Physiological consequences of CPAP therapy withdrawal in patients with obstructive sleep apnoea – an efficient experimental model

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Running head CPAP therapy withdrawal effects in OSA

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ABSTRACT

Randomised controlled trials (RCTs) on continuous positive airway pressure (CPAP) in obstructive sleep apnoea (OSA) are time consuming and their findings often inconclusive or limited due to suboptimal CPAP adherence of previously untreated patients with OSA. A short-term CPAP therapy withdrawal in patients with optimal CPAP adherence results in recurrence of OSA and its consequences and thus may serve as efficient study model to investigate both the consequences of untreated OSA and potential treatment alternatives to CPAP. The CPAP withdrawal protocol has been thoroughly validated and applied in several RCTs focusing on cardiovascular and metabolic consequences of untreated OSA and testing the effectiveness of treatment alternatives to CPAP.

Key words: obstructive sleep apnoea, continuous positive airway pressure, pathophysiology, randomised controlled trial

INTRODUCTION

Continuous positive airway pressure (CPAP) is the gold standard treatment for obstructive sleep apnoea (OSA).(1-4) CPAP is very effective in abolishing apnoea and hypopnoea and reverses the pathophysiologic consequences of OSA. Its effectiveness depends on a sufficient and regular usage. Randomised controlled trials (RCTs) in patients with moderate to severe OSA have shown that treatment with CPAP reduces excessive daytime sleepiness(1) and improves driving performance(5) and health related-quality of life(1). However, many conclusions on the effects of CPAP treatment in OSA come from population based epidemiological studies and robust evidence from randomised controlled interventional trials is often missing. There is still a need for well-designed RCTs to study the effects of CPAP therapy on diverse physiological and clinically relevant outcomes, e.g. cardio- and cerberovascular events. Conventional CPAP trials are typically limited by the unpredictable and usually suboptimal CPAP adherence of treatment naïve patients which lead to underestimation of treatment effects. Subjects who do not tolerate CPAP well and use it only intermittently during the night might even have negative effects such as disturbed sleep architecture and elevated blood pressure.(6) Taking this into consideration, the interpretation of the results of the often cumbersome conventional CPAP trials – with suboptimal therapy adherence – is hampered.

Additionally, there is interest in novel treatment modalities as alternative to CPAP since the latter is not tolerated by all patients and compliance with this treatment is often insufficient. We suggest a short-term CPAP withdrawal as an effective study model to investigate both the consequences of untreated OSA and potential treatment alternatives to CPAP.

The CPAP withdrawal model

In the CPAP withdrawal model, patients previously diagnosed with OSA and effectively treated and compliant with CPAP are randomised to either continue therapeutic CPAP or to withdraw it by the use of a subtherapeutic sham-CPAP device e.g. for two weeks. This model serves for double-blind randomised controlled trials. Measurements are performed at baseline on CPAP and at follow-up on either CPAP (control group) or sham-CPAP (intervention group) (see **figure 1**). Additional repeated measurements after randomisation can be inserted to assess gradual changes of outcomes. Furthermore, the traditional two-arm CPAP withdrawal model can be extended to a several-arm RCT to study therapy alternatives by adding a CPAP-withdrawal arm using the novel treatment. Therefore,

CPAP can be compared to novel treatments and/or to the withdrawal group serving as untreated control group with manifest disease.

This model uses medically well-characterised patients with OSA from large cohorts who are already being treated with CPAP. Sleep centres or CPAP providers usually have databases of treated OSA patients including information on their therapy compliance thus allowing fast recruitment. Carefully selected eligibility criteria (e.g. inclusion of patients with high long-term CPAP adherence and exclusion of professional drivers) have to be defined to make the design effective and safe. In general, persistence of OSA is confirmed by home overnight pulse-oximetry at the end of a four-night period off CPAP before study inclusion. This is important since the time of diagnosis of OSA and CPAP initiation might have been years ago and potential causal factors such as e.g. obesity might have changed.

DISCUSSION

Physiological effects of CPAP withdrawal

We have shown that a short-term CPAP withdrawal results in recurrence of OSA as indicated by changes in sleep study parameters as well as that recurrence of OSA in response to CPAP therapy withdrawal was associated with a deterioration of daytime symptoms and psychomotor performance, increases in blood pressure and heart rate as well as urinary catecholamines, peripheral endothelial dysfunction, disturbances of cardiac repolarisation, and changes in the metabolic breath profile.(7-10) However, we also demonstrated that a short-term CPAP withdrawal does not result in impaired myocardial perfusion despite the increase in blood pressure and other adverse effect of OSA.(11) This was an important message for patients with OSA and for physicians treating patients with sleep apnoea since a CPAP holiday is common even in compliant patients. Contrary to the hypothesis, we found that reactivation of intermittent hypoxia resulted in lessening of oxidative stress, potentially explained by hypoxic preconditioning.(12) The most important findings of the trials using the CPAP withdrawal protocol are described below (also see **figure 2** and **figure 3**).

The **proof of concept study** has defined the physiological effects of CPAP withdrawal on OSA recurrence, daytime symptoms, blood pressure, endothelial function, and systemic inflammation at one and two weeks after CPAP withdrawal.(7) Withdrawal of CPAP resulted in an increased apnoea-

hypopnoea-index (AHI) at one and two weeks to a comparable degree (mean difference in AHI change +31.9 (95%CI 20.1,43.7) and +33.5 (95%CI 22.4,44.6), respectively, p<0.001 for both comparisons) compared to continuation of CPAP.(7) However, subjective sleepiness as assessed by the Epworth Sleepiness Scale (ESS) increased gradually at one and two weeks in the CPAP withdrawal group compared to control group (mean difference in ESS change +1.9 (95%CI 0.4,3.3) and +2.7 (95%CI 1.2,4.3), p=0.015 and p<0.001, respectively).(7) Despite increased daytime sleepiness, the short-term CPAP withdrawal was not associated with deterioration in psychomotor performance, e.g. divided attention driving simulator and psychomotor vigilance task.(7) This study has established the CPAP withdrawal model and has shown that CPAP therapy withdrawal usually leads to a rapid recurrence of OSA accompanied by a gradual return of subjective daytime sleepiness. Additionally, the this RCT has shown that therapy withdrawal in OSA leads to increases in markers of sympathetic activity (but not systemic inflammation) and endothelial dysfunction as assessed by flow-mediated dilatation of the brachial artery – a well validated method to assess endothelial function.(7) Based on these findings, the hypothesis was postulated that CPAP withdrawal also results in dysfunction of the microvasculature and therefore in impairment of **myocardial perfusion**. To answer this question, a randomised controlled CPAP withdrawal trial assessing the change in myocardial blood flow during adenosine-induced vasomotor stress assessed by ^{13}N-ammonia positron emission tomography was conducted.(11) This is the current gold standard for the quantification of myocardial blood flow.(13) We found that myocardial blood flow does not change in response to recurrence of moderate to severe OSA after two weeks of CPAP withdrawal when compared to continuing CPAP therapy.(11) CPAP withdrawal also had no effect on other microvascular beds, e.g. the dermal microcirculation.(11) The confidence interval of the treatment effect clearly demonstrated that any relevant effect on myocardial perfusion can be excluded (treatment effect on hyperaemic myocardial blood flow: -0.01 ml/min/g, 95% CI -0.33 to +0.24ml/min/g, p = 0.91; minimally clinically important difference 0.75 ml/min/g, SD 0.85 ml/min/g).(11) This finding was unexpected because in theory, recurrence of OSA may impair myocardial perfusion by several possible mechanisms, including endothelial dysfunction in response to augmented sympathetic activity and increased oxidative stress due to intermittent hypoxia, as well as increased oxygen demand by increased cardiac work load due to accelerated heart rate and elevated blood pressure. However, this study clearly showed that there is no immediate adverse effect of CPAP therapy withdrawal on myocardial perfusion in patients with moderate to severe OSA, despite the recurrence of OSA and relevant increases in blood pressure. We

concluded that OSA patients are unlikely to be at risk for acute myocardial ischemia during short periods of treatment interruption such as on vacation. This finding was an important message for both clinicians and patients with OSA since “CPAP holidays” are common.

Whereas there is robust evidence for increased sympathetic activity as most relevant contributing factor for the systemic consequences of OSA, there is inconsistent data on the role of **oxidative stress** and systemic inflammation as potential consequences of intermittent hypoxia. In order to examine whether withdrawal of CPAP and thus reactivation of intermittent hypoxia would result in a rise of markers of oxidative stress, 59 patients with moderate to severe OSA were randomised to either continue therapeutic CPAP or to subtherapeutic CPAP (sham).(12) However, despite re-occurrence of intermittent hypoxia, there was no evidence of an increase in markers of oxidative stress in response to recurrence of OSA, e.g. early morning blood malondialdehyde – a sensitive marker of oxidative stress. Unexpectedly, OSA reactivation was associated with a significant reduction in urinary F2-isoprostane ($p=0.002$ compared to the control group) that showed a correlation with the oxygen desaturation index ($r = -0.41$, $p=0.001$).(12) This finding implied a reduction in oxidative stress. As possible explanation, a significant increase in superoxide dismutase – a marker of hypoxic pre-conditioning – was found in patients with untreated compared to those with treated OSA.(12)

Exhaled breath contains metabolic information on the pathophysiological state. We used the CPAP withdrawal protocol to test whether a disease specific profile of exhaled breath in patients with OSA can be detected by real-time exhaled breath analysis by mass spectrometry. Untargeted **exhaled breath analysis** was used to define the effect on metabolic changes of the breath profile.(10) Indeed, recurrence of OSA was accompanied by a specific change in exhaled breath pattern. The panel of discriminating mass-spectral features allowed separating between treated and untreated OSA with a sensitivity of 92.9% and a specifity of 84.6%.(10) There was also a good correlation between changes in breath signal intensity of these features and changes in oxygen desaturation index as measure of OSA severity.(10) These data supported the association of OSA with increased sympathetic activity and lipid peroxidation as well as changed interplay with the gut flora according to the compounds of the OSA-specific exhaled breath pattern. This withdrawal study has shown that exhaled breath analysis by real-time untargeted mass spectrometry allows rapid and non-invasive diagnosis of OSA with high diagnostic accuracy as well as identification of new biomarkers. This approach of breath profiling in OSA might be useful in both screening for OSA as well as monitoring treatment adherence.

Using data from this experimental protocol, we have tested additional hypotheses based on preliminary evidence from other experimental studies, with a focus on mechanisms explaining the observed increased incidence of cardiovascular disease in OSA. The blood pressure lowering effect of CPAP therapy in meta-analysis based on RCTs in previously untreated patients is probably underestimated due to suboptimal CPAP usage.(14) To measure the withdrawal effect on blood pressure and to find potential clinical **predictors of blood pressure response** to OSA treatment, data of 149 optimally CPAP compliant patients included in randomised-controlled CPAP withdrawal trials were analysed.(8) Consistent with the previous smaller withdrawal studies conducted under a similar protocol there was a significant increase in morning blood pressure and heart rate in the withdrawal group compared to the therapeutic CPAP group. OSA recurrence was associated with a clinically relevant increase in home systolic and diastolic blood pressure of approximately 9 and 8 mmHg, respectively.(8) This effect on blood pressure is considerably higher than in conventional CPAP trials. This might be explained by a maximal treatment or withdrawal effect due to the high CPAP adherence in the study population. The effect on blood pressure was underestimated when office values instead of home values were used. Keeping this in mind, home blood pressure instead of office blood pressure measurements should be used as an outcome in clinical trials.

This analysis has established that the blood pressure lowering effects of CPAP is highest in most severe OSA and in those on several antihypertensive drugs.(8)

In addition to systemic hypertension, **blood pressure variability** was suggested as an independent cardiovascular risk factor.(15) However, within the CPAP withdrawal trials randomising 183 patients to either continue therapeutic CPAP or to withdraw it, there was only a neglectable increase in within-visit variability in systolic office blood pressure, whereas there was no effect of withdrawing CPAP on other short-term blood pressure variability (within-visit) or on intermediate-term blood pressure variability (visit-to-visit, day-to-day).(16) The hypothesis that OSA contributes to vascular damage via elevated daytime blood pressure variability couldn’t be supported.

Untreated OSA has been associated with cardiac arrhythmias and increased incidence of sudden cardiac death.(17,18) Disturbed cardiac repolarisation induced by autonomic dysfunction has been suggested as potential underlying mechanism of arrhythmogenesis. Analysing electrocardiographic data from a CPAP withdrawal study, we found that CPAP withdrawal led to a statistically significant **prolongation of repolarisation** and an increase in the dispersion of transmural cardiac repolarisation

compared to therapeutic CPAP.(9) These changes showed a good correlation with the change in AHI.(9) These findings provided a mechanistic link between OSA and cardiac arrhythmia.

Patients with OSA suffer from cognitive impairment and were at increased risk of stroke in observational studies.(19) Using the randomised controlled CPAP withdrawal protocol, it was demonstrated that OSA is associated with **intermittent and sustained nocturnal cerebral tissue hypoxia** to a clinically relevant degree reported to cause functional impairment.(20,21) This study suggested that CPAP prevents the risk of nocturnal cerebral damage found in untreated OSA.

Most data on the association between OSA and activation of **(hypoxia-induced) inflammatory pathways** potentially promoting the observed adverse cardiovascular outcome comes from cell culture, animal or case control studies. RCTs on the effect of CPAP therapy on markers of systemic inflammation are inconclusive.(22,23) Interpretation is additionally complicated due to the common co-existence of OSA and obesity (potential adipose tissue-mediated inflammation). In 109 patients with OSA included in CPAP withdrawal trials – a real life model of intermittent hypoxia – levels of selected vascular inflammatory markers linked to hypoxia and previously reported to be altered in OSA were analysed, e.g. the endothelium-derived protein endocan, the endothelial-derived vasodilator adrenomedullin, and the vasoconstrictor endothelin-1.(24) Of interest, CPAP withdrawal led to a small but significant decrease in adrenomedullin compared to continuation of therapeutic CPAP. However levels of hypoxia-induced and other endothelial-derived inflammatory markers and vasoconstrictive substances were unchanged.(24) This is not in line with observational studies in OSA and models of intermittent or sustained hypoxia.

Currently, there are ongoing randomised controlled CPAP withdrawal trials to establish the effects of OSA on the retinal vascular reactivity (ISRCTN78082983) and on cerebrovascular reactivity (NCT02493673). Additionally, there is an ongoing CPAP withdrawal trial to evaluate whether patients with suboptimal CPAP usage actually benefit from treatment or not (NCT02781740).

The withdrawal model for assessment of treatment alternative

The CPAP withdrawal model can not only be applied to evaluate the pathophysiological consequences of OSA, but also to study the response to novel treatment approaches. The **Provent® trial** was a three-arm RCT studying the efficacy of a nasal expiratory positive airway pressure device to prevent the recurrence of OSA following the CPAP withdrawal. 67 patients with OSA previously on CPAP were randomised to either continue CPAP or to use the nasal EPAP-device or a sham-nasal

EPAP-device.(25) The trial found no therapeutic effect of Provent® on OSA compared to sham-Provent and thus the conclusion was drawn that the nasal EPAP device is ineffective and cannot be recommended as alternative treatment for OSA. Additionally, there is an ongoing CPAP withdrawal RCTs on the effects of supplemental oxygen in OSA (ISRCTN17987510) to answer the question whether intermittent hypoxia, arousals or the intrathoracic pressure swings are the major cause of the rise in daytime blood pressure in OSA.(26)

Other studies using therapy withdrawal in OSA

The concept of studying the pathophysiological consequences of OSA by a CPAP therapy withdrawal has been also been applied by other groups.(27) However, a short-term withdrawal (often just for one night) has mainly been used to study OSA in uncontrolled and non-randomised studies.(27-39) One crossover RCT used a CPAP withdrawal to study the effects of OSA on metabolic markers.(40) Another RCT studied the effect of CPAP withdrawal on olfactory function.(41) Additionally, one group also used a CPAP therapy withdrawal to study modafinil as a treatment alternative.(42-44) Withdrawal effects were not only studied in CPAP but also in electrical stimulation as treatment of OSA.(45)

Summary of the findings from the CPAP withdrawal model

In conclusion, the findings from the CPAP withdrawal RCTs have provided robust evidence for increased sympathetic activity in OSA associated with a considerable blood pressure increase, relevant cerebral hypoxia, and disturbed cardiac repolarisation. Furthermore, the blood pressure lowering effect of CPAP was underlined. Additionally, the findings of these trials challenged previous hypotheses on the role of intermittent hypoxia in oxidative stress and vascular inflammation and gave insight into so far unproven mechanisms of hypoxic preconditioning.

Strengths and limitations of the CPAP withdrawal model

The CPAP withdrawal model is a very effective design to study the pathophysiological consequences of OSA and treatment effects in well-characterised patients. The recruitment rate is considerably faster since it is based on databases of cohorts of already treated patients with OSA. Additionally, the duration of the intervention is limited. These two factors make the CPAP withdrawal model very time and cost effective. An additional advantage is that the short intervention period eliminates many potential confounders that do not change in the short-term (e.g. body mass index, obesity effect), and

the model allows studying OSA in a controlled fashion. The major benefit over conventional intention-to-treat randomised controlled CPAP trials using previously therapy naïve patients is that the CPAP withdrawal study overcomes the compliance problem by only including patients previously optimally adherent to CPAP. Thereby, a maximal treatment effect can be assumed. Treatment naïve patients with OSA may take time to become – or never become – established on CPAP therapy during the study period. The treatment effect in conventional CPAP trials is therefore usually diluted. Additionally, the effectiveness of novel therapies on OSA and its daytime symptoms can reliably be studied and compared to CPAP, the current gold-standard, as well as untreated OSA.

However, a major limitation is that the consequences of OSA recurrence during a short-term CPAP therapy withdrawal cannot be equated to long-term effects of untreated OSA. The question whether short- and long-term effect of untreated OSA are comparable remains unanswered. Withdrawing CPAP results in increased daytime sleepiness and reduced driving performance.(7,29,30) Therefore, one might raise the safety issue of withdrawing CPAP for two weeks. This is addressed by excluding professional drivers and patients with related work, informing patients on the expected increased sleepiness and reduced performance, and advising patients to avoid driving etc. during the study period. Therefore, the model is safe to evaluate treatment effects on OSA. In our experience, CPAP withdrawal has been well tolerated by the study participants, and CPAP holidays are common in real life.

CONCLUSION

The CPAP withdrawal model offers an experimental protocol to effectively study the pathophysiological effects of OSA as well as treatment effects in well-designed randomised controlled trials. Additionally, it can be used to provide RCT data on potential alternative treatment modalities in a head-to-head comparison to CPAP and to untreated OSA.

FIGURES

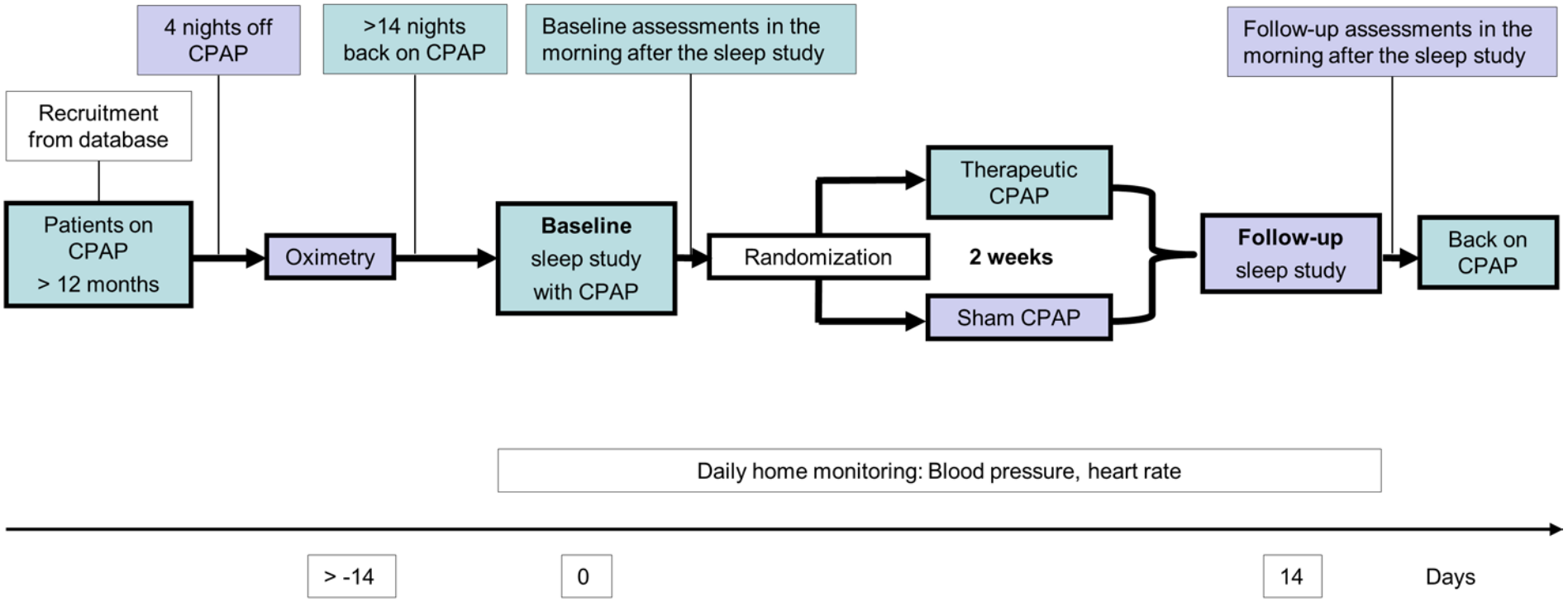
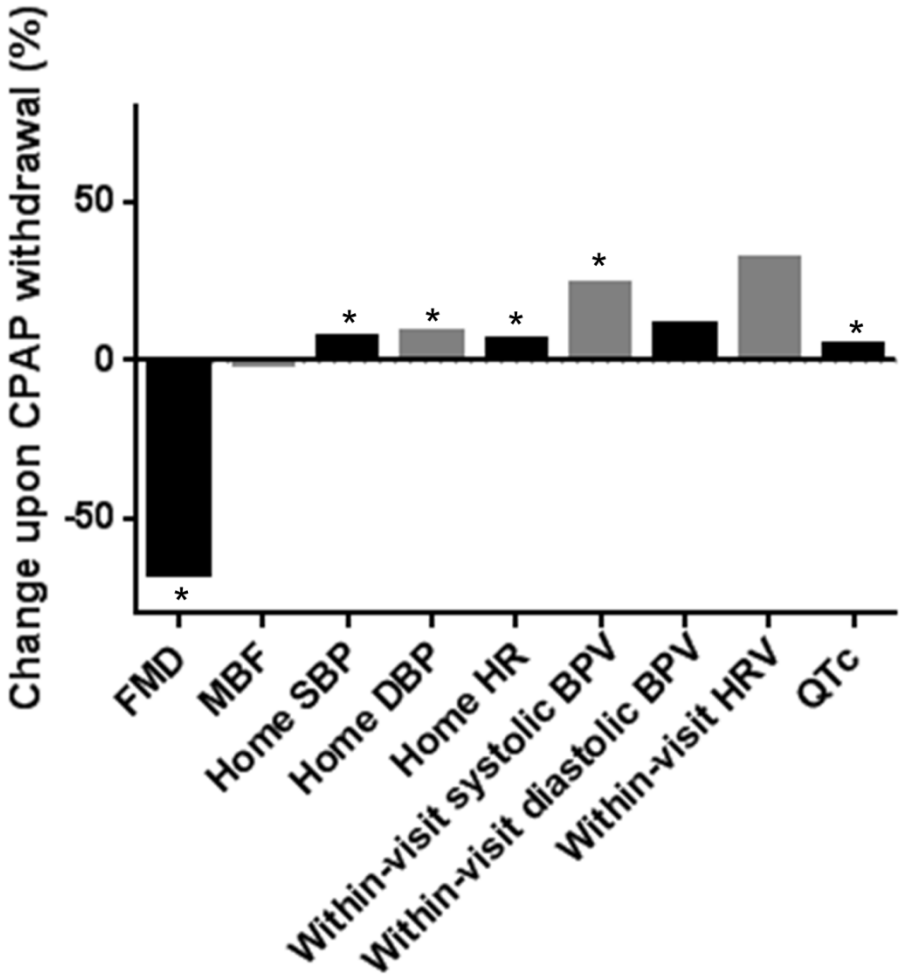

4 nights off CPAP
>14 nights back on CPAP
Baseline assessments in the morning after the sleep study
Follow-up assessments in the morning after the sleep study
Recruitment from database
Patients on CPAP > 12 months
Oximetry
Baseline sleep study with CPAP
Randomization
Therapeutic CPAP
2 weeks
Sham CPAP
Follow-up sleep study
Back on CPAP
Daily home monitoring: Blood pressure, heart rate
> -14
0
14
Days

Figure 2


Change upon CPAP withdrawal (%)
50
0
-50
*
*
*
*
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*
FMD
MBF
Home SBP
Home DBP
Home HR
Within-visit systolic BPV
Within-visit diastolic BPV
Within-visit HRV
QTc

Figure 3

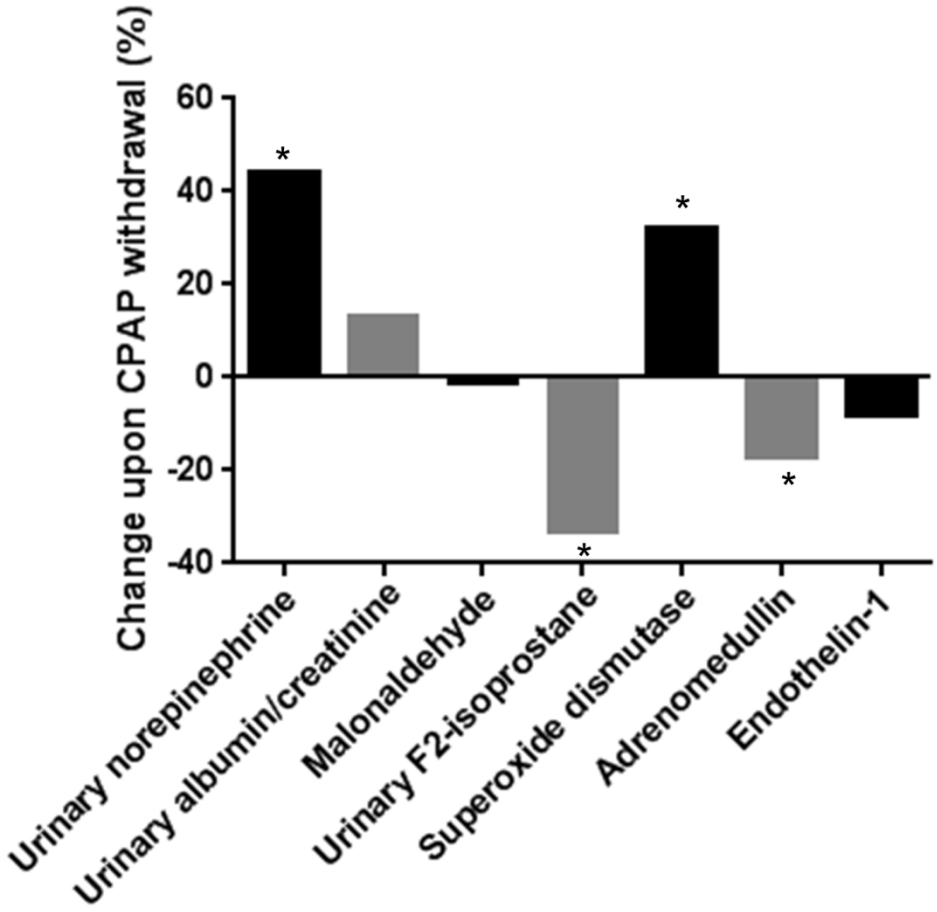
Change upon CPAP withdrawal (%)
60
40
20
0
-20
-40
*
*
*
*
Urinary norepinephrine
Urinary albumin/creatinine
Malonaldehyde
Urinary F2-isoprostane
Superoxide dismutase
Adrenomedullin
Endothelin-1

FIGURE LEGENDS

Figure 1: The traditional CPAP withdrawal model. Patients previously diagnosed with OSA compliant with CPAP for more than one year and with conferment persistence of OSA during a four-day period off CPAP during a pre-trial screening are included. After a baseline sleep study on CPAP and baseline assessments, patients are randomised to either continue therapeutic CPAP or to withdraw it by the use of a sham-device before returning for a follow-up sleep study and follow-up assessments after two weeks on the respective treatment.

Figure 2: Physiological effects of 14 days of CPAP withdrawal on cardiovascular outcomes in obstructive sleep apnoea. FMD = flow-mediated dilatation of the brachial artery (endothelial function), MBF = hyperaemic myocardial blood flow (myocardial perfusion in ammonia-positron emission tomography), CFR = coronary flow reserve (ammonia-positron emission tomography), SBP = systolic blood pressure, DBP = diastolic blood pressure, HR=heart rate, QTc = corrected QT interval. Statistically significant treatment effects ($p < 0.05$) are highlighted (*).

Figure 3. Effects of 14 days of CPAP withdrawal on blood and urinary markers in obstructive sleep apnoea. Statistically significant treatment effects ($p < 0.05$) are highlighted (*).

FOOTNOTES

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REFERENCES

1. Jenkinson C, Davies RJ, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999;353:2100-5.

2. Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862-5.

3. Patel SR, White DP, Malhotra A, et al. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Intern Med 2003;163:565-71.

4. Ballester E, Badia JR, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:495-501.

5. Hack M, Davies RJ, Mullins R, et al. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. Thorax 2000;55:224-31.

6. Bratton DJ, Stradling JR, Barbe F, et al. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. Thorax 2014.

7. Kohler M, Stoewhas AC, Ayers L, et al. 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;184:1192-9.

8. Schwarz EI, Schlatzer C, Rossi VA, et al. Effect of CPAP Withdrawal on BP in OSA: Data from Three Randomized Controlled Trials. Chest 2016;150:1202-10.

9. Rossi VA, Stoewhas AC, Camen G, et al. The effects of continuous positive airway pressure therapy withdrawal on cardiac repolarization: data from a randomized controlled trial. Eur Heart J 2012;33:2206-12.

10. Schwarz EI, Martinez-Lozano Sinues P, Bregy L, et al. Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnoea. Thorax 2016;71:110-7.

11. Schwarz EI, Schlatzer C, Stehli J, et al. Effect of CPAP Withdrawal on myocardial perfusion in OSA: A randomized controlled trial. Respirology 2016;21:1126-33.

12. Stradling JR, Schwarz EI, Schlatzer C, et al. Biomarkers of oxidative stress following continuous positive airway pressure withdrawal: data from two randomised trials. Eur Respir J 2015;46:1065-71.
13. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830-40.
14. Bratton DJ, Gaisl T, Wons AM, et al. 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.
15. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905.
16. Lettau F, Schwarz EI, Stradling JR, et al. Blood Pressure Variability in Obstructive Sleep Apnoea: Data from 4 Randomised Controlled CPAP Withdrawal Trials. Respiration 2017;93:311-8.
17. Namtvedt SK, Randby A, Einvik G, et al. Cardiac arrhythmias in obstructive sleep apnea (from the Akershus Sleep Apnea Project). Am J Cardiol 2011;108:1141-6.
18. Gami AS, Howard DE, Olson EJ, et al. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005;352:1206-14.
19. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182:269-77.
20. Schwarz EI, Furian M, Schlatzer C, et al. OSA results in nocturnal cerebral hypoxia which is prevented by CPAP - Data from a randomised controlled trial. European Respiratory Journal 2015;46.
21. Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. Stroke 2006;37:2720-5.
22. Kohler M, Ayers L, Pepperell JC, et al. Effects of continuous positive airway pressure on systemic inflammation in patients with moderate to severe obstructive sleep apnoea: a randomised controlled trial. Thorax 2009;64:67-73.
23. Drager LF, Bortolotto LA, Figueiredo AC, et al. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2007;176:706-12.
24. Turnbull CD, Rossi VA, Santer P, et al. Effect of OSA on hypoxic and inflammatory markers during CPAP withdrawal: Further evidence from three randomized control trials. Respirology 2017;22:793-9.
25. Rossi VA, Winter B, Rahman NM, et al. The effects of Provent on moderate to severe obstructive sleep apnoea during continuous positive airway pressure therapy withdrawal: a randomised controlled trial. Thorax 2013;68:854-9.

26. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7:677-85.
27. Phillips CL, Yang Q, Williams A, et al. The effect of short-term withdrawal from continuous positive airway pressure therapy on sympathetic activity and markers of vascular inflammation in subjects with obstructive sleep apnoea. J Sleep Res 2007;16:217-25.
28. Grunstein RR, Stewart DA, Lloyd H, et al. Acute withdrawal of nasal CPAP in obstructive sleep apnea does not cause a rise in stress hormones. Sleep 1996;19:774-82.
29. Yang Q, Phillips CL, Melehan KL, et al. Effects of short-term CPAP withdrawal on neurobehavioral performance in patients with obstructive sleep apnea. Sleep 2006;29:545-52.
30. Young LR, Taxin ZH, Norman RG, et al. Response to CPAP withdrawal in patients with mild versus severe obstructive sleep apnea/hypopnea syndrome. Sleep 2013;36:405-12.
31. Turkington PM, Sircar M, Saralaya D, et al. Time course of changes in driving simulator performance with and without treatment in patients with sleep apnoea hypopnoea syndrome. Thorax 2004;59:56-9.
32. Sforza E, Lugaresi E. Daytime sleepiness and nasal continuous positive airway pressure therapy in obstructive sleep apnea syndrome patients: effects of chronic treatment and 1-night therapy withdrawal. Sleep 1995;18:195-201.
33. Filtness AJ, Reyner LA, Horne JA. One night's CPAP withdrawal in otherwise compliant OSA patients: marked driving impairment but good awareness of increased sleepiness. Sleep Breath 2012;16:865-71.
34. Phillips CL, Yee B, Yang Q, et al. Effects of continuous positive airway pressure treatment and withdrawal in patients with obstructive sleep apnea on arterial stiffness and central BP. Chest 2008;134:94-100.
35. Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis 1993;147:1162-8.
36. Bonsignore MR, Parati G, Insalaco G, et al. Continuous positive airway pressure treatment improves baroreflex control of heart rate during sleep in severe obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2002;166:279-86.
37. Ip MS, Tse HF, Lam B, et al. Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med 2004;169:348-53.

38. Marrone O, Salvaggio A, Bonsignore MR, et al. Blood pressure responsiveness to obstructive events during sleep after chronic CPAP. Eur Respir J 2003;21:509-14.
39. Jun JC, Unnikrishnan D, Schneider H, et al. Effect of Acute Intermittent CPAP Depressurization during Sleep in Obese Patients. PLoS One 2016;11:e0146606.
40. Chopra S, Rathore A, Younas H, et al. Obstructive Sleep Apnea Dynamically Increases Nocturnal Plasma Free Fatty Acids, Glucose, and Cortisol during Sleep. J Clin Endocrinol Metab 2017.
41. Boerner B, Tini GM, Fachinger P, et al. Significant improvement of olfactory performance in sleep apnea patients after three months of nasal CPAP therapy - Observational study and randomized trial. PLoS One 2017;12:e0171087.
42. Williams SC, Rogers NL, Marshall NS, et al. The effect of modafinil following acute CPAP withdrawal: a preliminary study. Sleep Breath 2008;12:359-64.
43. Williams SC, Marshall NS, Kennerson M, et al. Modafinil effects during acute continuous positive airway pressure withdrawal: a randomized crossover double-blind placebo-controlled trial. Am J Respir Crit Care Med 2010;181:825-31.
44. Wang D, Bai XX, Williams SC, et al. Modafinil Increases Awake EEG Activation and Improves Performance in Obstructive Sleep Apnea during Continuous Positive Airway Pressure Withdrawal. Sleep 2015;38:1297-303.
45. Strollo PJ, Jr., Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med 2014;370:139-49.