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Early View

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Nocturnal cerebral hypoxia in obstructive sleep apnoea – a randomised controlled trial

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Take home message: Untreated OSA predisposes to severe cerebral hypoxia during sleep.

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ABSTRACT

Objectives. Cerebral hypoxia may promote cerebral damage in patients with obstructive sleep apnoea (OSA). We investigated whether OSA patients experience nocturnal cerebral hypoxia that is prevented by continuous positive airway pressure (CPAP).

Methods. OSA patients using CPAP underwent sleep studies including pulse oximetry (SpO_2) and near-infrared spectroscopy to monitor cerebral tissue oxygenation (CTO) at baseline and after 2 weeks on either subtherapeutic or therapeutic CPAP according to randomised allocation. Changes in oxygenation at end of the 2-week intervention were compared between groups.

Results. Among 21 patients (mean apnoea/hypopnoea-index 50.3/h), OSA recurred in all 9 using subtherapeutic and in 0 using therapeutic CPAP: mean (95%CI) between-group differences in changes of oxygen-desaturation-index baseline to 2 weeks +40.7/h(+31.1;+50.4) for SpO_2 and +37.0/h(+25.3;+48.7) for CTO (both $P<0.001$). Mean nocturnal SpO_2 and CTO decreased more in patients using subtherapeutic vs. therapeutic CPAP: -2.4%(-3.4;-1.1) and -3.8%(-7.4;-0.1), respectively, both $P<0.03$. Severe CTO-drops ≥13% associated with cerebral dysfunction in previous studies occurred in 4/9 patients using subtherapeutic but in 0/12 using therapeutic CPAP ($P=0.01$).

Conclusions: In patients with OSA, CPAP-withdrawal resulted in nocturnal cerebral deoxygenation suggesting a role of cerebral hypoxia in predisposing untreated OSA patients to cerebral damage.

Clinical trials registration number: NCT01797653.

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

INTRODUCTION

Obstructive sleep apnoea (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 auto-regulation 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 to that associated with cerebral dysfunction in patients undergoing unilateral carotid artery clamping during neurosurgery in previous studies.[11] The current trial was designed to test the hypothesis that OSA induces cerebral hypoxia that might expose patients with OSA to an 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 randomised 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 years with moderate to severe OSA, effectively treated by 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 PaO_2<9.0kPa or arterial $PaCO_2$>6kPa), unstable coronary or cerebral artery disease, severe arterial hyper- or hypotension, Cheyne-Stokes breathing or a history of a sleeping-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 randomisation. Therapeutic CPAP was provided with a REMstar autoCPAP device (Philips Respironics, PA, USA) operated in the previous mode and with the nose or full-face mask that the patient was used to. Subtherapeutic CPAP was provided with 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 < 2mbar.

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 haemoglobin 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 ≥3% dip lasting for at least 10 seconds in association with an apnoea/hypopnoea-related arterial oxygen desaturation (SpO_2-channel) (see further detailed explanations on CTO analysis in the online supplement).

Other outcomes of interest

Other outcomes were apnoea/hypopnoea-related CTO dips ≥13% – such desaturations were associated in previous studies in neurosurgical patients with neurophysiological signs of severe cerebral ischemia,[11] the cumulative night-time spent with apnoea/hypopnoea-related CTO dips of various severities including ≥13%, and the night-time spent with sustained CTO desaturations ≥13% from wakefulness baseline, the mean nocturnal arterial oxygen saturation (SpO_2), the ODI (≥4% dips in the SpO_2 signal), and mean nocturnal transcutaneous PCO_2. 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 both CTO and SpO_2 and NIRS-derived total cerebral haemoglobin concentration, a NIRS-derived

surrogate for regional cerebral blood volume, were computed. In theory, a perfect cerebrovascular auto-regulation 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).

Randomisation and blinding

Patients were randomised 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 summarised as medians (quartiles) and means (SD) depending on distribution. The primary analysis was performed as per protocol. The treatment effect was determined by computing mean differences and 95% confidence intervals (CI) of changes in outcomes between baseline and the follow-up in patients randomised to therapeutic and subtherapeutic CPAP. 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 (SpO_2 and CTO) using multiple regression. Cross-correlation analyses between both CTO and SpO_2 and tHb were performed to evaluate changes in cerebral blood volume in response to cerebral tissue and peripheral arterial 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 analysed 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**).

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/m2	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 apnoea. CPAP = continuous positive airway pressure. BMI = body mass-index. TIA = transient ischemic attack. AHI = apnoeas-hypopnoea-index. ODI = oxygen-desaturation-index. ESS = Epworth Sleepiness Scale (max. 24 points). There are no statistically significant differences in any baseline characteristic between groups.

Effects of CPAP-withdrawal on cerebral and peripheral arterial oxygen saturation and sleep apnoea

Physiologic recordings in a patient during application of subtherapeutic CPAP are illustrated in **figure 2**. Apnoea/hypopnoea-related CTO dips were generally less pronounced than corresponding SpO_2 dips and they were associated with a rise in tHb, the surrogate of regional cerebral blood volume, with a delay of about 30 seconds. The outcomes assessed at baseline and at the end of the two-week intervention period are summarised for the two groups in **table 2** and are illustrated in **figures 3 and 4**.

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 SpO_2 (%)	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
$ptcCO_2$ (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. SpO_2 and arterial ODI = mean nocturnal arterial oxygen saturation and arterial oxygen desaturation-index by finger pulse oximetry. AHI = apnoea/hypopnoea-index. $ptcCO_2$ = transcutaneous carbon dioxide tension.

At baseline (on therapeutic CPAP), patients in both groups had a normal SpO_2, AHI and ODI. At the end of the 2-weeks intervention, the number of cyclic dips in CTO ≥3%, in SpO_2 ≥4% and in the AHI had increased significantly more in the CPAP withdrawal group compared to patients continuing therapeutic CPAP. Moreover, the amplitude of apnoea/hypopnoea-related CTO dips ≥3% and the cumulative night-time spent in these dips were greater in the group using subtherapeutic CPAP (mean±SD amplitude 5.4 ±3.1%, cumulative night-time spent in CTO dips ≥3% 186 ±117 min) compared to the group using therapeutic CPAP (mean±SD amplitude 3.5 ±0.8%; cumulative night-time spent in CTO dips ≥3% 3 ±16 min; $p<0.001$ for both comparisons) (**figure 3**). Major CTO dips ≥13%, that were previously reported as the threshold for severe cerebral ischemia, were observed in 4/9 patients treated with subtherapeutic CPAP (see example in **figure 2**) but in none of the patients on therapeutic CPAP (chi square=6.6, p=0.01). The four patients with major apnoea/hypopnoea-related CTO dips ≥13% during subtherapeutic CPAP spent a median duration of 16.6 min (quartiles 3.7, 43.2) in dips with such severe desaturation. Both the mean nocturnal CTO and SpO_2 decreased significantly in the patients using subtherapeutic CPAP while these variables remained unchanged in patients using therapeutic CPAP (**table 2**). The time spent with sustained CTO desaturations ≥13% below wakefulness baseline was significantly greater with subtherapeutic (mean ±SD 34 ±65 min) compared to therapeutic CPAP (0 ±0 min; $p<0.017$).

CPAP withdrawal was associated with a significant increase in the peak negative cross-correlation coefficient between CTO and total haemoglobin (tHb) at a mean ±SD lag of 26 ±10 sec (**e-table 1, e-figures 1-2**) 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. Correspondingly, the peak negative cross-correlation coefficient between SpO_2 and tHb (at mean lag of 40 ±18 sec) increased during the 2-week intervention in patients using subtherapeutic CPAP but remained unchanged in patients using therapeutic CPAP (**e-table 2**).

There was no change in the mean nocturnal transcutaneous PCO_2. Subjective sleepiness assessed by the ESS significantly increased in response to CPAP-withdrawal when compared to continuing therapeutic CPAP (**table 2**).

DISCUSSION

This randomised, 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 SpO_2 which is prevented by therapeutic CPAP. In several patients, the apnoea/hypopnoea-related cyclic drops in CTO during CPAP withdrawal were of a magnitude and duration 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.

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 auto-regulation, 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. Robust evidence from randomised controlled interventional trials is missing. However, a matched analysis of CPAP adherent patients vs. usual care patients of the SAVE trial, a recent large randomised controlled trial on the effect of CPAP on cardiovascular events in OSA, has shown a significant reduction of cerebral events and stroke in the CPAP group (hazard ratio 0.52, 95%CI 0.30 to 0.90, p=0.02).[27]

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 the 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 and duration of cyclic and sustained CTO desaturations that occurred as a consequence of apnoeas/hypopnoeas 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% associated with exposure to an altitude of 2590 m observed in our previous study.[10] The proportion of patients with very large CTO dips >13% during use of subtherapeutic CPAP was considerable (44%). These patients spent a median time of 16.6 minutes with cyclic dips reaching this degree of cerebral hypoxemia. Moreover, in the whole group of patients using subtherapeutic CPAP, the median time of the night spent with a CTO desaturation ≥13% below wakefulness baseline was even 34 minutes. These findings are consistent with an exposure of the patients to cerebral hypoxia

sufficiently severe to represent a risk of cerebral dysfunction and ischemia.[11] For comparison, in a previous study, unilateral carotid artery clamping for only 2-3 min that caused CTO desaturations ≥13% in neurosurgical patients had induced cerebral dysfunction.[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.[28] 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.[29]

Intact cerebral auto-regulation 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.[30, 31] OSA was associated with impairment of cerebrovascular regulation in a population-based study.[32] Transcranial Doppler ultrasound and NIRS studies have suggested an ineffective auto-regulation in OSA.[33-37] 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 and SpO_2 desaturations based on an approach proposed in previous studies.[34] 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 larger during CPAP withdrawal than during therapeutic CPAP suggesting that the greater degree of variation in CTO and SpO_2 during OSA recurrence was met with larger changes in blood volume (**e-table 1 and 2**). 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. Cross-correlation analyses between tHb and $paCO_2$ would have provided additional comprehensive insights into the cerebral blood flow response to apnoea/hypopnoea-related changes in blood gases but were not feasible due to the slow response-time of transcutaneous capnography.

Despite a more pronounced fall in SpO_2 than in CTO during apnoeic events, the treatment withdrawal effect on mean CTO during the whole night was more pronounced than on mean nocturnal SpO_2 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 SpO_2 reflects oxygenation of the arterial blood.

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 randomised 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 dips and sustained nocturnal falls in cerebral oxygenation are not addressed in this study. Whether patients with OSA exhibit specific responses of cerebral perfusion to intermittent hypoxia – either pronounced due to endothelial dysfunction or attenuated due to hypoxic preconditioning – cannot be answered by the current study that did not include a control group of healthy subjects. Interestingly, Rupp et al.[38] found relatively less pronounced CTO dips in response to intermittent 2-min cycles of hypoxia in healthy subjects applied during 45 min. The mean amplitude ratio of CTO vs. SpO_2 dips vs. was 0.35, i.e., lower than the corresponding ratio of 0.48 in OSA patients using subtherapeutic CPAP in the current study.

Our non-invasive NIRS measurements recorded oxygenation of the frontal cortex only whilst other regions that are also susceptible to hypoxia such as the hippocampus and the cerebellum were not studied. However, multi-channel NIRS recordings revealed similar patterns of CTO changes in response to hypoxia and exercise in different regions of the prefrontal, premotor and motor cortex and magnetic resonance studies in patients with OSA identified structural changes in frontal and hippocampal territories that were both improved with CPAP therapy.[39, 40]

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 might be at increased risk of nocturnal cerebral damage.

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FIGURE CAPTIONS

Figure 1. Patient flow.

The CONSORT flow diagram is shown. CPAP: continuous positive airway pressure. NIRS: near-infrared spectroscopy.

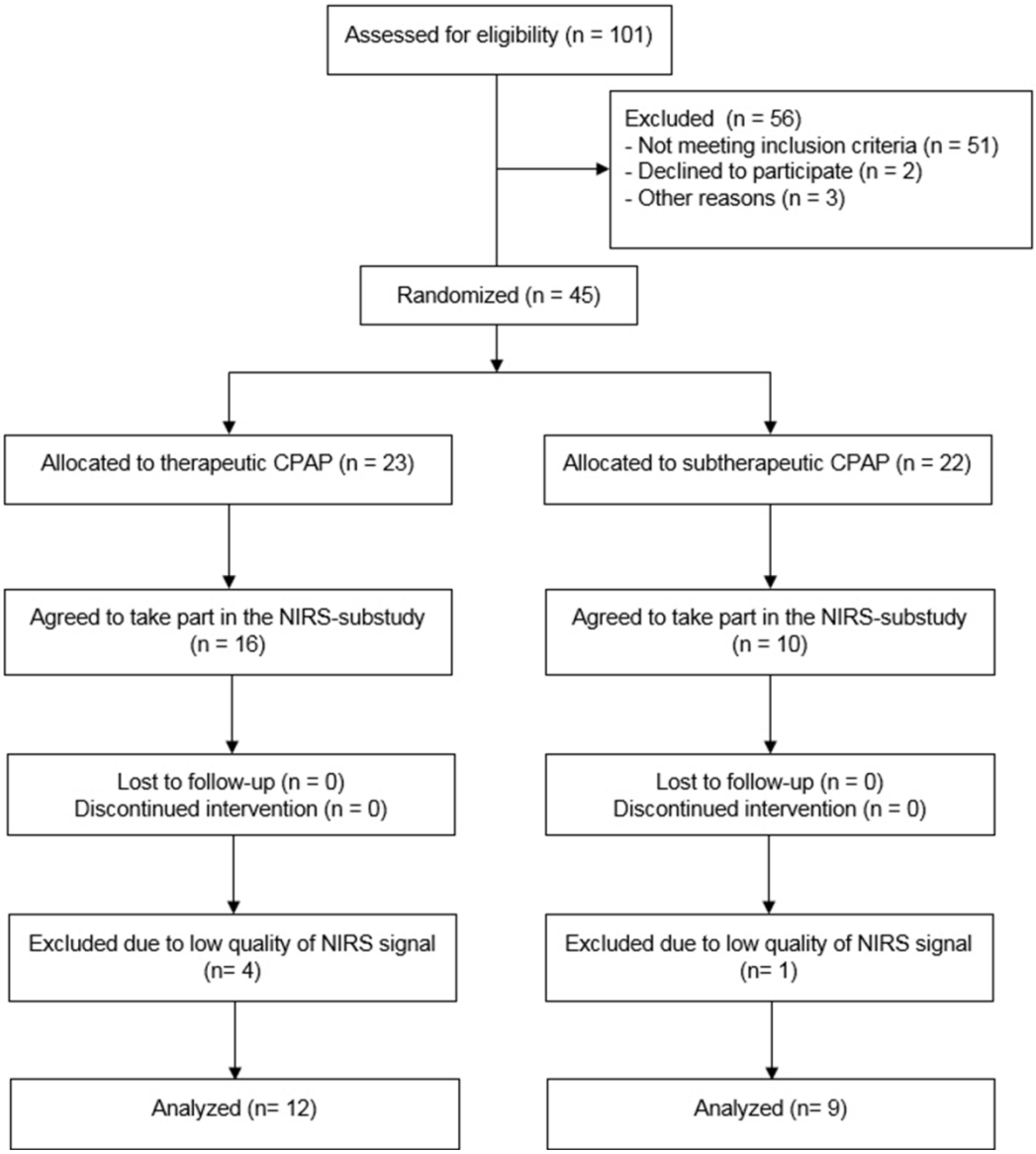


Figure 2. Nocturnal recordings in a patient using subtherapeutic CPAP.

The lefts panels show finger pulse oximetry (SpO_2), cerebral tissue oxygenation (CTO) and total haemoglobin (tHb, in arbitrary units) measured by near infra-red spectroscopy, heart rate (HR) and transcutaneous capnography ($ptcCO_2$) over a period of 1 hour; the right panels show a 5-min zoomed-in portion of the same channels. SpO_2 dips are larger than corresponding CTO dips. The increase in SpO_2 dips over the period from about 00:50 to 01:20 is associated with larger dips in CTO and a rise in transcutaneous $ptcCO_2$ and tHb consistent with an inflow of blood into the brain region exposed to more severe hypoxia and hypercapnia during this period. In the right panels, transient increases in tHb are seen in response to progressively larger SpO_2 and CTO dips with a delay of about 30 sec. Over the same period, ptcCO2 is also increasing but does not change with each event due to the slow response time of the measurement technique. Dashed horizontal lines in the CTO channel represent wakefulness baseline (left side) and local baseline of CTO dips (right side) and the corresponding 13% desaturation level associated with neurocognitive dysfunction in previous studies.

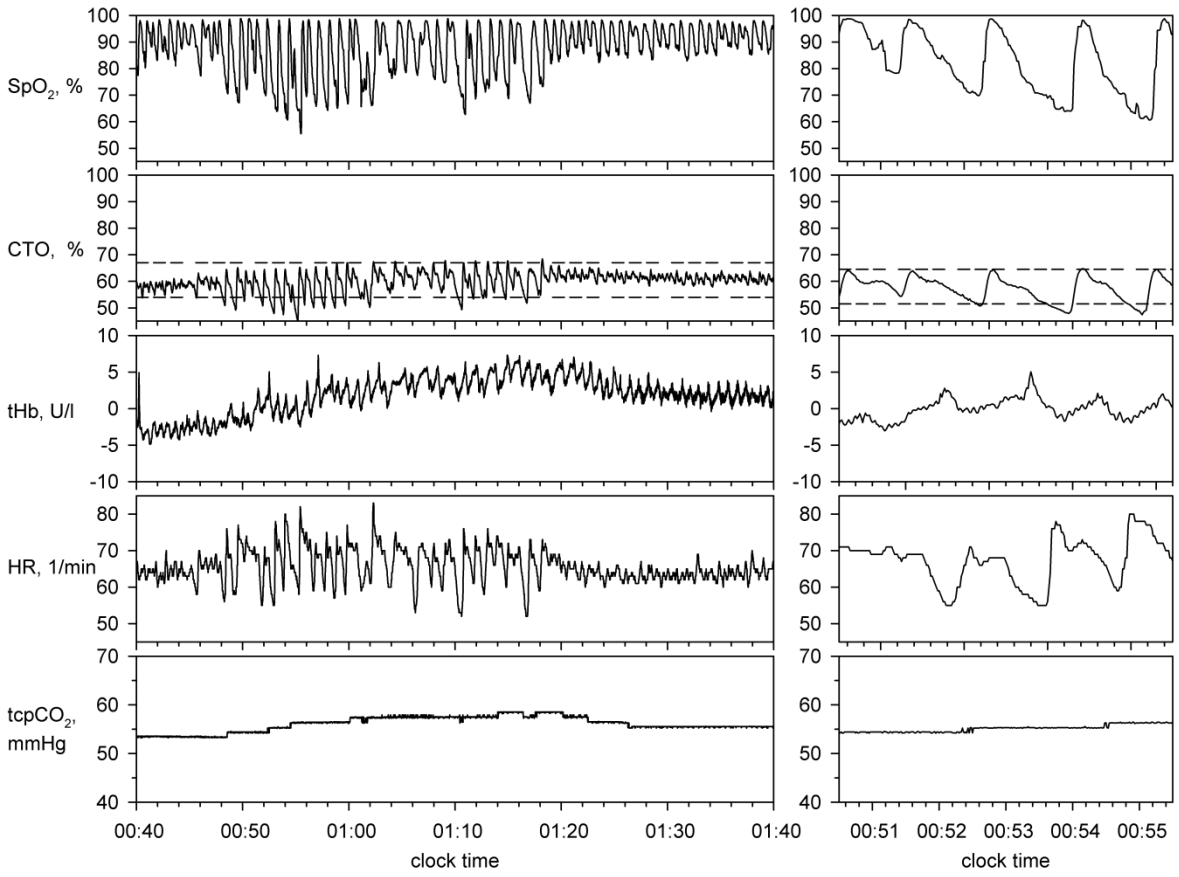

SpO2, %
CTO, %
tHb, U/l
HR, 1/min
tcpCO2, mmHg
clock time
clock time

Figure 3. CPAP withdrawal effect on cerebral oxygenation.

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.

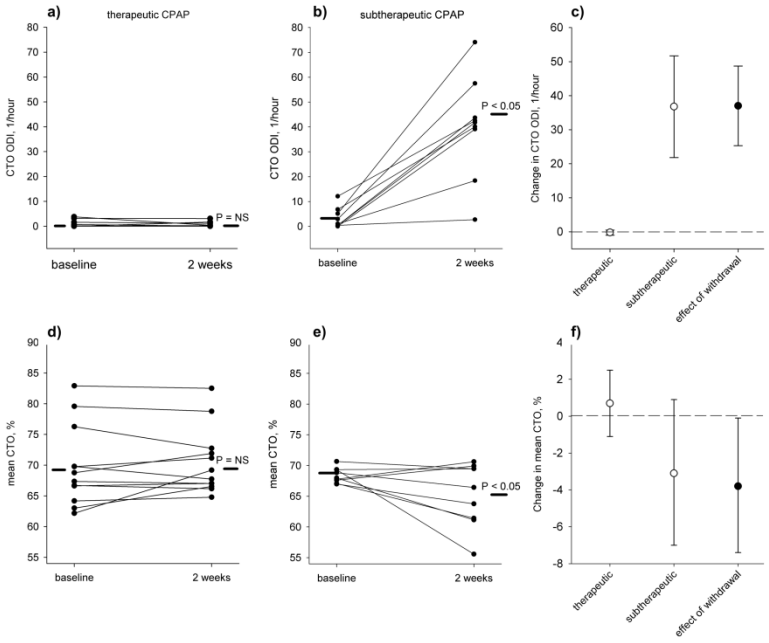
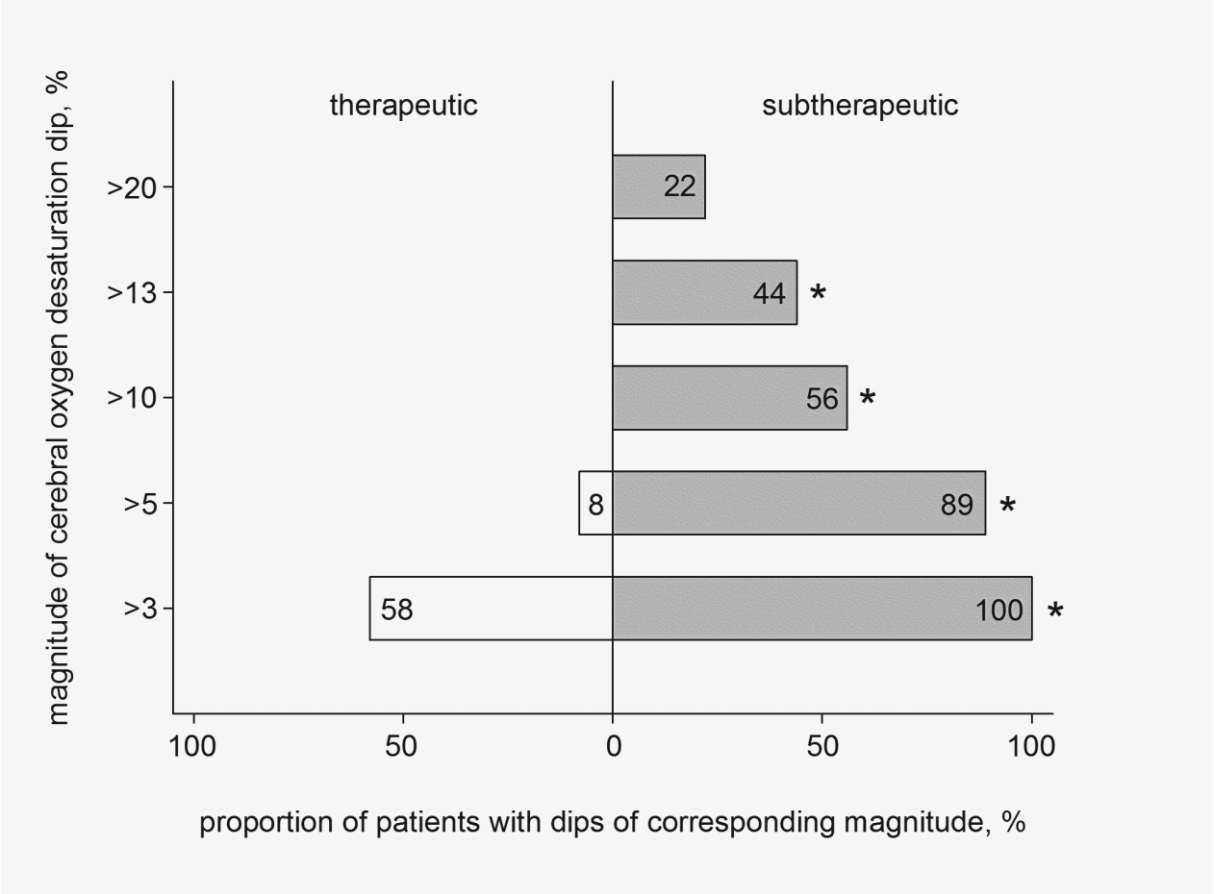


Figure 4. Degree of cerebral hypoxemia.

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.



Online Supplement

eMETHODS

Sleep studies

A polygraphic in-laboratory sleep study (Alice 5 Diagnostics System; Respironics, Pennsylvania, USA) measuring airflow by the CPAP device, respiratory inductance plethysmography, finger pulse oximetry, electrocardiogram, transcutaneous carbon dioxide, sleep position, and audio-visual recordings by an infrared video camera was performed along with cerebral, near-infrared spectroscopy (NIRS) at baseline and at follow-up.
All polygraphic records were scored manually according to the AASM task force criteria[1] by the same investigator. Apnoea was defined as a complete cessation of airflow for at least 10 seconds. Hypopnoea was defined by an at least 30% reduction in airflow (CPAP device flow) or thoraco-abdominal movement of pre-event baseline lasting at least 10 seconds in association with ≥ 4% arterial oxygen desaturation. OSA severity was quantified as the number of apnoeas and hypopnoeas (AHI) and oxygen desaturations ≥4% per hour of study (ODI).

Cerebral near-infrared spectroscopy

Near infrared spectrometry (NIRS, , NIRO 200NX, Hamamatsu Photonics, Hamamatsu City, Shizuoka Prefecture, Honshu, Japan) was used to monitor the concentrations of oxygenated, deoxygenated and total regional haemoglobin in the cerebral tissue by optodes placed bilaterally, high on the forehead as previously described.[2] The concentrations of oxygenated and deoxygenated haemoglobin ([O2Hb] and [HHb]) in the frontal cerebral tissue were continuously monitored at 1 Hz sampling rate. The cerebral tissue oxygen saturation (CTO = [O2Hb]/[O2Hb]+[HHb]) was computed as measure of oxygenation and the cerebral total tissue haemoglobin concentration (tHb = [O2Hb]+[HHb]) as a measure of regional cerebral blood volume. Signals were reviewed on a computer screen and portions showing artefacts with loss or abrupt changes in NIRS signals due to movement artefacts were excluded from analysis. Mean nocturnal CTO and CTO desaturation events defined as

transient dips of CTO ≥3% lasting for at least 10 seconds and associated with a respiratory event-related dip of finger pulse oximetry (SpO2) ≥4% were scored manually.

The threshold for CTO dips was selected lower (≥3%) than that of SpO_2 dips (≥4%) since previous studies have shown that apnoea/hypopnoea-related CTO dips were less pronounced than the corresponding SpO_2 dips, i.e., the mean amplitude ratio of CTO to SpO_2 dip was about 1/3.[2] To avoid erroneous scoring of spontaneous fluctuations in CTO due to physiological or technical measurement variability, we scored CTO dips only if they occurred in association with a corresponding SpO_2 dip. As the threshold for CTO dips was the same for analysis of all recordings on therapeutic and subtherapeutic CPAP, the conclusions related to the directional changes induced by CPAP withdrawal were independent of the selected threshold of CTO dips. To better assess the severity of cerebral hypoxemia related to apnoeas and hypopnoeas during therapeutic and subtherapeutic CPAP therapy, the proportion of patients with various thresholds of CTO dips from ≥3% to ≥20% were tabulated. In addition, the cumulative night-time spent with apnoea/hypopnoea-related CTO dips ≥13% and the cumulative night-time spent with sustained CTO desaturations ≥13% from wakefulness baseline (independent of respiratory events) were computed. This allowed comparison to data from neurosurgical patients in whom unilateral carotid artery clamping for 2-3 min associated with CTO desaturations ≥13% induced neurocognitive dysfunction.[3]

Previous studies have shown that apnoea/hypopnoea-related dips in CTO induce an increase in tHb, the surrogate of regional cerebral volume, presumably reflecting a compensatory inflow of blood into a region of cerebral tissue deoxygenation.[2, 4] Thus, assuming that transient drops in CTO would be associated with subsequent increases in tHb, we hypothesized that this would be reflected in negative peaks of the cross-correlation coefficient between CTO or SpO_2 and tHb with a tHb lag time of a few seconds. According to this concept, high negative values of coefficients of cross-correlation would indicate a strong response in terms of increase in blood volume, whereas low negative values would indicate a minor inflow of blood.

The cross-correlation analyses were performed on time series of CTO and SpO_2 vs. tHb, 400 to 1000 data points in lengths (i.e., 400 to 1000 sec) collected at the beginning, the middle and the end of the night. Changes from baseline to follow-up of the first negative peak cross-correlation coefficient (r_{max}) with positive lag (of tHb vs. CTO) and corresponding lag times were compared between groups (S-Figure 1 and S-Table 2).

eTABLES

e-Table 1: Cross-correlation of CTO and cerebral total haemoglobin during respiratory events.

	therapeutic CPAP (n=12)		subtherapeutic CPAP (n=9)		Effect of CPAP withdrawal		
	baseline	**follow-up**	**baseline**	**follow-up**	**Mean between-group difference of changes BL-FU with 95% CI**		**P**
r_{max}	-0.28 (0.07)	-0.27 (0.08)	-0.22 (0.08)	-0.27 (0.11)*	0.07	0.00, 0.13	0.046
Lag, r_{max} (sec)	28.0 (11.0)	29.7 (11.9)	31.2 (14.0)	25.7 (10.1)	-7.1	-16.1, 1.8	0.12

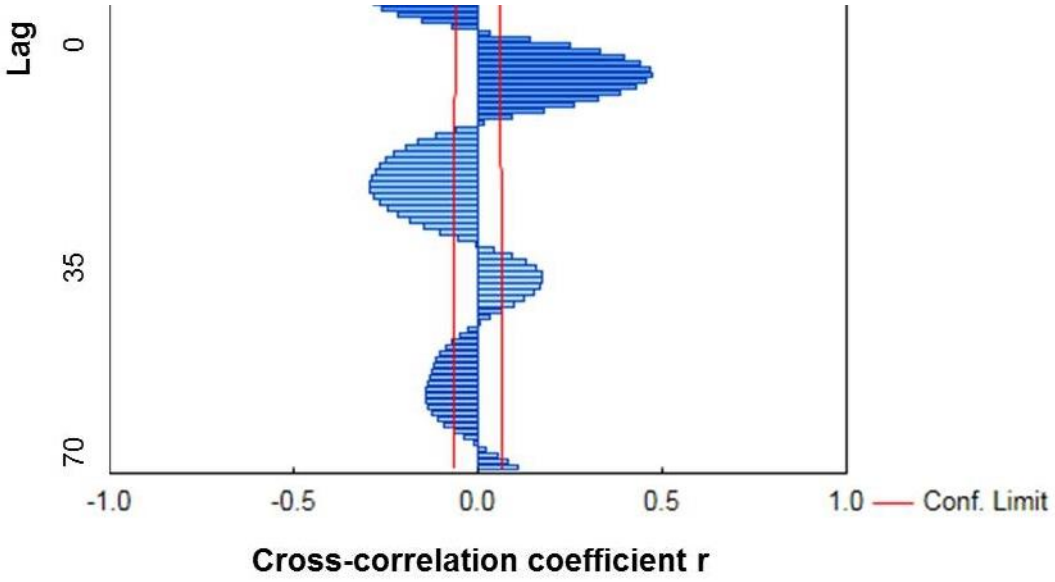
Values are means (SD) of the r_{max} (first negative peak in the cross-correlation coefficient) and of the lag time at which r_{max} occurred. CTO = cerebral tissue oxygenation. CPAP = continuous positive airway pressure. BL-FU = baseline to follow-up. * P=0.03.

e-Table 2: Cross-correlation of SpO_2 and cerebral total haemoglobin during respiratory events.

	therapeutic CPAP (n=12)		subtherapeutic CPAP (n=9)		Effect of CPAP withdrawal		
	baseline	**follow-up**	**baseline**	**follow-up**	**Mean between-group difference of changes BL-FU with 95%CI**		**P**
r_{max}	-0.18 (0.07)	-0.19 (0.09)	-0.16 (0.05)	-0.32 (0.09)*	0.14	0.03, 0.25	0.014
Lag, r_{max} (sec)	48.4 (14.7)	48.6 (17.5)	40.5 (14.8)	40.1 (18.1)	-0.5	-16.3, 15.2	0.94

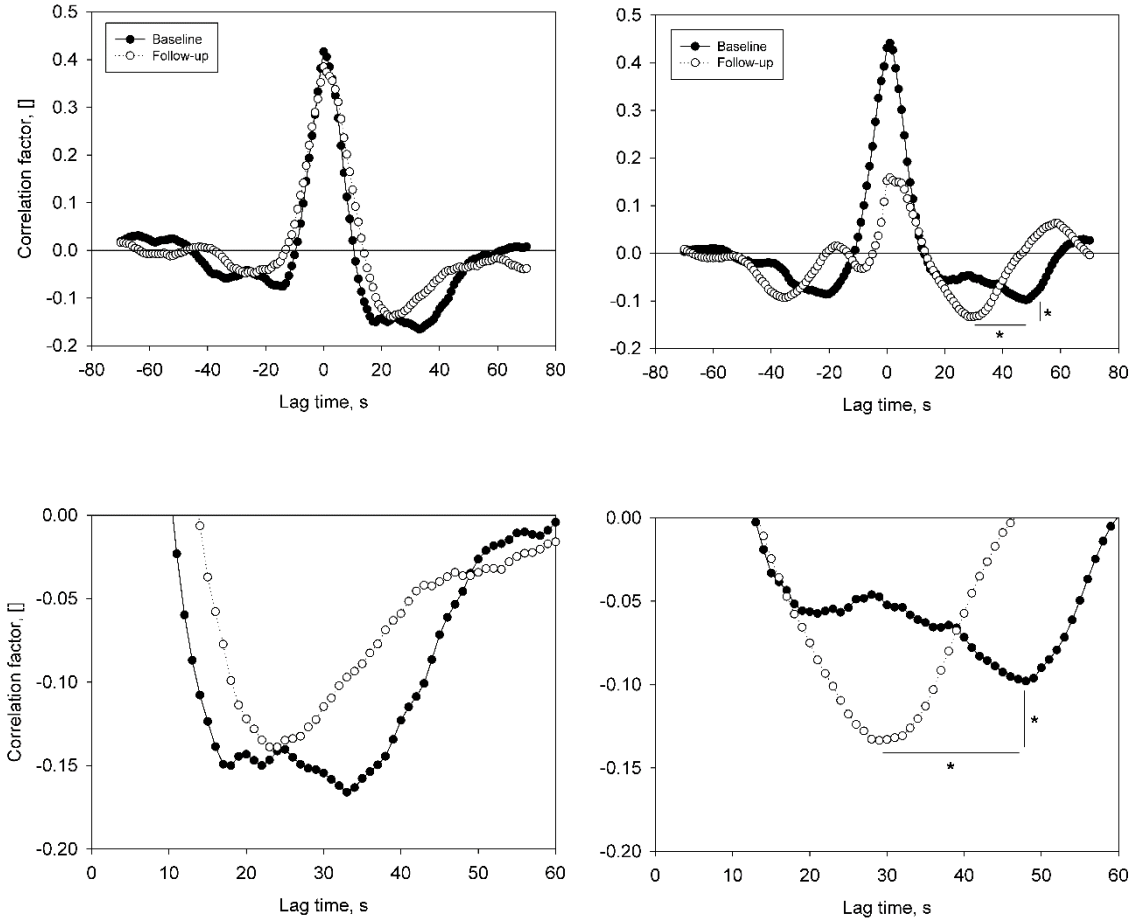
Values are means (SD) of the r_{max} (first negative peak in the cross-correlation coefficient) and of the lag time at which r_{max} occurred. CPAP = continuous positive airway pressure. SpO_2 = pulse oximetry. BL-FU = baseline to follow-up. * P=0.001

e-Figure 1



e-Figure 1. Example of a cross-correlation function of CTO and lagged total haemoglobin (lag 0 to +70) obtained from a sleep study of an individual patient using subtherapeutic CPAP. The first cycle with negative cross-correlations within the positive lag time frame was analysed. The red lines represent the 95% confidence limits of the mean coefficient of cross-correlation (r).

e-Figure 2



e-Figure 2. Cross-correlation of CTO and cerebral total haemoglobin (tHb) derived from NIRS. Group-means of cross-correlation coefficients are displayed as a function of lag time. Analyses were performed for three nocturnal intervals of 400 to 1000 sec duration for patients on therapeutic CPAP (left panels) and subtherapeutic CPAP (right panels) at baseline and at the corresponding follow-up. The upper panels show the lag time range of -70 to +70 sec, the lower panels show the same data zoomed into the range of lag 0 to 60 sec showing the first negative peak. In the right panels (subtherapeutic CPAP), note the significant increase in the negative peak of the cross-correlation coefficient and the decrease in the unlagged (lag = 0 sec) cross-correlation coefficient at follow-up compared to baseline.

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