

Nocturnal cerebral hypoxia in obstructive sleep apnea - data from a randomized CPAP withdrawal trial

Esther I Schwarz^{*1}, Michael Furian^{*1}, Christian Schlatzer¹, John R Stradling³, Malcolm Kohler^{1,2}, Konrad E Bloch^{1,2}

¹ Sleep Disorders Center and Pulmonary Division, University Hospital of Zurich, Zurich, Switzerland

² Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

³ Oxford Centre for Respiratory Medicine and Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK

* These two authors contributed equally to this work.

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Corresponding author address

Prof Konrad E Bloch, MD

Division of Pulmonology and Sleep Disorders Centre

University Hospital of Zurich

Raemistrasse 100, Zurich, Switzerland

phone: +41442553828; fax: +41442554451

email: konrad.bloch@usz.ch

At a Glance Commentary

Scientific Knowledge on the Subject:

Obstructive sleep apnea (OSA) has been associated with an increased risk of stroke in epidemiological studies. Suspected underlying mechanisms include cerebral hypoxia related to repetitive arterial oxygen desaturations and impaired cerebrovascular autoregulation.

What This Study Adds to the Field:

CPAP therapy withdrawal in OSA is associated with intermittent and sustained nocturnal cerebral tissue hypoxia to a clinically relevant degree reported to cause functional impairment. These findings suggest that patients with untreated OSA are at increased risk of nocturnal cerebral damage and stroke during sleep, a threat that may be prevented by CPAP therapy.

ABSTRACT

Rationale. Nocturnal cerebral hypoxia is suspected to promote cognitive impairment and stroke in patients with obstructive sleep apnea (OSA).

Objectives. To evaluate whether patients with OSA experience nocturnal cerebral hypoxia that is prevented by continuous positive airway pressure therapy (CPAP).

Methods. Patients with OSA using CPAP were randomized to either nocturnal therapeutic or subtherapeutic CPAP. Sleep studies including pulse oximetry (SpO₂) and near-infrared spectroscopy to monitor frontal cerebral tissue oxygenation (CTO) were performed at baseline and after 2 weeks. Between-group differences in changes, adjusted for baseline differences in oxygen desaturation indices (ODI) and mean nocturnal oxygen saturation, were computed.

Measurements and Main Results. 21 patients (mean±SD age 63.0±8.9yrs, apnea/hypopnea-index at diagnosis 50.3±19.1/h) participated. Compared to 12 patients using therapeutic CPAP, OSA recurred in those 9 patients using subtherapeutic CPAP; mean (95%CI) between-group differences in ODI-changes from baseline to 2 weeks were +40.7/h (+31.1 to +50.4) for SpO₂ and +37.0/h (+25.3 to +48.7) for CTO (P<0.001, both differences). Mean nocturnal SpO₂ and CTO, respectively, decreased more in patients using subtherapeutic vs. therapeutic CPAP [-2.4% (-3.4 to -1.1) and -3.8% (-7.4 to -0.1) respectively (P<0.03, both differences)]. Major CTO-drops of ≥13% (associated with cerebral dysfunction in previous studies) occurred in 4 of 9 patients using subtherapeutic, but in none using therapeutic CPAP (chi-square, P=0.01).

Conclusions: In patients with OSA, CPAP-withdrawal resulted in nocturnal cerebral deoxygenation that is prevented by CPAP therapy. The findings are consistent with a potential role of cerebral hypoxia in predisposing untreated OSA patients to stroke.

Trial registration number: NCT01797653.

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Key words: obstructive sleep apnea, continuous positive airway pressure, near-infrared spectroscopy, nocturnal cerebral tissue oxygenation, cerebral ischemia

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder associated with adverse vascular outcome.(1, 2) OSA has been associated with neurocognitive impairment(3) and increased risk of stroke and other manifestations of ischemic cerebrovascular disease in epidemiologic studies.(4-7) Proposed underlying mechanisms explaining the association between OSA and cerebral damage include cerebral hypoxia related to repetitive arterial oxygen desaturations, augmented sympathetic activity, endothelial dysfunction, and impaired cerebrovascular autoregulation in response to blood pressure surges and intermittent hypoxemia. A causal relationship between OSA and hypertension(8), as well as between OSA and peripheral vascular dysfunction(9), has been shown. However, less is known on cerebrovascular function and oxygenation in OSA patients. In a previous study using near-infrared spectroscopy (NIRS) to monitor cerebral oxygenation during sleep, in OSA patients discontinuing their CPAP therapy for a few nights, we observed considerable intermittent and sustained nocturnal cerebral deoxygenation, in particular at altitude.(10) The cerebral tissue oxygen saturation during sleep reached similarly low levels in previous studies to that associated with cerebral dysfunction in patients undergoing unilateral carotid artery clamping during neurosurgery.(11)The current trial was designed to test the hypothesis that OSA induces cerebral hypoxia that might expose patients with OSA to increased risk of cerebral ischemia, that can be prevented by CPAP therapy.The study was performed concurrently in participants of an investigation on the effects of OSA on coronary perfusion during CPAP withdrawal.(12)

METHODS

Trial Design

This study was conducted as a part of a randomized controlled trial assessing the effect of CPAP-withdrawal on myocardial perfusion in patients with OSA using long-term CPAP therapy (NCT01797653).(12) Participants of that study were asked to undergo nocturnal monitoring of cerebral oxygenation, in addition to cardiorespiratory sleep studies, while being treated with therapeutic or subtherapeutic CPAP. The study was approved by the local ethics committee (KEK-ZH-Nr. 2012-0511) and written informed consent was obtained from all participants.

Participants

Patients aged 20 to 75 yrs with moderate to severe OSA, effectively treated with CPAP were recruited. Patients were eligible if they were treated with CPAP for more than one year, showed a minimal adherence of 4 hours per night, and had an oxygen desaturation index (ODI) of at least 20/h both at the time of initial OSA diagnosis, as well as during a current 4-day period off CPAP (to confirm persistence of at least moderate OSA). Patients with previous respiratory failure (awake $\text{PaO}_2 < 9.0 \text{ kPa}$ or arterial $\text{PaCO}_2 > 6 \text{ kPa}$), unstable coronary or cerebral artery disease, severe arterial hyper- or hypotension, Cheyne-Stokes breathing, or a history of a sleepiness-related accident were excluded.

Intervention and assessments

Outcomes were assessed at baseline on therapeutic CPAP and after two weeks of treatment with either therapeutic or subtherapeutic CPAP according to randomization. Therapeutic CPAP was provided with a REMstar autoCPAP device (Philips Respironics, PA, USA) operated in the mode and with the nose or full-face mask that the patient was used to.

Subtherapeutic CPAP was provided with the REMstar autoCPAP device with modified tubing incorporating a restrictor at the airflow outlet and additional leaks near the mask to prevent rebreathing; maximal mask pressure was $<2\text{mbar}$.

Polygraphic in-laboratory cardio-respiratory sleep studies measuring airflow, respiratory inductance plethysmography, finger pulse oximetry (SpO_2), electrocardiogram and transcutaneous carbon dioxide tension (Microgas, Radiometer, Basel, Switzerland) were performed along with cerebral near-infrared spectroscopy (NIRS). Regional cerebral tissue oxygenation (CTO) and cerebral total hemoglobin concentration (tHb) were continuously recorded over the night using a NIRO 200NX device (Hamamatsu Photonics, Hamamatsu City, Japan). Optodes were placed bilaterally on the skin high on the forehead where bone thickness is minimal (FP1/2 location of the 10/20 system) as previously described.⁽¹⁰⁾ NIRS data were sampled at 1 Hz along with other polygraphic data in a polysomnography device (Alice 5, Philips Respironics, city, USA). Subjective sleepiness was assessed by the Epworth Sleepiness Scale (ESS).⁽¹³⁾

Main outcomes of interest

The co-primary outcomes of the study were changes in mean nocturnal CTO and in CTO desaturation index (cODI). A CTO desaturation was defined as a $\geq 3\%$ dip lasting for at least 10 seconds in association with an arterial oxygen desaturation (SpO_2 -channel).

Secondary outcomes of interest

Other outcomes were major falls of CTO by $\geq 13\%$ – such transient falls associated in previous studies in neurosurgical patients with neurophysiological signs of severe cerebral ischemia,⁽¹¹⁾ the mean nocturnal arterial oxygen saturation (SpO_2), and the ODI ($\geq 4\%$ dips in the SpO_2 signal). In order to evaluate the effect of cerebral deoxygenation on cerebral blood volume, as an index of the cerebrovascular response to hypoxia, coefficients of cross-

correlation between CTO and NIRS-derived total cerebral hemoglobin concentration (a NIRS-derived surrogate for regional cerebral blood volume) were computed. In theory, a perfect cerebrovascular autoregulation would result in a coefficient of cross-correlation of -1 between the two variables, this is because drops in CTO would be compensated for by an increase in blood volume to maintain oxygen delivery; conversely, a coefficient of +1 would indicate absence of such compensation (see online supplement).

Randomization and blinding

Patients were randomized to either subtherapeutic or continuation of therapeutic CPAP by a computer software minimizing for differences in ODI, body-mass-index, vascular disease as reported previously.(12) Patients and outcome assessors remained blinded to the allocation.

Data analysis

The sample size estimation was based on the main outcome of the trial evaluating coronary perfusion. There was no basis from previous studies to perform an a-priori sample size estimation in the current exploratory study of CTO. Data are summarized as medians (quartiles) and means (SD) depending on distribution. The primary analysis was performed as per protocol. Treatment effects of therapeutic versus subtherapeutic CPAP treatment were determined by comparing the baseline versus follow-up mean differences (and 95% confidence intervals, CI) of the outcomes of interest. A two-sided $p < 0.05$ in independent t-tests or Mann Whitney U-tests was considered statistically significant. Analyses were adjusted for differences in baseline mean oxygen saturation and oxygen desaturation index (SpO₂ and CTO) using multiple regression. Cross-correlation analyses between CTO and tHb were performed to evaluate changes in cerebral blood volume in response to cerebral tissue deoxygenation as described in the online supplement.

RESULTS

Participants

The patient flow is shown in **figure 1**. 26 patients with moderate to severe OSA included in the myocardial perfusion study(12) took part in the current NIRS-study (therapeutic CPAP n = 16 and subtherapeutic CPAP n = 10). Data of five patients (one in the sub- and four in the therapeutic CPAP group) could not be analyzed because of poor NIRS signal quality. Data from 21 patients were available for analysis. Characteristics of patients in the two study arms were similar (**table 1**).

Effects of CPAP-withdrawal on cerebral oxygen and sleep apnea

The outcomes assessed at baseline and at the end of the two-week intervention period are summarized for the two groups in **table 2** and are illustrated in **figures 2 and 3**. At baseline (on their usual CPAP), patients in both groups had a normal SpO₂, AHI and ODI. At the end of the two-weeks intervention, cyclic drops in CTO $\geq 3\%$, in SpO₂ $\geq 4\%$ and in the AHI had increased significantly more in the CPAP withdrawal group compared to patients continuing therapeutic CPAP. The magnitude of CTO desaturations was greater in the group using subtherapeutic compared to the group with therapeutic CPAP (**figure 3**). A major fall of CTO by $\geq 13\%$, that was previously reported as the threshold for severe cerebral ischemia, was observed in 4/9 patients treated with subtherapeutic CPAP but in none of the patients on therapeutic CPAP (chi square=6.6, p=0.01). Moreover, the mean nocturnal CTO and SpO₂ decreased in the patients using subtherapeutic CPAP, while these variables remained unchanged in patients using therapeutic CPAP.

CPAP withdrawal was associated with a significant increase in the negative cross-correlation between CTO and total hemoglobin (tHb) at a lag of 26 (SD 10) sec (**table E2, figures E1-2**) while there was no significant change in the peak negative cross-correlation coefficient in

patients using therapeutic CPAP. The lag time of the maximal cross-correlation coefficients did not change in either group.

There was no change in the mean nocturnal transcutaneous PCO₂. Subjective sleepiness assessed by the ESS significantly increased in response to CPAP-withdrawal when compared to continuing therapeutic CPAP (**table 2**).

DISCUSSION

This randomized, controlled trial in patients with moderate to severe OSA demonstrates that withdrawing therapeutic CPAP results in recurrence of nocturnal breathing disturbances causing major cyclical and persistent drops in CTO and SpO₂ which is prevented by therapeutic CPAP. In several patients, the apnea/hypopnea-related cyclic drops in CTO during CPAP withdrawal were of a magnitude reported to cause cerebral dysfunction in patients undergoing unilateral carotid artery clamping during neurosurgery.(11) Therefore, the current data supports a potential role of untreated OSA in predisposing to neuronal damage with brain dysfunction and an increased risk of stroke that may be reduced by CPAP therapy.

Several epidemiological studies have shown a strong association between OSA and the incidence of stroke as well as other manifestations of ischemic cerebrovascular disease.(4-7) Imaging studies have shown metabolic and structural changes in the brain of patients with OSA associated with cognitive dysfunction, similar to that observed in patients with multi-infarct syndrome.(14-19) In a meta-analysis of prospective observational studies, the pooled relative risk of stroke in OSA, compared to the control group, was 2.0 (95%CI 1.4-2.9).(20) Another meta-analysis including 8435 patients also found a significant association between OSA and stroke risk with an odds ratio for incident stroke of 2.24 (95%CI 1.57-3.19) in OSA, which was even higher in males, and also correlated with OSA severity.(21) Over 10 years,

14% of patients with severe OSA are predicted to experience a stroke.(22) Potential mechanisms explaining this association – besides the role of OSA in development of established risk factors for stroke such as hypertension and probably atrial fibrillation – are impaired cerebral perfusion by disturbed endothelial function(9) and cerebral autoregulation, autonomic dysregulation(23), repetitive shear stress by nocturnal blood pressure surges, blunted nocturnal dipping blood pressure pattern, and increased intracranial pressure(24, 25) leading to a decreased cerebral perfusion pressure. Based on epidemiological observational studies, CPAP is suggested to improve the cerebro- and cardiovascular outcome in OSA patients(4, 26)and to reduce the risk of stroke. However, robust evidence from randomized controlled interventional trials is missing.

The current study provides new evidence that OSA causes cerebral tissue hypoxia that is prevented by therapeutic CPAP. The mean nocturnal CTO measured during CPAP withdrawal of 65% in this current study is the same as that observed in our previous study in OSA patients discontinuing CPAP therapy for a few days studied at an altitude of 490 m before travelling to 2590 m.(10) The current data extend these earlier findings by providing detailed information on the magnitude of cyclic CTO desaturations that occurred as a consequence of apneas/hypopneas over the course of entire nights. More than half of the patients in the current study revealed CTO desaturations >10% (**figure 3**), i.e. exceeded the decrease in mean nocturnal CTO of 8% that is associated with exposure to an altitude of 2590 m observed in our previous study. The proportion of patients with large, to very large, drops in CTO by >13% during use of subtherapeutic CPAP was considerable (44%). It is consistent with an exposure of these patients to cerebral hypoxia sufficiently severe to represent a risk of cerebral dysfunction and ischemia.(11) Other, uncontrolled observations in sleeping OSA patients during shorter periods of 1-2 hours revealed a baseline CTO of 65% and desaturations up to 8% in OSA patients with a broad range of severity.(27) In one study, OSA patients had a lower mean nocturnal CTO (57%) than healthy controls (62%) and this was

related in part to the older age of OSA patients; the extent of CTO desaturations was not reported.(28)

Intact cerebral autoregulation is required to maintain a constant tissue perfusion during changes in blood pressure. Additional physiological mechanisms that control the cerebral perfusion contribute to the prevention of hypoxia and hypercapnia of the brain tissue.(29, 30) OSA was associated with impairment of cerebrovascular regulation in a population-based study.(31) Transcranial Doppler ultrasound and NIRS studies have suggested an ineffective autoregulation in OSA.(32-36) This finding led to the conclusion that OSA patients might be particularly susceptible to nocturnal cerebral ischemia due to repetitive decreases in cerebral blood flow and hypoxemia.

In the current study we employed cross-correlation analysis to investigate the changes in tHb, the NIRS-derived surrogate of regional cerebral blood volume, following CTO desaturations based on an approach proposed in previous studies.(33) We found a negative peak in the cross-correlation coefficients between these variables at a lag in tHb of a few seconds, consistent with an influx of blood in response to hypoxia. The peak negative cross-correlation was even larger during CPAP withdrawal than during therapeutic CPAP suggesting that the greater degree of variation in CTO during OSA recurrence was met with larger changes in blood volume. Thus, some degree of response of the cerebral circulation to alterations in cerebral hypoxia seemed to be preserved in OSA patients chronically treated with CPAP even after short-term withdrawal. However, due to the delay and/or insufficient magnitude of this response, the brain was not protected from relevant desaturations which was consistent with our previous observations.(10) Nevertheless, the desaturations in CTO were less pronounced than those of the arterial blood (**table 2**).

Despite a more pronounced fall in SpO₂ than in CTO during apneic events (see **table E1**), the treatment withdrawal effect on mean CTO during the whole night was more pronounced than on mean nocturnal SpO₂ measured by finger pulse oximetry (-3.8% vs. 2.3%, see **table 2**) – a

finding that may be related to the different physiologic basis of the two signals, i.e. CTO reflecting an average of oxygen saturation in all vessels included in the NIRS sample volume (mainly capillaries) while SpO₂ reflects oxygenation of the arterial blood. However, differences in the physiologic control of cerebral and arterial PO₂ are also conceivable.

A limitation of the current RCT is the relatively low number of participants not allowing any subgroup analysis to predict which patient characteristics were associated with the most pronounced cyclic and persistent cerebral deoxygenation. However, the randomized design and the application of a short-term CPAP-withdrawal in treated OSA patients allowed effectively investigating treatment effects. Nevertheless, the long-term consequences of OSA-induced cyclic drops and sustained nocturnal falls in cerebral oxygenation are not addressed in this study.

Conclusion

The current study shows that OSA results in intermittent and sustained nocturnal cerebral tissue deoxygenation to a degree reported to cause cerebral dysfunction. These findings suggest that patients with untreated OSA are at increased risk of nocturnal cerebral damage, a threat that may be prevented by CPAP therapy.

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FIGURE LEGENDS

Figure 1. Patient flow.

Figure 2. Individual plots showing cerebral oxygen desaturation index (cODI), and the mean nocturnal cerebral tissue oxygenation (CTO) in both groups at baseline and at the 2-weeks follow-up.

Figure 3. Percent of patients in each group reaching a certain degree of maximal falls in CTO. A decrease in CTO by >13% was associated with cerebral dysfunction in neurosurgical patients in a previous study. * Chi-square test significant $P < 0.05$.

Table 1. Patient characteristics.

	therapeutic CPAP (n = 12)	subtherapeutic CPAP (n = 9)
Age, mean (SD), years	61.8 (10.8)	64.7 (5.5)
Male sex, No (%)	10 (83)	8 (89)
BMI, mean (SD), kg/m ²	33.6 (5.4)	34.9 (6.2)
Neck circumference, mean (SD), cm	43.5 (4.7)	44.1 (4.5)
ESS at diagnosis, mean (SD), points	14.3 (3.4)	12.1 (5.7)
AHI at diagnosis, mean (SD), events per hour	52.1 (19.8)	47.9 (19.0)
ODI at diagnosis, mean (SD), events per hour	47.6 (14.7)	50.0 (15.3)
AHI on CPAP, mean (SD), events per hour	2.3 (2.4)	4.9 (4.6)
ODI on CPAP, mean (SD), events per hour	2.5 (2.7)	5.1 (5.0)
CPAP compliance, mean (SD), hh:mm	07:05 (01:26)	06:27 (01:32)
Active smoker, No. (%)	3 (25)	1 (13)
Former smoker, No. (%)	3 (25)	6 (75)
Hypertension, No. (%)	7 (58)	4 (50)
Diabetes mellitus, No. (%)	0	0
Coronary artery disease, No. (%)	2 (17)	2 (25)
Stroke / TIA, No. (%)	0	0

OSA = obstructive sleep apnea. CPAP = continuous positive airway pressure. BMI = body mass-index. TIA = transient ischemic attack. AHI = apnoeas-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. Effect of CPAP withdrawal

	therapeutic CPAP (n=12)		subtherapeutic CPAP (n=9)		Effect of CPAP withdrawal		
	baseline	2-weeks follow-up	baseline	2-weeks follow-up	Mean difference in change	95%CI	adj. p-value*
Cerebral ODI (1/h)	0.8 (1.3)	0.6 (71.0)	3.2 (4.1)	40.0 (20.5)	37.0	25.3 to 48.7	<0.001
Arterial ODI (1/h)	2.5 (2.7)	3.1 (3.4)	5.1 (5.0)	48.3 (17.9)	41.0	31.7 to 50.3	<0.001
Mean nocturnal CTO (%)	69.8 (6.6)	70.5 (5.4)	68.4 (1.2)	65.3 (5.2)	-3.8	-7.4 to -0.1	0.025
Mean nocturnal SpO2 (%)	94.7 (1.8)	94.6 (1.6)	94.4 (1.1)	92.1 (1.8)	-2.3	-3.4 to -1.1	<0.001
AHI (events/h)	2.3 (2.4)	2.8 (2.9)	4.9 (4.6)	47.6 (18.0)	40.7	31.1 to 50.4	<0.001
ptcCO2 (mmHg)	54.2 (4.5)	56.1 (7.8)	56.2 (8.3)	56.6 (9.7)	-1.4	-10.8 to 7.9	0.18
Epworth score	7.3 (4.3)	7.8 (3.4)	7.3 (3.2)	10.2 (4.4)	3.3	1.6 to 5.0	<0.001

*adjusted for baseline differences

CTO and cerebral ODI = mean nocturnal cerebral tissue oxygenation and cerebral tissue oxygen desaturation index by near infrared spectroscopy. SpO2 and arterial ODI = mean nocturnal arterial oxygen saturation and arterial oxygen desaturation-index by finger pulse oximetry. AHI = apnea/hypopnea-index. ptcCO2 = transcutaneous carbon dioxide tension.

ILLUSTRATIONS

Figure 1

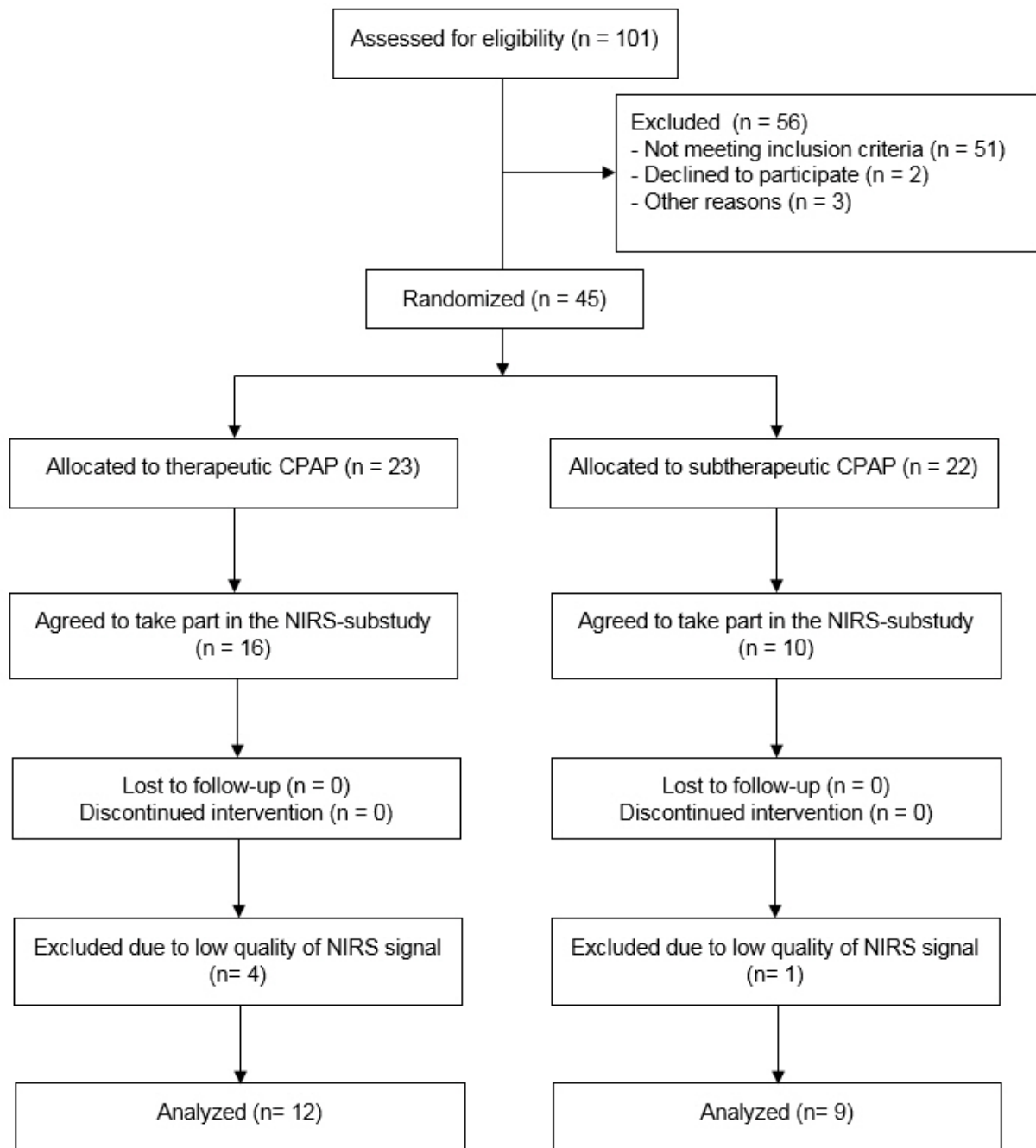


Figure 2

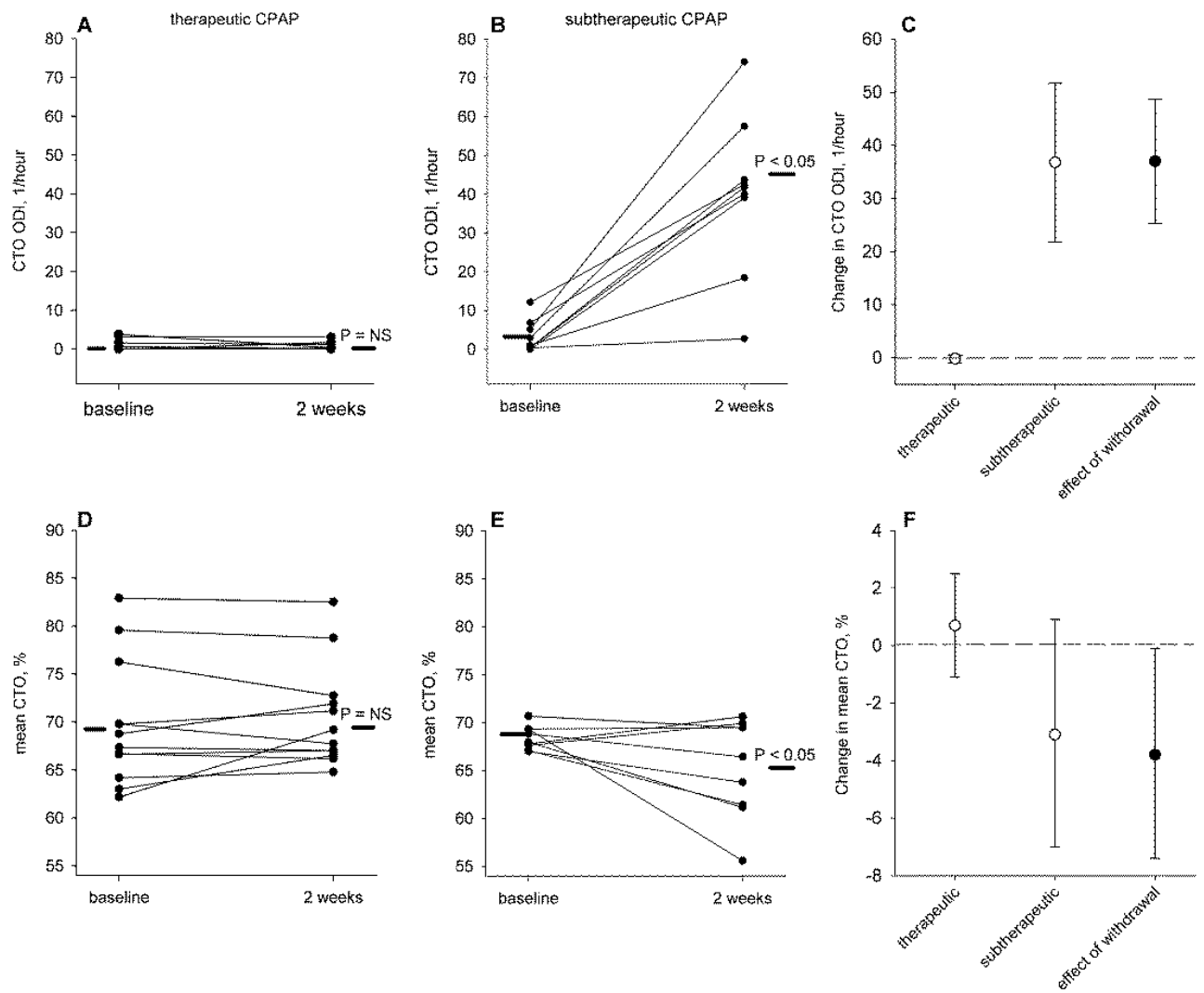


Figure 3

