Blood pressure variability in OSA – data from four randomised-controlled CPAP-withdrawal trials

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Abstract

Background: Increased daytime blood pressure variability (BPV) is associated with cardiovascular risk. Preliminary data suggests that obstructive sleep apnoea (OSA) might contribute to increased daytime BPV.

Objective: The aim of this study was to evaluate the effect of continuous positive airway pressure (CPAP) therapy withdrawal on daytime BPV.

Methods: 183 patients previously diagnosed with OSA and treated with CPAP were randomised to either continue or withdraw CPAP within four trials. Office morning BP was measured in triplicate at baseline and follow-up (day 14). In addition, participants performed BP measurements at home on a daily basis (days 1-13). The main outcome of interest was the treatment effect on within-visit-BPV expressed as standard deviation (SD) of triplicate measurements. Additional outcomes included morning home BPV and day-to-day home BPV.

Results: Within-visit variability of systolic BP significantly increased in response to recurrence of OSA in the CPAP-withdrawal group (difference between groups in SD of systolic BPV +1.14 mmHg, 95%CI +0.20/+2.09, p=0.02). There was no statistically significant effect on within-visit variability of diastolic BP (p=0.38) or heart rate (p=0.07). Neither morning home BP variability (systolic BPV, p=0.81; diastolic BPV, p=0.46) nor day-to-day variability of home BP measurements (systolic BPV, p=0.61; diastolic BPV, p=0.58) differed significantly between groups.

Conclusion: CPAP withdrawal results in a minor increase of within-visit variability of office systolic BP but has no effect on home BPV or day-to-day BPV. Although the treatment effect may be blunted by antihypertensives, it is unlikely that OSA contributes to cardiovascular risk via elevated daytime BPV.

Introduction

Obstructive sleep apnoea (OSA) has been identified as a common factor associated with hypertension and cardiovascular disease (CVD) although potential causal mechanisms have not been fully elucidated [1]. The prevalence of OSA is likely to further increase as a result of increasing obesity. [2] Observational and population-based epidemiological studies have shown that untreated moderate-to-severe OSA is associated with hypertension and adverse cardiovascular outcome. [3-7] However, randomised controlled trials on the effects of continuous positive airway pressure (CPAP) therapy have so far only established a causal association between OSA and diurnal hypertension.[8] Hypertension is an established risk factor for CVD. [9] In recent years, not only sustained blood pressure (BP) elevation itself, but blood pressure variability (BPV) has also been recognised as an important predictor for CVD [10-12]; there seems to be a connection between high BPV and increased cardiovascular morbidity and mortality, even in patients with well-controlled BP. [11-14] These findings have been linked to alteration of vascular reactivity due to, amongst other factors, increased arterial stiffness and endothelial dysfunction. [15-17] Similarly, impaired endothelial function has been observed in OSA patients [18-20], possibly linking the underlying pathophysiology of OSA and elevated BPV. Furthermore, the consequences of OSA involve numerous mechanisms such as autonomic dysregulation and increased sympathetic activity, thus linking OSA to elevated BP levels and potentially to increased BPV. [21, 22] One might therefore hypothesize that not only elevated BP levels, but also increased BPV, may be caused by OSA and contribute to the associated adverse cardiovascular outcomes.

An association between the severity of OSA and BPV has previously been described in physiologic and observational studies. [23, 24] While it could be shown that CPAP therapy effectively abolishes OSA [25], improves endothelial function [26, 27] and reduces BP [8], there is controversial data on the effect of CPAP therapy on daytime BPV.[28, 29] Although there have been studies on the association of OSA and BPV, evidence from randomised controlled interventional trials is missing.

Short-term CPAP therapy withdrawal has been shown to result in the recurrence of OSA and its consequences such as increased blood pressure, sympathetic activity and impaired endothelial function [20, 30]. Therefore, we considered this study design suitable to evaluate the effects of CPAP-

withdrawal on BPV. We hypothesized that the recurrence of OSA in response to therapy withdrawal would result in an increase of within-visit BPV as well as short-term morning home BPV and intermediate-term day-to-day BPV.

Methods

Trial Design and Intervention

Four randomised controlled trials, which allocated CPAP-treated patients to either continue or withdraw CPAP for two weeks, were conducted in Zurich and Oxford between 2010 and 2015.[20, 30-32] Patients registered in the sleep database of the Sleep Disorders Centre and Pulmonary Division of the University Hospital Zurich, Zurich, Switzerland, and of the Centre for Respiratory Medicine, Oxford, UK were recruited. Baseline examinations were performed on therapeutic CPAP therapy in both study arms. In the morning after baseline sleep studies, patients were randomly assigned to either continue therapeutic CPAP or to withdraw CPAP (subtherapeutic sham-CPAP or non-therapeutic nasal device) and returned two weeks later for the follow-up sleep study on the assigned treatment. Morning blood pressure was measured daily in triplicate during the study period. The studies were approved by the research ethics committee in Zurich (EK-1600, KEK-ZH-2012-051) and Oxford (11/NW/0370). Written informed consent was obtained from all participants. The trials were registered prior to commencement (clinicaltrials.gov: NCT01332175, NCT01797653, NCT02050425; controlled-trials.com: ISRCTN 93153804).

Participants

Subjects with known OSA were recruited from the Sleep Disorders Centre and Pulmonary Division of the University Hospital Zurich, Zurich, Switzerland, and of the Centre for Respiratory Medicine, Oxford, UK. Patients aged 20-75 years with an oxygen desaturation index (ODI) of at least 10/h[20, 30] or 20/h[31, 32] in their in-laboratory sleep study at the time of diagnosis were eligible if they had been treated with CPAP for at least 1 year (compliance of ≥4h/night) and currently had an ODI >10/h[20, 30] or >20/h[31, 32] in a nocturnal pulse oximetry on the last night of a four night period off CPAP treatment. Exclusion criteria were ventilatory failure, Cheyne-Stokes respiration, unstable or untreated vascular disease, inadequately controlled arterial hypo- or hypertension, professional driving, and a previous traffic accident associated with sleepiness.

Outcomes

The main outcome of interest was the treatment effect on within-visit BPV (standard deviation (SD) of three repeated office BP measurements (day 0 and day 14)). Other outcomes of interest were short-

term morning home BPV (mean daily SD of three repeated home BP measurements over two weeks: ($SD_{triplet1}$ + $SD_{triplet2}$ + … + $SD_{triplet13}$)/13) and intermediate-term day-to-day BPV (SD of daily mean home BP over two weeks: SD of (BP_1 + BP_2 + … + BP_{13})), as well as heart rate variability (HRV) over the whole study period, and effects on sleep apnoea severity (oxygen desaturation index (ODI)).
After the baseline and follow-up sleep study, morning office BP and HR were measured in triplicate (one minute intervals) with a validated standard digital automatic monitor (Omron Healthcare Co., Kyoto, Japan). In addition, patients measured their home morning BP and HR in triplicate with the same device each day during the study period. Measurements were performed according to a standardised protocol: in a sitting position after a period of rest of ≥5 minutes, immediately after getting up, before breakfast and before intake of antihypertensive drugs, 1 minute intervals between the three measurements.
Sleep studies and therapy devices (CPAP, subtherapeutic CPAP and ineffective nasal devices) have previously been described. [20, 30-32]

Randomisation and Blinding

Methods of randomisation and blinding were reported previously.[20, 30-32] Patients and investigators were blinded to treatment allocation.

Statistical Methods

A per protocol analysis was performed. Kolmogorov-Smirnov-test was used to test for normality of data distribution. For the main outcome of interest, between-group differences in change of within-visit BPV from baseline to follow-up were adjusted for baseline differences using linear regression models. For additional outcomes, between-group differences in patients randomised to continue or withdraw therapeutic CPAP were analysed with independent t-tests for normally distributed and with Mann Whitney U tests for non-normally distributed data. Analyses were conducted at a two-sided significance level of < 0.05. Statistica (version 12 for Windows, StatSoft Inc., Tulsa, OK, USA) was used for statistical analyses.

Results

Participants

Of the 183 participants randomised to either continue therapeutic CPAP (n=81) or withdraw CPAP (n=102), 175 completed the trial and provided blood pressure data (**figure 1**). Two patients in the therapeutic CPAP and 4 patients in the withdrawal group discontinued the intervention. One participant in each group did not measure blood pressure on a daily basis. Recruitment for the first trial [20] started in August 2009 and the last patient's visit [32] took place in August 2015. Baseline characteristics of the two treatment groups were comparable and are shown in **table 1**.

Treatment effect on within-visit variability of BP and HR

CPAP withdrawal was associated with a statistically significant increase in within-visit variability of office systolic BP (between-group change in SD +1.14 mmHg, 95%CI +0.20/+2.09, p=0.02), whereas it had no effect on variability of office diastolic BP (+0.36 mmHg, 95%CI -0.45/+1.18, p=0.38) compared with continuing therapeutic CPAP (**table 2, figure 2**). There was a trend towards higher within-visit HRV in the CPAP therapy withdrawal group compared to continuation of therapeutic CPAP (between-group change in SD +0.67 bpm, 95%CI -0.05/+1.39, p=0.07) (**table 2**).
Additionally, changes in absolute office BP and HR are given as supplemental digital content 1 (table).

Longitudinal variability of morning home BP and HR

Short-term variability of neither systolic home BP (difference between groups in SD 0.06 mmHg, 95%CI -0.39/+0.50, p=0.81), nor diastolic home BP (difference between groups in SD +0.13 mmHg, 95%CI -0.21/+0.48, p=0.46) or heart rate (difference between groups in SD +0.13 bpm, 95%CI -0.20/+0.47, p=0.43) differed significantly between the two treatment groups over the study period (**table 3, figure 3**).

Longitudinal day-to-day variability in home BP and HR

Day-to-day variability of systolic BP (difference between groups in SD +0.19 mmHg, 95%CI -0.53/+0.90, p=0.61), diastolic BP (difference between groups in SD -0.14 mmHg, 95%CI -0.62/+0.35, p=0.58) and heart rate (difference between groups in SD +0.26 bpm, 95%CI -0.48/+0.99, p=0.49) did

not differ significantly between therapeutic CPAP and CPAP withdrawal over the study period of two weeks (**table 3**).

Treatment effect on OSA severity and daytime sleepiness

CPAP-withdrawal was associated with a return of OSA (between group change in AHI +29.4, 95%CI +25.1/+33.7, p<0.001) accompanied by an increase in daytime sleepiness (between group change in ESS +2.1, 95%CI +1.2/+2.9, p<0.001) compared to therapeutic CPAP (**table 4**).

Discussion

This analysis on the effect of CPAP therapy withdrawal on daytime BPV has found a slight increase in within-visit variability of systolic office BP in patients with moderate-to-severe OSA. Although our data from several randomised controlled trials has demonstrated this modest effect of recurrence of OSA on short-term variability of *office BP*, it has not found an effect of OSA on short-term variability (morning BPV over two weeks) or intermediate-term variability (day-to-day variability over two weeks) of *home BP*. Furthermore, the treatment effect on systolic within-visit BPV seems rather modest and presumably is unlikely to be relevant. [33]

Using the same trial design, previous CPAP-withdrawal studies have found an increase in BP [20, 31, 34] and sympathetic activity [20], and reductions in endothelial function [20, 27, 30] accompanying the return of OSA, indicating a possible pathophysiological explanation for higher BPV. Thus a marginally accentuated within-visit variability of office SBP might mostly be explained by a higher susceptibility to the “white coat”-effect [35] as a consequence of an increased sympathetic tone in untreated OSA.

To our knowledge, this is the largest data collection on treatment effects of CPAP therapy on daytime BPV in patients with OSA. Whether the findings of short-term therapy withdrawal are comparable to long-term effects of CPAP therapy remains uncertain. However, as previously shown [20], even short-term CPAP withdrawal usually leads to a rapid recurrence of OSA and is associated with distinct pathophysiological consequences such as impaired endothelial function, increased urinary catecholamine excretion, and elevation of both blood pressure and heart rate. Treatment effects of CPAP therapy are often underestimated due to poor patient compliance. Therefore, in our trials, only previously optimally CPAP adherent patients were randomized to either continue or withdraw CPAP therapy, and a per protocol analysis was employed, so a maximal treatment effect could be expected. Thus, the applied study model can be deemed suitable to evaluate the physiological and therapeutic effects on BPV.

Despite convincing pathophysiological concepts linking the effects of OSA and their possible influence on BPV [16, 23, 24, 36], previous trials evaluating the effects of CPAP therapy on BPV have come to contradictory conclusions. Altered blood pressure variability has been found in previously untreated and otherwise healthy OSA patients. [24] In a recent uncontrolled prospective study, Pengo et al.[29] investigated changes in within-visit variability of office BP in 78 newly diagnosed patients suffering

from severe OSA. The analysis was stratified according to whether patients were hypertensive or not. Hypertensive subjects were not treated with antihypertensive medication either prior to or during the intervention period. Patient data were recorded at baseline and again two weeks after initiating CPAP therapy. At follow-up, a reduction of within-visit variability of office systolic BP and heart rate could be detected and, while observed in both groups, this reduction was more pronounced in hypertensive patients, most likely reflecting the effect of CPAP therapy on sympathetic activation. Although in our study the majority of subjects were diagnosed with hypertension, BP in all participants was well controlled, thus possibly masking a larger effect of CPAP withdrawal on systolic BP variability.
In contrast, a randomised placebo-controlled trial of only 41 OSA patients with a respiratory disturbance index (RDI) >15/h could not find a beneficial effect of one week of CPAP therapy on BPV.[28] Although higher RDI and elevated urine norepinephrine were positively related to BPV, there was no significant effect due to therapeutic CPAP versus placebo, as BPV declined equally in both study arms. However, all of these studies were based on a rather small study population.
Taking into account the existing evidence from the aforementioned trials [24, 28, 29], and adding the results of our analysis of randomised controlled trials, the data suggest that CPAP has at most only a minor effect on daytime BPV.

Although we used standardized BP measurement methods to compile the data presented in our study, there are some possible limiting factors. First, the treatment intervention lasted for only two weeks. Secondly, analysis of BPV including home measurements of BP relies on patient compliance. Even though patients were instructed as to when and how to correctly use the measurement device, there was only limited possibility to ensure the proper conduct of those measurements. While 24h-ambulatory and beat-to-beat BPV provide different pathophysiological information on daytime blood pressure variability [37], standardized visit-to-visit office BPV and day-to-day home BPV have been shown to predict outcome in other patient groups and are an accepted method to assess BPV. [11, 38, 39] Perhaps most importantly, antihypertensive medication is known to have an effect on BPV which depends on the type of medication. Calcium channel blockers and beta blockers are commonly used to treat hypertension. However, they seem to have opposite effects on BPV, independent of their general effects on mean BP. In contrast to beta blockers, calcium channel blockers have been shown to effectively and consistently reduce BPV. [40] As patients in this study were asked to continue their medication regimen over the course of the intervention, it is conceivable that despite recurrence of

OSA, more distinct changes in BPV may have been masked by medication. In this cohort all hypertensive subjects were treated, and BP at baseline in these patients was well controlled. On the other hand, whereas in the current study medication was not withheld, in the trial by Bao et al. [28] patients were taken off anti-hypertensive medication for three weeks prior to beginning of the study, and still there was no effect of CPAP on BPV.

The results of this study, coming from four well-designed randomized-controlled trials, provide data regarding CPAP therapy effects on daytime BPV. Despite this lack of evidence of CPAP therapy withdrawal importantly affecting daytime BPV, repetitive *nocturnal* BP surges up to 80 mmHg seen with OSA due to apnoea and hypopnoea-associated arousals [41] are abolished by CPAP therapy. Therefore, a long-term beneficial effect on the cardiovascular system of CPAP on BPV may still be possible. Steinhorst et al. [23] recently showed that hypertension is primarily associated with increased night time BPV rather than daytime BPV. OSA affects cardiovascular regulatory mechanisms most dramatically during sleep, therefore potentially explaining a lack of a strong association between OSA and daytime BPV. The pathophysiology of OSA in hypertension is linked to a blunting of the physiologic nocturnal dipping pattern of BP and arousal-associated repetitive BP surges, thus possibly having an impact on the development of resistant hypertension in OSA patients. [42] However, characteristics of blood pressure changes in OSA also include impaired baroreflex and sustained daytime hypertension, especially in the morning. [43, 44] Consecutively we expected morning BPV to be affected by the nocturnal consequences of OSA, an assumption that could not entirely be verified. However, since OSA is common, often co-existent with a cluster of traditional cardiovascular risk factors and can be effectively treated, investigation of preventive effects of CPAP remains a topic for future long-term trials.

In summary, while within-visit variability of SBP slightly increased in response to CPAP therapy withdrawal, the clinical relevance of this change is disputable despite a possible blunting effect of antihypertensive drugs on BPV. In conclusion, it is unlikely that OSA contributes to cardiovascular risk via elevated daytime BPV.

Table 1: Baseline patient characteristics

	therapeutic CPAP (n = 78)	CPAP withdrawal (n = 97)
Age [years]	63.4 (7.9)	63.5 (8.9)
Male sex; N (%)	64 (82)	81 (83.5)
BMI [kg/m2]	33.6 (5.8)	33.5 (5.9)
Neck circumference [cm]	44.1 (4.1)	44.0 (4.1)
Never smoker, N (%)	38 (48.7)	39 (40.2)
Current smoker, N (%)	9 (11.5)	12 (12.4)
Former smoker, N (%)	31 (39.7)	46 (47.4)
Hypertension, N (%)	50 (64.1)	74 (76.3)
Mean number of antihypertensive drugs	1.4 (1.4)	1.6 (1.4)
Calcium antagonist, N (%)	19 (24.4)	30 (30.9)
Beta-blocker, N (%)	19 (24.4)	24 (24.7)
ACE inhibitor or ARB, N (%)	40 (51.3)	60 (61.9)
Diabetes, N (%)	19 (24.4)	24 (24.7)
Dyslipidaemia, N (%)	31 (39.7)	36 (37.1)
Original AHI [events/h]	44.0 (21.5)	43.6 (20.1)
Original ODI [events/h]	37.3 (18.6)	37.6 (18.0)
Original ESS score	13.8 (3.3)	13.9 (3.7)

Data are presented as means (standard deviation) unless otherwise mentioned. CPAP = continuous positive airway pressure. BMI = body mass index. ACE = angiotensin converting enzyme. ARB = angiotensin receptor blocker. AHI = apnoea-hypopnoea-index. ODI = oxygen desaturation index. ESS = Epworth Sleepiness Scale

Table 2: Treatment effects on within-visit office blood pressure and heart rate variability

	therapeutic CPAP (n = 78)		CPAP withdrawal (n = 97)		treatment effect*		
	baseline	follow-up	baseline	follow-up	difference of change between groups	95%CI	p-value
SD office SBP (mmHg)	4.55 (2.90)	4.37 (2.19)	4.88 (2.59)	5.52 (3.69)	+ 1.14	+0.20, +2.09	0.02
SD office DBP (mmHg)	3.26 (2.26)	3.48 (2.44)	3.04 (1.93)	3.82 (2.91)	+ 0.36	-0.45, + 1.18	0.38
SD office HR (bpm)	2.38 (2.05)	1.98 (1.79)	1.86 (1.36)	2.58 (2.72)	+0.67	-0.05, +1.39	0.07

Data are presented as means (standard deviation) unless otherwise mentioned CPAP = continuous positive airway pressure. CI = confidence interval. SD = standard deviation. SBP = systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate. bpm = beats per minute. mmHg = millimetres of mercury.

* Treatment effect adjusted for baseline differences.

Table 3: Longitudinal short- and intermediate-term home blood pressure and heart rate variability (day 1-13)

	therapeutic (n = 78)	withdrawal (n = 97)	difference between groups	95%CI	p-value
Longitudinal short-term morning home blood pressure and heart rate variability (day 1-13) [1]					
SD SBP (mmHg)	4.97 (1.57)	5.03 (1.42)	+ 0.06	-0.39, +0.50	0.81
SD DBP (mmHg)	3.37 (1.09)	3.50 (1.20)	+ 0.13	-0.21, +0.48	0.46
SD HR (bpm)	2.19 (1.01)	2.32 (1.19)	+ 0.13	-0.20, +0.47	0.43
Longitudinal intermediate-term day-to-day home blood pressure and heart rate variability (day 1-13) [2]					
SD SBP (mmHg)	6.88 (2.45)	7.06 (2.33)	+0.19	-0.53, +0.90	0.61
SD DBP (mmHg)	4.73 (1.70)	4.59 (1.53)	-0.14	-0.62, +0.35	0.58
SD HR (bpm)	4.73 (2.58)	4.99 (2.35)	+0.26	-0.48, +0.99	0.49

Data are presented as means (standard deviation) unless otherwise mentioned CPAP = continuous positive airway pressure. CI = confidence interval. SD = standard deviation. SBP = systolic blood pressure. DBP = diastolic blood pressure. HR = heart rate. bpm = beats per minute. mmHg = millimetres of mercury.

[1] Mean daily SD of three repeated home BP measurements over two weeks: (SDtriplet1 + SDtriplet2 + … + SDtriplet13) / 13

[2] SD of daily mean home BP over two weeks: SD of (BP1 + BP2 + … + BP13)

Table 4: Treatment effects on OSA severity and daytime sleepiness.

	therapeutic CPAP (n = 78)		CPAP withdrawal (n = 84)		treatment effect		
	baseline	**follow-up**	**baseline**	**follow-up**	**difference of change between groups**	**95%CI**	**p-value**
AHI	2.4 (2.3)	3.2 (3.8)	2.8 (3.4)	33.1 (19.3)	+29.4	25.1, 33.7	< 0.001
ODI	2.9 (4.0)	2.9 (3.6)	3.3 (3.9)	34.4 (19.3)	+31.1	26.9, 35.4	< 0.001
ESS	7.2 (3.5)	7.0 (4.0)	7.6 (3.6)	9.5 (4.4)	+2.1	1.2, 2.9	< 0.001

Data are presented as means (standard deviation) unless otherwise mentioned CPAP = continuous positive airway pressure. CI = confidence interval. AHI = apnoea-hypopnoea index in events per hour. ODI = oxygen desaturation index in events per hour. ESS = Epworth Sleepiness in points (max. 24 points).

Figure Legends

Figure 1

Patient flow

Figure 2

Individual plots showing changes in within-visit blood pressure variability from baseline to follow-up in the group continuing therapeutic CPAP (left) and in the group withdrawn from CPAP therapy (right).

Figure 3

Short-term variability of morning home systolic blood pressure after randomisation over the study period compared between the two groups. Each point represents the standard deviation of a triplicate measurement of systolic home blood pressure (group mean) over 13 days after randomisation.

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