypoxia whilst having a minimal effect on the AHI and autonomic arousals. Supplemental oxygen had no effect on morning heart rate, daytime sleepiness, hsCRP, urinary volume, and only partially reduced overnight sympathetic activity. Whilst the exact mechanisms underlying the attenuation of BP rises by oxygen during CPAP withdrawal are not clear, intermittent hypoxia, and not arousal-mediated sympathetic activation, appears to be the likely dominant cause of daytime increases in BP in OSA. This was a physiological mechanistic study and future research is needed to see if this translates into a potential clinical benefit. Previous trials assessing supplemental oxygen in OSA excluded patients with the most severe hypoxia, and this is probably the group most likely to benefit from oxygen treatment. CPAP has a greater effect on BP in patients with resistant hypertension. Thus, the effect of supplemental oxygen on BP should be assessed in patients with OSA and resistant hypertension, with significant nocturnal intermittent hypoxia, where CPAP is not indicated or tolerated, but with careful monitoring of carbon dioxide levels.

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	Mean ± SD, Median (IQR) or Number (%)		
	All Patients (n=25)	*Treatment Order Oxygen- Air (n=16)*	*Treatment Order Air-Oxygen (n=9)*
Age (years)	62.7 ± 6.9	61.0 ± 7.4	65.8 ± 4.8
Male gender	21 (84%)	14 (88%)	7 (78%)
BMI (kg/m^2)	35.3 ± 6.7	36.1 ± 7.1	34.0 ± 6.3
Neck circumference (cm)	44.2 ± 4.1	45.3 ± 3.7	42.4 ± 4.2
$ODI_{\geq 4\%}$ at diagnosis (/hour)	48.0 (25.3, 68.2)	50.0 (26.1, 70.1)	45.7 (24.1, 65.7)
$ODI_{\geq 4\%}$ off CPAP in screening (/hour)	34.5 (26.3, 46.5)	42.7 (30.5, 54.3)	26.7 (25.2, 34.3)
CPAP usage (h/night)	6.5 ± 0.2	6.6 ± 0.3	6.3 ± 0.2
On regular anti-hypertensives	16 (64%)	11 (69%)	5 (56%)

Table 1: Baseline characteristics for patients who underwent randomisation and completed the trial. Characteristics are shown for all patients and divided into groups by treatment order.

	Oxygen		*Air*		Difference in mean change, oxygen versus air (95% CI)	p value
	Baseline/ run-in	Follow-up	Baseline/ run-in	Follow-up		
Systolic BP (mmHg)	129.6 ± 15.1	129.8 ± 13.6	129.2 ± 14.1	136.1 ± 14.9	-6.6 (-11.3 to -1.9)	**0.008**
Diastolic BP (mmHg)	79.3 ± 8.0	81.6 ± 8.0	78.3 ± 7.8	85.3 ± 9.6	-4.6 (-7.8 to -1.5)	**0.006**
Heart rate (bpm)	61.9 ± 9.4	64.1 ± 9.1	61.7 ± 8.3	64.9 ± 8.9	-1.0 (-3.9 to +1.9)	0.50

Table 2: Home BP (primary outcome) and home heart rate (secondary outcome) data at baseline/run-in and at two-week follow-up for the supplemental oxygen and air (sham) arms. Baseline/run-in and follow-up data are displayed as mean ± standard deviation. P

values and 95% confidence intervals (95% CI) were calculated using paired t-tests. P<0.05 highlighted in bold.

Office BP and heart rate recordings						
	Oxygen		*Air*		Between groups difference, oxygen versus air	P value
	Baseline/ run-in	Follow-up	Baseline/ run-in	Follow-up		
Systolic BP (mmHg)	132.4 ± 16.7	130.9 ± 15.3	128.0 ± 13.7	134.8 ± 15.5	-8.3 (-15.3 to -1.3)	**0.02**
Diastolic BP (mmHg)	80.8 ± 9.4	79.6 ± 8.2	78.9 ± 9.9	84.0 ± 9.2	-6.3 (-11.0 to -1.6)	**0.01**
Heart rate (bpm)	66.3 ± 13.5	67.6 ± 13.0	65.6 ± 11.9	67.8 ± 14.0	-0.8 (-4.1 to +2.5)	0.61
Overnight pulse oximetry and sleep study parameters						
ODI (/h)	-	6.4 (4.0, 14.7)	-	32.5 (25.6, 47.0)	-23.8 (-31.0, -16.3)	**<0.001**
Mean oxygen saturations (%)	-	96.9 ± 1.2	-	92.6 ± 1.8	+4.3 (+3.6 to +4.9)	**<0.001**
Time O_2 sats <90% (%)	-	2.0 (0.3, 3.9)	-	14.3 (5.9, 21.2)	-9.8 (-16.7, -4.3)	**<0.001**
Heart rate rises > 6bpm index (/h)	-	27.1 (21.4, 37.4)	-	31.9 (24.0, 44.3)	-3.7 (-9.1, -0.8)	**0.006**
Mean heart rate (bpm)	-	61.5 (53.5, 64.0)	-	62.0 (55.4, 65.1)	-1.2 (-2.8, +1.1)	0.12
AHI (/h)	-	30.4 (23.6, 42.6)	-	34.4 (22.7, 44.4)	-3.6 (-10.2, +10.1)	0.98
Measures of sleepiness						
ESS	7.0 ± 4.8	9.0 ± 4.2	6.3 ± 3.8	8.8 ± 4.5	-0.6 (-2.5 to +1.4)	0.56
OSLER (s)	2400 (1285, 2400)	1746 (770, 2400)	2400 (1286, 2400)	2025 (956, 2400)	0 (-425, +14)	0.50
Urinary measurements						
Rate of urine production (ml/h)	66.7 (48.6, 95.8)	85.1 (59.0, 111.8)	66.7 (46.8, 105.1)	95.8 (56.3, 116.7)	+0.4 (-18.2 to +19.0)	0.97
Normetadrenaline (nmol/µmol)	121.7 (85.2, 145.3)	140.0 (116.8, 186.2)	107.5 (79.7, 137.6)	134.7 (113.7, 199.7)	-12.8 (-35.3 to +9.6)	0.25
Metadrenaline (nmol/µmol)	34.1 (28.3, 44.6)	37.9 (27.1, 43.2)	35.1 (24.8, 43.6)	37.3 (26.9, 46.8)	-0.6 (-6.9, +5.7)	0.84
Blood measurements						
hsCRP (mg/l)	2.7 (0.9, 3.5)	2.0 (0.7, 3.8)	1.1 (0.5, 2.8)	1.7 (0.9, 2.6)	-0.4 (-3.7, +0.6)	0.12
Venous base excess (mmol/l)	+1.6 ± 2.5	+3.2 ± 2.2	+3.0 ± 2.3	+1.5 ± 1.9	+3.1 (+1.8 to +4.4)	<0.001

Table 3: Secondary and exploratory outcome data for the supplemental oxygen and air arms at baseline/run-in and at two-week follow-up. For office BP and heart rate, measures of sleepiness, urinary measurements, and blood measurements, the difference in the change of

values from baseline to follow-up was compared, oxygen versus air. For overnight oximetry and home sleep study parameters the absolute differences in values at follow-up were compared, oxygen versus air. Normetadrenaline and metadrenaline excretions were corrected by urinary creatinine concentrations. Baseline and follow-up data are expressed as mean ± SD or median (first quartile, third quartile) and for oxygen/air differences, data are expressed as mean (95% CI lower limit to upper limit) or median (first quartile, third quartile). Differences were compared using paired t-tests or Wilcoxon rank tests as appropriate. P<0.05 highlighted in bold.