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.

Acknowledgements

This work was funded by the Oxford Radcliffe Hospital Charitable Funds and ResMed UK. This research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not

necessarily of the NHS, the NIHR, or the Department of Health. NP was supported by a NIHR Academic Clinical Lectureship.

References

1. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046–53.

2. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071–8.

3. Davies CW, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. Thorax 2000;55:736–40.

4. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.

5. Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJO. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002;359:204–10.

6. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. JAMA 2015;314:2280-93.

7. Hu X, Fan J, Chen S, Yin Y, Zrenner B. The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich) 2015;17:215–22.

8. Schwarz EI, Puhan MA, Schlatzer C, Stradling JR, Kohler M. Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. Respirol 2015;20:889–95.

9. Lawes CMM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancet (London, England) 2008;371:1513–8.

10. Davies RJ, Crosby J, Vardi-Visy K, Clarke M, Stradling JR. Non-invasive beat to beat arterial blood pressure during non-REM sleep in obstructive sleep apnoea and snoring. Thorax 1994;49:335–9.

11. Ringler J, Basner RC, Shannon R, Schwartzstein R, Manning H, Weinberger SE, Weiss JW. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. J Appl Physiol (1985) 1990;69:2143–8.

12. Ali NJ, Davies RJ, Fleetham JA, Stradling JR. The acute effects of continuous positive airway pressure and oxygen administration on blood pressure during obstructive sleep apnea. Chest 1992;101:1526–32.

13. Lesske J, Fletcher EC, Bao G, Unger T. Hypertension caused by chronic intermittent hypoxia--influence of chemoreceptors and sympathetic nervous system. J Hypertens 1997;15:1593–1603.

14. Tamisier R, Pépin JL, Rémy J, Baguet JP, Taylor JA, Weiss JW, Lévy P. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. Eur Respir J 2011;37:119–128.

15. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997;99:106-9.

16. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7:677–685.

17. Mehta V, Vasu TS, Phillips B, Chung F. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. J Clin Sleep Med 2013;9:271–279.

18. Mills PJ, Kennedy BP, Loredo JS, Dimsdale JE, Ziegler MG. Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. J Appl Physiol (1985) 2006;100:343–348.

19. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, Tracy RP, Rueschman M, Blumenthal RS, Lewis EF, Bhatt DL, Redline S. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med 2014;370:2276–2285.

20. Kohler M, Stoewhas A-C, Ayers L, Senn O, Bloch KE, Russi EW, Stradling JR. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2011;184:1192–1199.

21. Schwarz EI, Schlatzer C, Rossi VA, Stradling JR, Kohler M. Effect of CPAP-withdrawal on blood pressure in OSA: data from three randomized-controlled trials. Chest 2016;510:1202-1210.

22. Turnbull CD, Petousi N, Sen D, Stradling JR, Kohler M. The effect of supplemental oxygen on blood pressure in obstructive sleep apnoea during CPAP withdrawal. BTS Winter meeting, London, Dec 2017.

23. Turnbull C, Sen D, Stradling J, Petousi N. Effect of supplemental oxygen on morning blood pressure ina randomised controlled CPAP withdrawal trial in patients with OSA. ATS Conference, San Diego, May 2018.

24. Norman RG, Goldring RM, Clain JM, Oppenheimer BW, Charney AN, Rapoport DM, Berger KI. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. J Appl Physiol (1985) 2006;100:1733–1741.

25. Pitson DJ, Stradling JR. Autonomic markers of arousal during sleep in patients undergoing investigation for obstructive sleep apnoea, their relationship to EEG arousals, respiratory events and subjective sleepiness. J Sleep Res 1998;7:53–59.

26. Davies RJ, Jenkins NE, Stradling JR. Effect of measuring ambulatory blood pressure on sleep and on blood pressure during sleep. BMJ 1994;308:820–823.

27. Fletcher EC, Bao G, Li R. Renin activity and blood pressure in response to chronic episodic hypoxia. Hypertens 1999;34:309–314.

28. Lindgren P, Manning J. Decrease in cardiac activity by carotid sinus baroceptor reflex. Acta Physiol Scand 1965;63:401–408.

29. Fletcher EC, Lesske J, Qian W, Miller CC, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. Hypertension 1992;19:555–561.

30. Balachandran JS, Bakker JP, Rahangdale S, Yim-Yeh S, Mietus JE, Goldberger AL, Malhotra A. Effect of mild, asymptomatic obstructive sleep apnea on daytime heart rate variability and impedance cardiography measurements. Am J Cardiol 2012;109:140–145.

31. Loredo JS, Ancoli-Israel S, Kim E-J, Lim WJ, Dimsdale JE. Effect of continuous positive airway pressure versus supplemental oxygen on sleep quality in obstructive sleep apnea: a placebo-CPAP-controlled study. Sleep 2006;29:564–571.

32. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims H, Taylor AJ, Meredith IT, Kaye DM. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation. 2015;131:2143-50.

33. Hollier CA, Harmer AR, Maxwell LJ, Menadue C, Willson GN, Unger G, Flunt D, Black DA, Piper AJ. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study. Thorax 2014;69:346–353.

34. Mokhlesi B, Hagen EW, Finn LA, Hla KM, Carter JR, Peppard PE. Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. Thorax 2015;70:1062–1069.

	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.