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Effect of CPAP-withdrawal on blood pressure in OSA: data from three randomized-controlled trials

Esther I Schwarz[1], MD, Christian Schlatzer[1], MD, Valentina A Rossi[1], MD,

John R Stradling[2], MD, Malcolm Kohler[1,3], MD

[1] Sleep Disorders Center and Pulmonary Division, University Hospital of Zurich, Zurich, Switzerland
[2] National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Foundation Trust and University of Oxford
[3] Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

Running head: Blood pressure response to CPAP-withdrawal.

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Corresponding author address
Prof Malcolm Kohler
Chair Respiratory Medicine, Clinical Director
Division of Pulmonology and Sleep Disorders Centre
University Hospital of Zurich
Raemistrasse 100, Zurich, Switzerland
email1: malcolm.k@bluewin.ch; email2: malcolm.kohler@usz.ch

ABBREVIATION LIST

AHI = apnea hypopnea index

ANOVA = analysis of variance

BMI = body mass index

BP = blood pressure

CI = confidence interval

CPAP = continuous positive airway pressure

DBP = diastolic blood pressure

ESS = Epworth sleepiness scale

HR = heart rate

ODI = oxygen desaturation index

OSA = obstructive sleep apnea

RCT = randomized controlled trial

SBP = systolic blood pressure

SD = standard deviation

ABSTRACT

Background: Based on meta-analyses, the blood pressure (BP) lowering effect of continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea (OSA) is reported to be approximately 2-3mmHg. This figure is derived from heterogeneous trials, often limited by poor CPAP-adherence, and thus possibly underestimating the treatment effect. We analyzed morning BP data from three randomized controlled CPAP withdrawal trials which included only patients with optimal CPAP-compliance.

Methods: Within the three trials, 149 OSA patients on CPAP were randomized to continue therapeutic CPAP (n=65) or to withdraw CPAP (n=84) for two weeks. Morning BP was measured at home before, and after sleep studies in hospital.

Results: CPAP-withdrawal was associated with a return of OSA (apnea-hypopnea index (AHI) at baseline 2.8/h, at follow-up 33.2/h). Systolic office BP increased in the CPAP-withdrawal group, compared to CPAP-continuation, by +5.4mmHg (95%CI 1.8-8.9mmHg, p=0.003), and systolic home BP by +9.0mmHg (95%-CI 5.7-12.3mmHg, p<0.001). Diastolic office BP increased by +5.0mmHg (95%CI 2.7-7.3mmHg, p<0.001), and diastolic home BP by +7.8mmHg (95%CI 5.6-10.4mmHg, p<0.001).

AHI, baseline home systolic BP, statin usage, gender, and number of antihypertensive drugs were all independently associated with systolic BP change in multivariate analysis, controlling for age, BMI, smoking, diabetes, and sleepiness.

Conclusions: CPAP-withdrawal results in a clinically relevant increase in BP, which is considerably higher than in conventional CPAP trials, and is also underestimated when office BP is used. Greater OSA severity is associated with a higher BP rise in response to CPAP-withdrawal.

Clinical trial registration: ClinicalTrials.gov (NCT01332175 & NCT01797653) and Controlled-Trials.com (ISRCTN 93153804).

Key words: obstructive sleep apnea, continuous positive airway pressure, blood pressure, cardiovascular risk

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder hallmarked by repetitive oxygen desaturations and arousals during sleep. Its prevalence is increasing and a large proportion of adults have undiagnosed OSA.[1,2] There is accumulating evidence for an independent association of OSA with arterial hypertension, vascular endothelial dysfunction and high prevalence of cardiovascular events.[3] OSA is recognized in guidelines as a common and modifiable risk factor for secondary systemic hypertension, especially in patients with resistant hypertension.[4-7]

The most important suggested pathophysiologic mechanisms of hypertension in OSA include intermittent hypoxia leading to increased oxidative stress, augmented sympathetic activity, endothelial dysfunction, and less importantly, intrathoracic pressure changes resulting in increased transmural pressure on the heart and blood vessels, leading to cardiac and vascular remodeling in the long-term.[8-10] Augmented sympathetic activity and autonomic abnormalities such as chemo- and baroreflex dysfunction in OSA have been shown to persist during daytime wakefulness.[11] Typical characteristics of BP changes in OSA are blunting of the physiologic nocturnal dipping pattern, arousal-associated repetitive blood pressure surges, daytime hypertension, mainly in the morning, and impaired baroreflex.[12-16]

The most effective treatment for OSA is continuous positive airway pressure (CPAP) preventing pharyngeal collapse during sleep. CPAP may alleviate the acute detrimental cardiovascular consequences of OSA, and thus reduce cardiovascular risk in treated patients. This might be important as most OSA patients are obese and they commonly present with numerous cardiovascular risk factors. Results from large randomized controlled long-term trials addressing the question whether CPAP results in reduced cardiovascular events and mortality in high cardiovascular risk patients with OSA are forthcoming.[17,18]

Based on meta-analyses, the BP lowering effect of CPAP therapy is approximately 2.5 mmHg for systolic blood pressure (SBP) and 2.0 mmHg for diastolic blood pressure (DBP).[19-

[24] These figures come from pooled studies including diverse groups of patients in terms of OSA severity, prevalence of hypertension, drug therapy, range of intervention time, compliance with CPAP, and methods of BP assessment. However, other randomized controlled trials (RCTs) in patients with OSA of greater severity have shown a much larger BP reduction by CPAP therapy. The meta-analyses have not found any consistent patient characteristics that predict which patients will lower their BP on CPAP treatment. Characteristics that help identify such patients would be useful in clinical practice.

Traditionally, parallel RCTs on the effects of CPAP are often limited by poor CPAP compliance in previously CPAP-naïve patients, and considerable heterogeneity among the recruited patients. Short-term CPAP-withdrawal in pretreated and adherent patients is a promising model to efficiently investigate CPAP treatment effects in OSA. Changes after short-term withdrawal compared to a control population continuing CPAP can be attributed to OSA because the physiological consequences are reactivated by CPAP-withdrawal, and patients serve as their own controls for confounding factors that do not change in the short-term.

The aims of this study were to quantify the effect of two weeks of CPAP-withdrawal on morning BP and to identify potential clinical predictors of BP response. We hypothesized that CPAP-withdrawal leads to a significant and clinically important increase in morning BP.

MATERIAL AND METHODS

Subjects

153 patients with established moderate to severe OSA on CPAP therapy previously participated in three randomized controlled trials[25-27] with similar design and were allocated to continue therapeutic CPAP (n = 66) or to withdraw therapy (n = 87) for two weeks. Eligibility criteria are provided in the online-supplement. The studies were approved by the research

ethics committees in Zurich (EK-1600, KEK-ZH-2012-051) and Oxford (11/NW/0370). Written informed consent was obtained from all participants.

Study design and intervention

Baseline examinations were performed on therapeutic CPAP therapy in both study arms. After baseline assessments, patients were randomly assigned to either continue therapeutic CPAP or to withdraw CPAP (subtherapeutic CPAP or non-therapeutic nasal device). Methods of randomization and blinding were reported previously.[25-27]

Outcomes

The treatment effect on SBP and DBP was the primary outcome of interest. Other outcomes were changes in heart rate (HR), apnea-hypopnea index (AHI) and oxygen desaturation index (ODI), and association between potential predictors and blood pressure changes.

Measurements

Sleep studies and assessment of sleepiness

In-hospital polygraphic sleep studies as previously described[25-27] were completed at baseline and after two weeks, and analyzed manually according to standard methods (see online-supplemental material).[28] In addition, subjective sleepiness was assessed using the Epworth sleepiness scale (ESS).

CPAP devices and CPAP-withdrawal

All patients allocated to therapeutic CPAP received either a REMstar (PhilipsRespironics, PA, USA) or an S8 CPAP device (ResMed-Ltd, Basel, Switzerland and Abingdon, UK) adjusted to the patients' usual CPAP settings. Those allocated to CPAP-withdrawal received either a subtherapeutic CPAP device as previously described[25,27] or an ineffective nasal device[26]

depending on the particular study. Information on treatment adherence was downloaded from the internal memory of the CPAP device.

Blood pressure and heart rate

Patients measured their morning blood pressure and heart rate in triplicate (one minute intervals) at home on the day before the sleep studies with a validated standard digital automatic monitor (OmronHealthcare-Co., Kyoto, Japan). Patients were instructed to measure BP and HR in the sitting position after a period of rest of 5 minutes before breakfast and before the intake of their antihypertensive drugs. Office blood pressure was measured with the same device in the morning after the sleep studies. See online-supplemental material. The average of the three measurements of each day was used for further analysis.

Statistical analysis

An intention-to-treat-analysis – by the use of the last observation carried forward as imputation method – and a per-protocol-analysis were performed. As we were primarily interested in the true physiological effect, the results from the per protocol population are reported as the main outcome. Between-group differences in outcomes in patients randomized to continue therapeutic or withdraw CPAP were analyzed with independent t-tests for normally distributed continuous variables, and Mann Whitney U tests for non-normally distributed data. Treatment effects were adjusted for baseline differences and the three different original studies using multiple linear regression models.

An ANOVA with Fisher's post-hoc test was used to assess the differences in BP change between subgroups of hypertensive patients (differentiated by the number of antihypertensive drugs).

Multiple linear regression analyses, with changes in home SBP or DBP as dependent variable, were conducted to determine factors independently associated with BP change (see online-supplemental material).

A two-sided p-value of <0.05 defined statistical significance. Statistica (version 12 for Windows, StatSoft Inc., Tulsa, OK, USA) was used for statistical analyses.

RESULTS

Study profile and patient characteristics

Of the 153 participants in the original trials, complete BP data were available for a total of 149 patients that were randomized to continue (n=65) or withdraw CPAP (n=84) therapy. Two participants withdrew due to excessive daytime symptoms on subtherapeutic CPAP, and in two patients home BP data were not fully documented. The CONSORT diagram is shown in **figure 1**. The imbalance in the participant numbers between the two arms is due to allocation to three treatment groups (two of which correspond to a CPAP therapy withdrawal) in one of the original RCTs.[26] The two study arms were similar regarding baseline patient characteristics (**table 1**). All participants received the intended intervention. The numerical imbalance in the two treatment groups results from three allocation arms in one of the original trials (CPAP, placebo and real but ineffective nasal device).[26]

Blood pressure change

The effect of CPAP-withdrawal on SBP using office values was +5.4mmHg (95%CI 1.8-8.9mmHg, p=0.003) and using home values was +9.0mmHg (95%-CI 5.7-12.3mmHg, p<0.001), when compared to continued therapeutic CPAP. The treatment effect on DBP was +5.0mmHg (95%CI 2.7-7.3mmHg, p<0.001) using office values and +7.8mmHg (95%CI 5.6-

10.0mmHg, p<0.001) using home values (**table 2 and figure 2**). Results from the intention to treat analysis are shown in the supplementary file (**e-table 1**).

CPAP-withdrawal resulted in an increase of 20.2 % in defined hypertension (when using a threshold of >140 mmHg in SBP or >90 mmHg in DBP) in previously normotensive participants (27.4% hypertensive at baseline, 47.6% hypertensive at follow-up), whereas therapeutic CPAP resulted in normotensive BP values in 15.4% of previously hypertensive individuals (between group difference 35.6%) (see **e-table 2**).

There was a statistically significant relationship between an increasing number of antihypertensives prescribed and a greater rise in SBP after CPAP-withdrawal, as determined by one-way ANOVA ($F(3,56) = 2.87$, $p = 0.044$) (**figure 3**). A Fisher's post-hoc test revealed that the rise in SBP after CPAP-withdrawal was statistically significantly higher in subjects using four different types of antihypertensive drugs compared to those using only one ($p = 0.005$) or two ($p = 0.021$) types.

In multivariate regression modelling (**table 3**), after correction for covariates, change in AHI, baseline SBP, statin usage, gender, and number of antihypertensive drugs used all remained independently associated with SBP change (for effect direction see **table 3**). The model explained 37% of the variance in SBP response. Change in DBP was independently predicted by baseline DBP, AHI and statins (model explained 35% of the variance in DBP). Similar results were achieved by using ODI as the measure of OSA severity.

DISCUSSION

This analysis shows that CPAP-withdrawal for two weeks results in a statistically significant and clinically relevant increase in both home SBP and DBP of approximately 9 and 8 mmHg, respectively. The observed effect of CPAP on BP was larger when home BP measurements rather than office BP were used, and was considerably larger than in previous conventional

CPAP trials. The severity of the recurring OSA was an independent predictor of BP response, even after controlling for confounding variables.

Although three quarters of patients were taking antihypertensive drugs, they experienced a statistically significant rise in blood pressure after CPAP-withdrawal. The BP changes following CPAP-withdrawal versus the control subjects were more pronounced in those with an initially lower BP on CPAP, implying that OSA is an important mediator of secondary hypertension in these patients. In our first RCT using short-term CPAP-withdrawal, relapse of OSA was associated with increased urinary catecholamine excretion and progressively impaired endothelial function after one and two weeks, but not markers of systemic inflammation, suggesting that augmented sympathetic activity and endothelial dysfunction are underlying mechanisms for the observed BP increase.[25,29-31]

Multivariate regression analysis taking into account covariates that were not affected by the intervention showed that baseline BP and returning OSA severity were important predictors of BP response to CPAP-withdrawal. The proposed model explained 37% of the variance in SBP response (and 35% of variance in DBP). Our model predicts a SBP rise of 2.1 mmHg and a DBP rise of 3.8 mmHg with every increase of AHI by 10/h. In theory, if the relationship is essentially linear, a subject with an AHI of 30/h could therefore be expected to have a 5.3mmHg higher SBP and a 9.5mmHg higher DBP compared to a subject without OSA. However, this assumption is speculative and based on a small study population. Furthermore, there is evidence for a threshold effect between sleep apnea severity and hypertension.[32] The results of our analysis suggest that male subjects with more severe OSA are at increased risk of relevant BP increases during short-term CPAP-withdrawal, whilst statins might curb BP swings. This protective effect may be explained by statins beneficial effect on endothelial function, which has previously been shown to worsen during CPAP-withdrawal.[25] However, much of the variation in BP response to CPAP therapy remains unexplained. Essential hypertension, concomitant risk factors for hypertension and

characteristics of OSA (such as the degree of apnea-related arousals and hypoxemia) as well as genetic differences, for example of hypoxic chemosensitivity, may play a role in BP variability. The contribution of genetic background to BP variability may account for up to 30–40% of divergences, and factors such as sodium, alcohol, and caffeine consumption may modify this interaction.[4]

Regression models have shown that the effect of CPAP-withdrawal on BP was stronger in patients having more severe OSA. From a pathophysiological point of view, this makes sense as more severe OSA is expected to result in more severe intermittent hypoxia and higher increase in sympathetic activity. There was a trend towards a more pronounced BP increase in response to CPAP-withdrawal in patients with a baseline home SBP >130mmHg (see figure 4). Interestingly, when using office instead of home BP values, patients having a lower baseline BP showed a more pronounced BP increase in response to recurrence of OSA. This might also show that office BP should not be used as outcome in clinical trials because the treatment effect on BP might be underestimated due to a white coat effect.

Despite the significant but only modest antihypertensive effect of CPAP in meta-analyses, subgroups with more severe OSA and better therapy compliance or resistant hypertension were shown to have a more pronounced BP response.[19,33,34] Epidemiological studies have shown a dose-response relationship between OSA and blood pressure, independent of known confounding factors.[35-37] However, there are sparse data and considerable uncertainty regarding determinants of BP response to CPAP therapy. Our study is consistent with the RCT by Pepperell et al.[38] showing an independent association between OSA severity and BP response to treatment. However, another non-randomized study on the effect of CPAP on BP has produced conflicting results. Robinson et al.[39] found that change in sleepiness assessed by ESS was an independent predictor of BP response to CPAP therapy, whereas OSA severity was not.

There are some limitations to this study. The acute effects of CPAP-withdrawal might be different from the long-term effects of CPAP in OSA due to slow adaptive changes. Up to now, there are no data directly comparing the effect of CPAP withdrawal on BP with conventional trials in CPAP naïve patients. Thus it remains uncertain if an optimal use of CPAP in a comparable, therapy naïve OSA population, would decrease BP to the same degree. The observed larger effect on BP in the CPAP withdrawal model is most likely explained by the very high compliance with CPAP in the withdrawal trials. This is supported by the findings of previous studies reporting a dose dependent effect of CPAP on BP in OSA.[19,40] However, it cannot be entirely excluded that the treatment effect on BP would be smaller after several months of CPAP withdrawal.

The role of CPAP-withdrawal in increasing nocturnal BP is not directly addressed in this study which has only looked at the effect of CPAP-withdrawal on morning BP. 24h-ambulatory blood pressure measurements would have allowed to study BP response to CPAP withdrawal more reliably and to gain information on a circadian pattern of blood pressure changes. Part of the treatment effect on home – not office – BP is due to a significant decrease in the control group on therapeutic CPAP. This is most likely explained by the very high treatment adherence during the study period.

Last a short-term CPAP therapy withdrawal leading to OSA recurrence does not allow studying any long-term effects and consequences, such as cardiovascular events.

Implications for research: BP readings may be inappropriately elevated when measured in hospital due to the well-known white coat effect due to increased sympathetic activity, which may mask some of the OSA and CPAP related effects. Thus, home BP measurements should be encouraged to assess treatment effects. Self-monitoring BP results in several readings and ensures better accuracy.[41] BP self-monitoring can easily be implemented in clinical trials – in

the short- and long-term – by dispensing automated devices and instructing patients. European and American guidelines recommend home BP monitoring.[41,42]

A short-term CPAP-withdrawal in previously highly therapy compliant patients is an effective way to study pathophysiologic consequences of OSA, because differences between baseline and follow-up measurements can be attributed to detrimental effects of returning OSA. This model uses patients as their own controls and thus eliminates potential confounders, as they remain stable over a short-time (e.g. BMI).

Clinical implications: Short-term CPAP-withdrawal, e.g. during a holiday, may result in a considerable and clinically relevant increase in BP in OSA patients. Male patients with resistant hypertension and severe OSA may be particularly vulnerable to major increases in BP during CPAP-withdrawal. However, a recent randomized controlled trial could not find any effect of OSA recurrence in short-term therapy withdrawal and its associated increase in BP on myocardial perfusion.[27] Whether this BP increase is important for other target organs such as the brain is unknown.

CONCLUSIONS

Short-term CPAP-withdrawal in patients with OSA results in a significant and clinically relevant increase in morning BP. BP changes were considerably more pronounced in our study compared to previous conventional CPAP trials. BP response is underestimated when using office measurements. OSA severity seems to be an important independent predictor of BP response to CPAP-withdrawal.

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Guarantor

Prof Malcolm Kohler is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the integrity of the submission as a whole.

Author contributions

Conception and design: EIS, MK, JRS. Data acquisition: EIS, CS, VAR. Analysis and interpretation of data: EIS, MK, JRS. Drafting the article: EIS, MK. Revising the article for important intellectual content and final approval: All authors.

Competing interests

None of the authors has a competing interest regarding this manuscript.

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Trial registration

The trials are registered at ClinicalTrials.gov, registration number NCT01332175 & NCT01797653, and at Controlled-Trials.com, registration number ISRCTN 93153804.

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Table 1: Patient characteristics.

	therapeutic CPAP (n = 65)	**CPAP withdrawal (n = 84)**
age [years]	62.8 (7.9)	62.8 (9.0)
male sex (%)	53 (82%)	73 (87%)
BMI [kg/m2]	33.8 (5.9)	33.3 (5.9)
neck circumference [cm]	44.1 (4.2)	44.4 (3.9)
never smoker (%)	28 (43)	35 (42)
current smoker (%)	9 (14)	11 (13)
former smoker (%)	28 (43)	38 (45)
hypertension (%)	42 (65)	65 (77)
mean number of antihypertensive drugs	1.4 (1.3)	1.6 (1.3)
diabetes (%)	14 (22)	22 (26)
dyslipidemia (%)	24 (37)	32 (38)
coronary artery disease (%)	8 (12)	11 (13)
SBP [mmHg]	132.7 (15.2)	131.0 (14.4)
DBP [mmHg]	81.1 (11.2)	81.8 (9.1)
HR [beats/min]	66.2 (9.8)	66.3 (10.2)
original AHI [events/h]	41.6 (20.7)	43.1 (20.8)
original ODI [events/h]	34.2 (16.7)	36.8 (18.1)
original ESS	13.9 (3.3)	14.1 (3.6)
ODI at 4 days off CPAP [events/h]	27.6 (13.0)	29.7 (15.1)

OSA = obstructive sleep apnea. CPAP = continuous positive airway pressure. BMI = body mass index. SBP = systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate. AHI = apnea hypopnea index. ODI = oxygen desaturation index. ESS = Epworth Sleepiness Scale (max. 24 points). Data are presented as mean (standard deviation) unless otherwise mentioned.

Table 2: Change in blood pressure, heart rate and OSA severity.

	therapeutic CPAP (n = 65)		CPAP withdrawal (n = 84)		treatment effect		
	baseline	follow-up	baseline	follow-up	difference of change between groups	95%CI	p-value
office SBP	133.3 (15.0)	130.3 (15.5)	132.0 (15.0)	135.5 (13.0) †	5.37	1.84, 8.91	0.003
office DBP	82.0 (10.3)	80.5 (9.8)	81.5 (8.6)	85.0 (8.9)*	4.99	2.72, 7.26	< 0.001
office HR	66.7 (9.3)	66.6 (8.6)	66.3 (10.5)	70.6 (11.8)*	4.48	2.02, 6.95	<0.001
home SBP	133.3 (13.5)	128.1 (13.2)*	130.6 (13.9)	135.1 (15.1)*	9.02	5.74, 12.30	< 0.001
home DBP	82.8 (9.0)	78.9 (9.2)*	82.2 (8.1)	86.2 (9.0)*	7.81	5.57, 10.04	< 0.001
home HR	67.4 (8.7)	66.4 (9.5)	67.0 (10.4)	70.2 (12.4) †	4.26	1.46, 7.06	0.003
AHI	2.1 (2.2)	2.4 (2.5)	2.8 (3.4)	33.2 (19.9)*	29.83	25.01, 34.66	< 0.001
ODI	2.4 (3.5)	2.5 (3.7)	3.2 (3.9)	34.2 (19.7)*	31.28	26.56, 36.00	< 0.001
ESS	7.5 (3.5)	7.2 (4.1)	7.7 (3.5)	9.7 (4.4)*	2.32	1.37, 3.26	< 0.001

Treatment effect adjusted for baseline differences and study. Data are presented as means (standard deviation) unless otherwise mentioned (95%CI). CPAP = continuous positive airway pressure. CI = confidence interval. SBP = systolic blood pressure in mmHg. DBP = diastolic blood pressure in mmHg. HR = heart rate in bpm. AHI = apnea hypopnea index in events per hour. ODI = oxygen desaturation index in events per hour. ESS = Epworth Sleepiness in points (max. 24 points).

* $p < 0.001$ for within-group change.

† $p < 0.01$ for within-group change.

Table 3: Multiple linear regression analysis for change in blood pressure.

Model A with home SBP as dependent variable. R2 = 0.37. F = 6.83. p < 0.001.			
independent variable	beta	SE of beta	p-value
baseline SBP	-0.51	0.07	<0.001
AHI	0.21	0.07	0.006
statins	-0.24	0.08	0.003
gender	0.20	0.08	0.009
mean number of antihypertensive drugs	0.17	0.08	0.047
diabetes	0.13	0.08	0.102
smoking	-0.11	0.07	0.148
ESS at follow-up	-0.04	0.07	0.605
BMI	0.04	0.09	0.652
age	0.03	0.08	0.717

Model B with home DBP as dependent variable. R2 = 0.35. F = 7.15. p < 0.001.			
independent variable	beta	SE of beta	p-value
baseline DBP	-0.41	0.07	<0.001
AHI	0.38	0.07	<0.001
statins	-0.21	0.08	0.013
gender	0.12	0.08	0.126
diabetes	0.103	0.08	0.177
mean number of antihypertensive drugs	0.04	0.08	0.621
smoking	-0.01	0.07	0.845
BMI	-0.02	0.08	0.849
age	0.00	0.08	0.908
ESS at follow-up	0.00	0.08	0.986

SBP = systolic blood pressure. DBP = diastolic blood pressure. AHI = apnea hypopnea index. ESS = Epworth Sleepiness Scale. BMI = body mass index. Categorical/binary independent variables: statins, gender, diabetes, smoking. Continuous independent variables: baseline SBP and DBP, AHI, BMI, age, ESS.

Figure legends

Figure 1:

Study profile.

Figure 2:

Individual plot of change in systolic blood pressure from baseline to follow-up in the group withdrawing CPAP therapy (left) and in the group continuing therapeutic CPAP (right).

Figure 3:

Mean changes of systolic blood pressure by CPAP-withdrawal among the subgroup of hypertensive patients (n = 63/84) using different numbers of antihypertensive drugs: subjects using one type (n = 20), two types (n = 23), 3 types (n = 12) and four types (n = 8) of antihypertensive drugs. One-way analysis of variance demonstrated a statistically significant difference in BP response in groups on different numbers of antihypertensive drugs (p = 0.044). Vertical bars denote 95% confidence intervals.