

# **Effect of CPAP withdrawal on myocardial perfusion in OSA**

## **- a randomized controlled trial**

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**Summary at a glance**

CPAP is suggested to reduce the vascular risk in OSA. This randomized controlled trial tested whether recurrence of OSA by therapy withdrawal has an impact on myocardial perfusion. OSA recurrence has no adverse effect on myocardial perfusion and microvascular function, despite clinically relevant increases in blood pressure and heart rate.

## **Abstract**

**Background:** Obstructive sleep apnea (OSA) is highly prevalent and associated with an increased incidence of cardiovascular events. Endothelial dysfunction is the proposed causative mechanism. Continuous positive airway pressure (CPAP) is presumed to improve cardiovascular outcome in OSA. CPAP withdrawal was recently shown to lead to peripheral endothelial dysfunction. However, it is not known whether short-term CPAP withdrawal results in acute impairment of myocardial perfusion in OSA.

**Methods:** In this double-blind randomized controlled study, 45 patients with moderate to severe OSA previously optimally adherent to CPAP were assigned to either subtherapeutic or continuing therapeutic CPAP for two weeks. The primary outcome was adenosine-induced myocardial blood flow (MBF) as a measure of endothelial function, assessed by  $^{13}\text{N}$ -ammonia positron emission tomography. Secondary outcomes were measures of dermal and renal microvascular function, morning blood pressure (BP) and heart rate.

**Results:** Despite return of OSA producing significant increases in BP (+9.1 mmHg, 95%CI +4.9 to +13.4 mmHg,  $P<0.001$ ) and heart rate (+9.6 bpm, 95%CI +4.6 to +14.6 bpm,  $P<0.001$ ), CPAP withdrawal had no significant effect on maximal myocardial perfusion capacity (hyperaemic MBF -0.01 ml/min/g, 95%CI -0.33 to +0.24 ml/min/g,  $P=0.91$ ), nor renal and dermal microvascular function, when compared to continuing therapeutic CPAP.

**Conclusions:** In patients with OSA, a short-term CPAP withdrawal does not lead to detectable impairment of coronary endothelial function, as has been demonstrated in the brachial artery, despite a clinically relevant increase in BP of nearly 10mmHg. In addition there was no evidence of an impairment of renal or dermal microvascular function.

**Trial registration number:** NCT01797653.

**Key words:** cardiovascular consequences, continuous positive airway pressure, microvascular endothelial function, myocardial perfusion, obstructive sleep apnea.

**Short title:** Myocardial perfusion in OSA.

## Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder with increasing prevalence<sup>1, 2</sup> that has been associated with increased prevalence of coronary heart disease and incidence of adverse cardiovascular outcomes.<sup>3-7</sup> It is estimated that up to 13% of men and 6% of women aged between 30 and 70 years suffer from moderate to severe OSA, many of whom have no overt symptoms and therefore do not seek medical attention.<sup>1, 8</sup> Its high prevalence and associated consequences make OSA a relevant health problem.

The most effective treatment for OSA is continuous positive airway pressure (CPAP). CPAP has been shown to improve brachial artery endothelial dysfunction<sup>9-11</sup> and blood pressure (BP)<sup>12</sup> in randomized controlled trials and to reduce cardiovascular events in observational studies.<sup>5, 13, 14</sup> As OSA usually returns within a few nights off CPAP therapy, this treatment is considered to be necessary on a nightly basis to prevent deleterious consequences of OSA. However, adherence to therapy is often limited.<sup>15</sup> Even patients compliant with therapy sometimes intermittently discontinue CPAP, e.g. on weekends or on vacation, and during episodes of nasal congestions. Short-term CPAP withdrawal has recently been shown to lead to an increase in BP, heart rate, urinary catecholamine excretion and impaired peripheral vascular function in the brachial artery.<sup>9</sup>

It is not known whether short-term CPAP therapy withdrawal and the return of OSA affects myocardial endothelial function, and microvascular function in other vascular beds. Therefore, the aim of this randomized controlled study was to test the hypothesis that CPAP withdrawal would result in a deterioration of myocardial endothelial function, increase BP, and impair microvascular function of the kidneys and the skin.

## **Material and Methods**

### ***Study design***

A randomized, double-blind, placebo-controlled, parallel-group study (therapeutic versus subtherapeutic CPAP) including 45 patients with moderate to severe OSA, previously optimally adherent to CPAP therapy, was conducted to evaluate the effects of CPAP withdrawal on myocardial perfusion, as well as on dermal and renal microvascular function during a two week period.

### ***Subjects***

Patients previously diagnosed with OSA by an in-laboratory sleep study and treated with CPAP who were registered in a database of the Sleep Disorders Center and Pulmonary Division of the University Hospital Zurich, were eligible for the trial if they met the following inclusion criteria: age between 20 and 75 years, original oxygen desaturation index (ODI) of  $>20/h$  and an Epworth Sleepiness Scale (ESS) of  $>10$ , current ODI  $>20/h$  ( $\geq 4\%$  dips) during an ambulatory nocturnal pulse oximetry performed on the last night during a four-night period without CPAP, treated with CPAP for  $>12$  months (compliance  $>4h/night$ , apnea-hypopnea index (AHI)  $<10/h$  according to CPAP-machine download), and current ESS  $<10$ .

Patients with previous ventilatory failure (awake  $SpO_2 < 93\%$  or  $PaCO_2 > 6$  kPa), unstable and untreated coronary or peripheral artery disease, severe arterial hypertension or hypotension ( $>180/110$  or  $<90/60$  mmHg), Cheyne-Stokes breathing, acute inflammatory disease, or a history of any sleep-related accident, or who were current professional drivers, were excluded.

### ***Sample size***

The sample size was estimated on the assumption that a minimally clinically important change in the primary outcome following CPAP withdrawal, adenosine-induced hyperaemic myocardial blood flow (MBF), between active treatment and placebo is 0.75 (SD 0.85) mL/min/g. This threshold has been determined as it represents the standard deviation (SD) of hyperaemic blood flow as assessed by quantitative PET in our institution<sup>16</sup> and in a typical population with cardiovascular risk factors.<sup>17</sup>

Based on this assumption, the power calculation indicated that 21 patients would be required in each arm to ensure that this minimally important difference in the primary outcome was not missed with a power of 80%. According to previous experience<sup>9</sup>, a possible dropout rate of approximately 6% was taken into account, thus the total number of patients who had to be recruited was adjusted to 45.

### ***Patient evaluation and follow-up***

The study was conducted at the University Hospital Zurich. Recruitment started in February 2013 and the last patient follow-up was completed in December 2013. The trial was conducted according to the Declaration of Helsinki. The study protocol was approved by the cantonal ethics committee of Zurich (KEK-ZH-Nr. 2012-0511) and registered at ClinicalTrials.gov (NCT01797653). Written informed consent was obtained from all participants before inclusion.

After confirmation of persistence of relevant OSA (ODI >20/h,  $\geq 4\%$ -dips) by home overnight pulse oximetry (Pulsox-300i, Konica Minolta Sensing Inc., Osaka, Japan) on the last night of a four-night period off CPAP, eligible patients resumed therapy with CPAP for at least two weeks before baseline assessments were performed. After the in-laboratory baseline sleep study on therapeutic CPAP (see online-supplement), patients were randomized to either subtherapeutic or continuation of therapeutic CPAP for two weeks. Allocation was generated by the process of minimization to reduce imbalances in baseline characteristics associated with the endpoints. A MS-DOS program (MINIM, London, UK) for introducing minimization in clinical trials allocated participants to one of the two treatment arms by using three minimization criteria for allocation: OSA severity, BMI and absence or presence of an atherosclerotic end-organ disease.

Follow-up assessments for all outcomes were performed after two weeks. Participants and outcome assessors remained blinded to the treatment assignment. The member of the research team who allocated the patients did not take part in outcome assessments.

### ***Primary outcome***

Hyperaemic myocardial blood flow

The primary outcome measure was the change in global myocardial blood flow (MBF) during coronary and myocardial vasodilation induced by adenosine, from baseline to follow-up, assessed by  $^{13}\text{N}$ -ammonia positron emission tomography / computed tomography (PET/CT) (see online-supplement), which is a well-established gold standard for the quantification of MBF.<sup>17-19</sup>

### ***Secondary outcome measures***

Resting myocardial blood flow and coronary flow reserve by  $^{13}\text{N}$ -ammonia PET

Resting MBF and coronary flow reserve (CFR) served as secondary outcome measures. CFR was calculated as the ratio of hyperaemic to resting MBF, an alternative way of expressing the endothelial function measured by adenosine-induced vasodilation but corrected for unstimulated flow, and a CFR  $\geq 2.0$  was considered normal.<sup>20</sup> It

represents the ability of the microvasculature to respond to a stimulus since microvessels are primarily responsible for resistance and thus the vasodilatory reserve of the myocardium.<sup>16</sup>

#### Blood pressure and heart rate

BP and heart rate were measured in triplicate in the morning after the sleep studies with a standard digital automatic monitor (Omron Healthcare Company, Kyoto, Japan). The average of the three measurements was used for further analysis.

#### Renal microvascular endothelial function

As a measure of renal microvascular function urinary albumin excretion rate was assessed by measurement of albumin/creatinine ratio in the first morning urine sample.<sup>21</sup>

#### Dermal microvascular endothelial function

Dermal microvasculature function was non-invasively assessed by Laser Doppler Flowmetry with PeriFlux (Perimed AB, Järfälla, Stockholm, Sweden) - as previously described and validated<sup>22</sup> – by measuring reactive hyperaemia in the forearm skin following proximal arterial occlusion for 4 minutes (see online-supplement). Measurements were performed after 20 minutes of rest in a temperature-controlled room.

#### *Sleep studies and CPAP devices*

At baseline and at two weeks, participants underwent in-hospital respiratory polygraphy (Alice 5 Diagnostics System; Respiromics, Pennsylvania, USA) (see online-supplement). All polygraphic records were scored manually according to the AASM task force criteria<sup>23</sup> by the same investigator. OSA severity was quantified as the number of apneas and hypopneas (AHI) and oxygen desaturations  $\geq 4\%$  per hour of study (ODI). Subjective sleepiness was assessed by using the ESS. Data on treatment adherence were downloaded from the internal memory of the CPAP devices.

All patients received a REMstar autoCPAP device (Philips Respironics, PA, USA). In the therapeutic limb, CPAP pressure and mode were set according to the previous individual settings. In patients allocated to CPAP withdrawal, the subtherapeutic pressure was achieved by setting the CPAP machine to the lowest pressure, insertion of a flow-restricting connector at the machine outlet, and insertion of extra holes in the collar of the tube at the end of the mask to allow air escape and to prevent rebreathing of CO<sub>2</sub>.<sup>24</sup>

### ***Data analysis***

Normally distributed data are expressed as mean (standard deviation) and non-normally distributed data as median (interquartile range). The analysis was performed on an intention-to-treat basis. Comparisons of outcomes between the therapeutic and subtherapeutic CPAP group were performed by chi-square tests for categorical variables, independent t-tests for normally distributed, and Mann-Whitney U tests for non-normally distributed continuous variables. Differences between medians in non-parametric tests and confidence intervals for the difference were computed based on the Hodges Lehmann method. In addition, a multivariate analysis including the baseline value of each outcome as covariate was performed to account for baseline differences between groups. A two-sided P-value <0.05 was considered to be statistically significant. Statistical analyses were performed using Statistica (version 12 for Windows, StatSoft Inc., Tulsa, OK, USA).



## Results

### *Trial profile and patient characteristics*

The trial profile is shown in figure 1. A total of 45 patients with moderate to severe OSA were randomized to therapeutic (n=23) or subtherapeutic (n=22) CPAP. The two study arms were similar regarding patient characteristics (table 1). All participants received the intended intervention and no participant withdrew or was lost to follow-up. Ammonia-PET data of one patient in the therapeutic CPAP group could not be analyzed because of very low imaging quality due to extracardial tracer activity.

### *Effects of CPAP withdrawal on hyperaemic myocardial blood flow*

Hyperaemic MBF did not change significantly after two weeks of CPAP withdrawal when compared to continuing CPAP therapy (difference between median changes -0.01 ml/min/g, 95%CI -0.33 to +0.24 ml/min/g, P=0.91) (table 2, figure 2 and table S1).

### *Effects of CPAP withdrawal on secondary outcomes*

#### Coronary flow reserve

CFR did not change significantly after two weeks of CPAP withdrawal when compared to continuing therapeutic CPAP (difference between median changes +0.02, 95%CI -0.38 to +0.42, P=0.93) (table 2 and table S1).

#### BP and heart rate

Compared with continuing CPAP, two weeks of CPAP withdrawal led to a statistically significant increase in systolic BP (mean difference in change, +10.8 mmHg, 95%CI +5.2 to +16.4 mmHg, P<0.001), diastolic BP (mean difference in change, +7.5 mmHg, 95%CI +3.5 to +11.5 mmHg, P<0.001), and heart rate (mean difference in change, +9.6 bpm, 95%CI +4.6 to +14.6 bpm, P<0.001) (table 3 and figure S1).

#### Urinary albumin/creatinine ratio

Urinary albumin/creatinine ratio did not change significantly in response to CPAP withdrawal (difference between median changes +0.05 mg/mmol, 95%CI -0.09 to +0.23 mg/mmol, P=0.46) (table 2, table S2 and figure S2).

#### Peak flow in Laser Doppler Flowmetry

Measures of dermal microvascular endothelial function did not change significantly after two weeks of CPAP withdrawal when compared to therapeutic CPAP (mean difference in peak flow +0.97 perfusion units, 95%CI -12.66 to +14.61 perfusion units, P=0.89) (table 2, table S2 and figure S3).

### ***Effects of CPAP withdrawal on OSA***

At two weeks, withdrawal of CPAP was associated with return of OSA as evidenced by a significant increase in AHI (mean difference in change, +39.7/h, 95%CI +32.7 to +46.7/h, P<0.001) and ODI (mean difference in change, +39.7/h, 95%CI +32.4 to +46.9/h, P<0.001) as well as by an increase of subjective sleepiness assessed by the ESS (mean difference in change, +3.3 points, 95%CI +1.6 to +5.0 points, P<0.001) compared with continuing therapeutic CPAP (table 3).

After including the baseline value of each outcome, there still was no significant effect of CPAP withdrawal on myocardial perfusion, renal or dermal microvascular function.

## Discussion

This randomized controlled trial investigated the effects of short-term CPAP therapy withdrawal on myocardial perfusion in patients with moderate to severe OSA, and showed that two weeks of therapy discontinuation did not result in impaired myocardial endothelial function as assessed by quantitative myocardial perfusion with PET – despite the recurrence of OSA and considerable increased BP and heart rate. In addition we were unable to demonstrate changes in renal or dermal microvascular function. Thus, OSA patients seem not to be at risk for acute myocardial ischemia during short periods of treatment interruption such as on vacation.

A protective effect of CPAP on the cardiovascular system has been proposed from the findings of non-randomized long-term cohort studies, which found a significantly higher incidence of cardiovascular events in patients with severe untreated OSA, compared to CPAP-treated patients.<sup>5, 25</sup> These findings are in concordance with various other trials which found beneficial effects of CPAP therapy on diverse measures of cardiovascular risk such as endothelial function and BP.<sup>10, 11, 13, 14, 26</sup>

So far there have been only limited and uncontrolled preliminary data on myocardial perfusion in OSA, suggesting that CPAP treatment for several months improves myocardial perfusion reserve as assessed by magnetic resonance imaging and myocardial contrast echocardiography.<sup>27, 28</sup> In concordance with this data on myocardial perfusion in OSA<sup>27, 28</sup>, baseline myocardial blood flow in our OSA population (although on CPAP) was lower than reported for healthy subjects.<sup>28</sup> In the current study, <sup>13</sup>N-ammonia-PET has been used as well established gold-standard for quantitative assessment of MBF and CFR. These two parameters have been shown to be highly reproducible in repeated measurements and sensitive to pharmacologic and physiologic stimuli, such as antioxidants or exposure to hypoxia, and have been proposed as parameter for treatment monitoring as they represent strong predictors of coronary artery disease and fatal cardiac events.<sup>18-20, 29, 30</sup> Since MBF and CFR can change substantially within hours in response to drugs and hypoxia, two weeks of OSA recurrence are considered an adequate stimulus. In theory, recurrence of OSA during CPAP therapy interruption might impair myocardial perfusion by several possible mechanisms, mainly reduced endothelial function<sup>9</sup> in response to augmented sympathetic activity<sup>31</sup> and increased oxidative stress due to intermittent hypoxia, as well as increased oxygen demand by accelerated heart rate<sup>9</sup>, and elevated blood pressure<sup>9</sup>. However, the findings of the current trial show that recurrence of moderate to severe OSA by interruption therapy does not affect hyperaemic myocardial perfusion. Indeed, the patients in the CPAP withdrawal arm, who had significant coronary artery disease, did not experience a worsening of symptoms, or any changes in hyperaemic MBF. As hyperaemic MBF and CFR are excellent predictors of long term outcome, our findings may lend support to the interpretation that withdrawal of CPAP is unlikely to increase the acute risk of major adverse cardiac events, although such

endpoints were beyond the power of the present study. While such a negative finding may appear at odds with previous results indicating acute endothelial dysfunction in the forearm after CPAP withdrawal, differences in the nature of the various vascular beds, including the role of autoregulation of critical organ perfusion compared to peripheral circulation, may account for the variability in the acute response.<sup>32, 33</sup> This is supported by the fact that the correlation between endothelial function of peripheral conduit arteries and the coronary arteries is rather weak.<sup>34, 35</sup> Another explanation might be that in OSA the heart has been preconditioned by factors such as increased sympathetic activity, intermittent hypoxia, and thus myocardial perfusion may be less affected by therapy withdrawal in the short-term.<sup>36</sup>

There are some preliminary data from observational and non-randomized studies that OSA is associated with microangiopathy of the kidneys and skin<sup>37, 38</sup>, and that microvascular endothelial function may be improved by CPAP therapy.<sup>28</sup> In the current randomized controlled trial recurrence of OSA was not associated with impaired microvascular function – neither in the renal nor dermal microvascular system despite acute OSA-induced sympathetic nervous system activation, recurrent intermittent hypoxia, and increased BP.

The sample size of the current study might appear as a limitation even though sample size estimation based on a minimally clinically important difference in the primary outcome. However, the very small width of the 95% confidence interval of the treatment effect on hyperaemic MBF showing the possible effect size demonstrates a sufficient power. The population of the current study consists of a selected group of OSA patients with optimal treatment adherence, and thus, one may argue that the results are not generalizable to other patients without caution. However, the effects of therapy withdrawal seen in these patients with optimal CPAP compliance would be expected to be even smaller in patients with less favourable therapy adherence. Furthermore, the current trial included a representative OSA population including patients with a wide range of disease severity (original AHI 20/h to 94/h) with and without coronary heart disease.

In summary, we found no immediate adverse effects of short-term CPAP therapy withdrawal and thus OSA recurrence on myocardial perfusion, coronary endothelial function, or microvascular function in patients with moderate to severe OSA, despite clear effects on blood pressure and heart rate.

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### ***Contributorship***

Study concept and design: Kohler, Stradling, Schwarz, Bloch, Kaufmann. Collection, analysis and interpretation of the data: Schwarz, Schlatzer, Stehli, Kaufmann, Bloch, Stradling, Kohler. Drafting the manuscript: Schwarz, Kohler. Revision of the article for important intellectual content and final approval of the manuscript for publication: all authors. Statistical analysis: Schwarz, Kohler. Obtained funding: Kohler, Stradling, Bloch. Administrative, technical and material support: Schwarz, Schlatzer, Bloch, Kohler. Study supervision: Schwarz, Kohler.

## **Compliance with Ethical Standards**

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Role of the Sponsors: The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

### ***Conflicts of interest***

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

### ***Ethical approval***

The study has been approved by the cantonal ethics committee of Zurich (KEK-ZH-Nr. 2012-0511) and all procedures in this study involving human participants have been performed in accordance with the ethical standards of the local ethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

### ***Informed Consent***

Informed consent was obtained from all individual participants included in the study.

### ***Trial registration***

The trial was registered in Clinical.Trials.gov, identification number NCT01797653.

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## Tables

**Table 1. Patient characteristics at baseline.**

	therapeutic CPAP (n = 23)	subtherapeutic CPAP (n = 22)
Age, mean (SD), years	60.6 (9.6)	64.5 (7.2)
Male sex, No (%)	19 (82.6)	18 (81.8)
BMI, mean (SD), kg/m <sup>2</sup>	33.1 (5.1)	33.8 (6.3)
Neck circumference, mean (SD), cm	43.5 (4.4)	43.5 (4.0)
Former or active smoker, No. (%)	13 (56)	13 (59)
Active smoker, No. (%)	6 (26)	3 (14)
Former smoker, No. (%)	7 (30)	10 (45)
Hypertension, No. (%)	13 (57)	15 (68)
Diabetes mellitus, No. (%)	3 (13)	5 (23)
Statins, No. (%)	10 (43)	8 (35)
Coronary artery disease, No. (%)	4 (17)	2 (9)
Stroke / TIA, No. (%)	2 (9)	2 (9)
Peripheral arterial disease, No. (%)	0	0
OSA diagnosed since, mean (SD), years	4.7 (3.6)	6.2 (4.6)
AHI at diagnosis, mean (SD), events per hour	46.5 (22.0)	50.5 (20.2)
ODI at diagnosis, mean (SD), events per hour	46.0 (18.6)	49.6 (19.6)
ESS at diagnosis, mean (SD), points	14.0 (2.6)	14.8 (4.0)
AHI on CPAP, mean (SD), events per hour	2.1 (2.0)	3.7 (3.5)
ODI on CPAP, mean (SD), events per hour	2.6 (2.4)	3.9 (3.8)
CPAP compliance, mean (SD), hh:mm	07:04 (01:29)	06:58 (01:26)
ODI 4 nights off CPAP, mean (SD), events per hour	31.2 (13.0)	36.5 (15.4)

OSA = obstructive sleep apnea. CPAP = continuous positive airway pressure. BMI = body mass-index. TIA = transient

ischemic attack. AHI = apnea-hypopnea-index. ODI = oxygen-desaturation-index. ESS = Epworth Sleepiness Scale (max. 24 points). There are no statistically significant differences in any baseline characteristic between groups.

**Table 2. Outcomes – Myocardial perfusion and dermal and renal microvascular function.**

	therapeutic CPAP (n=23)		subtherapeutic CPAP (n=22)		treatment effect		
	baseline	follow-up	Baseline	follow-up	difference in change	95% CI	p-value
<b><sup>13</sup>N-ammonia cardiac PET</b>							
hyperemic MBF, median (IQR)	1.46 (1.18-2.31)	1.54 (1.20-2.22)	1.93 (1.51-2.43)	1.95 (1.47-2.28)	-0.01	-0.33, 0.24	0.91
CFR, median (IQR)	2.21 (1.92-2.54)	2.31 (2.03-2.88)	2.36 (2.13-3.24)	2.53 (2.08-3.05)	0.02	-0.38, 0.42	0.93
<b>Laser Doppler Flowmetry</b>							
PF, mean (SD)	49.18 (21.19)	47.61 (21.01)	38.24 (15.84)	37.64 (15.26)	0.97	-12.66, 14.61	0.89
<b>Urinalysis</b>							
ACR, median (IQR)	0.41 (0.26-0.70)	0.33 (0.19-0.70)	0.36 (0.24-1.00)	0.47 (0.26-0.77)	0.05	-0.09, 0.23	0.46

CI = confidence interval. MBF = myocardial blood flow [ml/min/g]. Hyperaemic MBF = hyperaemic MBF during adenosine stress. CFR = coronary flow reserve. PF = peak flow [perfusion units]. ACR = albumin/creatinine ratio [mg/mmol]. Non-normally distributed data are presented as median (interquartile range) and normally distributed data as mean (SD).

**Table 3. Outcomes from sleep studies and blood pressure monitoring.**

	therapeutic CPAP (n=23)		subtherapeutic CPAP (n=22)		treatment effect		
	baseline	follow-up	baseline	follow-up	difference in change	95% CI	p-value
<b>AHI</b>	2.07 (1.97)	2.53 (2.43)	3.66 (3.52)	43.83 (16.24)	39.71	32.67, 46.74	< 0.001
<b>ODI</b>	2.57 (2.39)	2.89 (2.97)	3.92 (3.75)	43.92 (17.06)	39.67	32.44, 46.91	< 0.001
<b>ESS</b>	7.00 (2.63)	7.13 (3.24)	6.59 (2.87)	10.00 (4.32)	3.28	1.60, 4.96	< 0.001
<b>SBP</b>	132.96 (13.54)	131.25 (13.82)	126.06 (14.49)	135.14 (11.88)	10.79	5.20, 16.37	< 0.001
<b>DBP</b>	84.78 (11.02)	84.12 (9.51)	80.35 (8.19)	87.23 (8.54)	7.49	3.47, 11.51	< 0.001
<b>HR</b>	68.75 (7.36)	67.17 (7.14)	68.05 (9.99)	76.05 (11.30)	9.58	4.56, 14.60	< 0.001

CI = confidence interval. AHI = apnea-hypopnea-index [events/h]. ODI = oxygen-desaturation-index [events/h]. ESS =

Epworth Sleepiness Scale (max. 24 points). SBP = systolic morning blood pressure [mmHg]. DBP = diastolic morning blood pressure [mmHg]. HR = morning heart rate [bpm]. Data are presented as mean (SD).

## Figure legends

### Fig. 1

Trial profile. CONSORT flow diagram. 45 eligible patients with moderate to severe OSA were randomly assigned to either continue therapeutic CPAP or to withdraw it by the use of a subtherapeutic sham-device. All patients received the intended intervention and completed the study. OSA = obstructive sleep apnea. CPAP = continuous positive airway pressure

### Fig. 2

Effect of CPAP withdrawal on hyperaemic myocardial blood flow. Whisker Box-Plots (median; box: 25%-75%; whisker: minimum-maximum) of hyperaemic myocardial blood flow during adenosine stress at baseline (black) and after two weeks (blue) in patients allocated to therapeutic CPAP (left) and subtherapeutic CPAP (right). Recurrence of OSA for two weeks was not associated with a significant effect on hyperaemic myocardial blood flow when compared to the CPAP treated group. CPAP = continuous positive airway pressure