Nocturnal cerebral hypoxia in obstructive sleep apnoea – a randomised CPAP withdrawal trial

Esther I Schwarz, Michael Furian, Christian Schlatzer, John R Stradling, Malcolm Kohler, Konrad E Bloch.

Online Supplement

METHODS

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).

Table S1: 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.

Table S2: 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

Figure S1

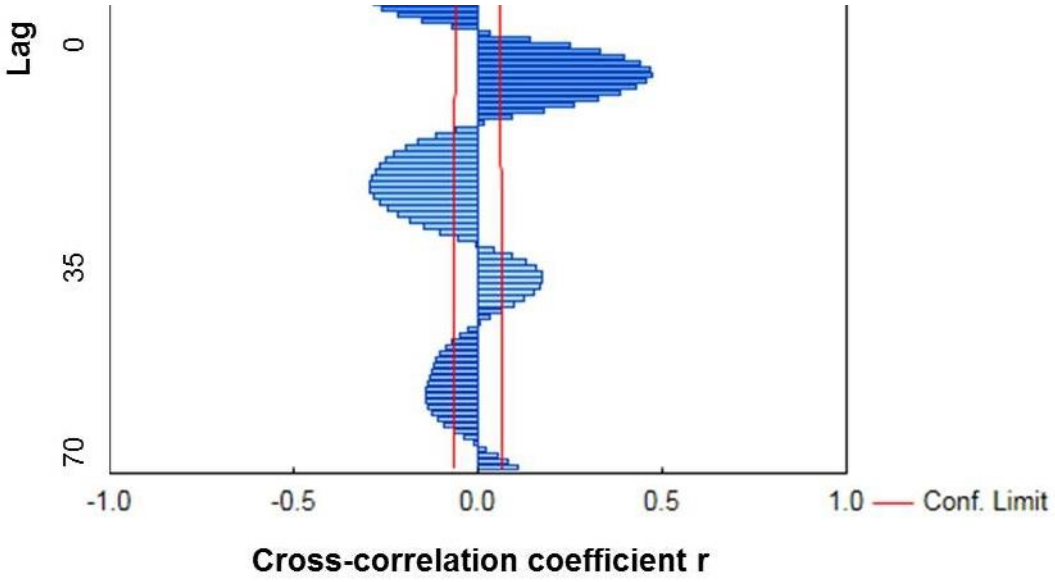

Figure S1. Example of a cross-correlation function of CTO and lagged total haemoglobin (lag 0 to +70) obtained from a sleep study of an individual patient using subtherapeutic CPAP. The first cycle with negative cross-correlations within the positive lag time frame was analysed. The red lines represent the 95% confidence limits of the mean coefficient of cross-correlation (r).

Figure S2

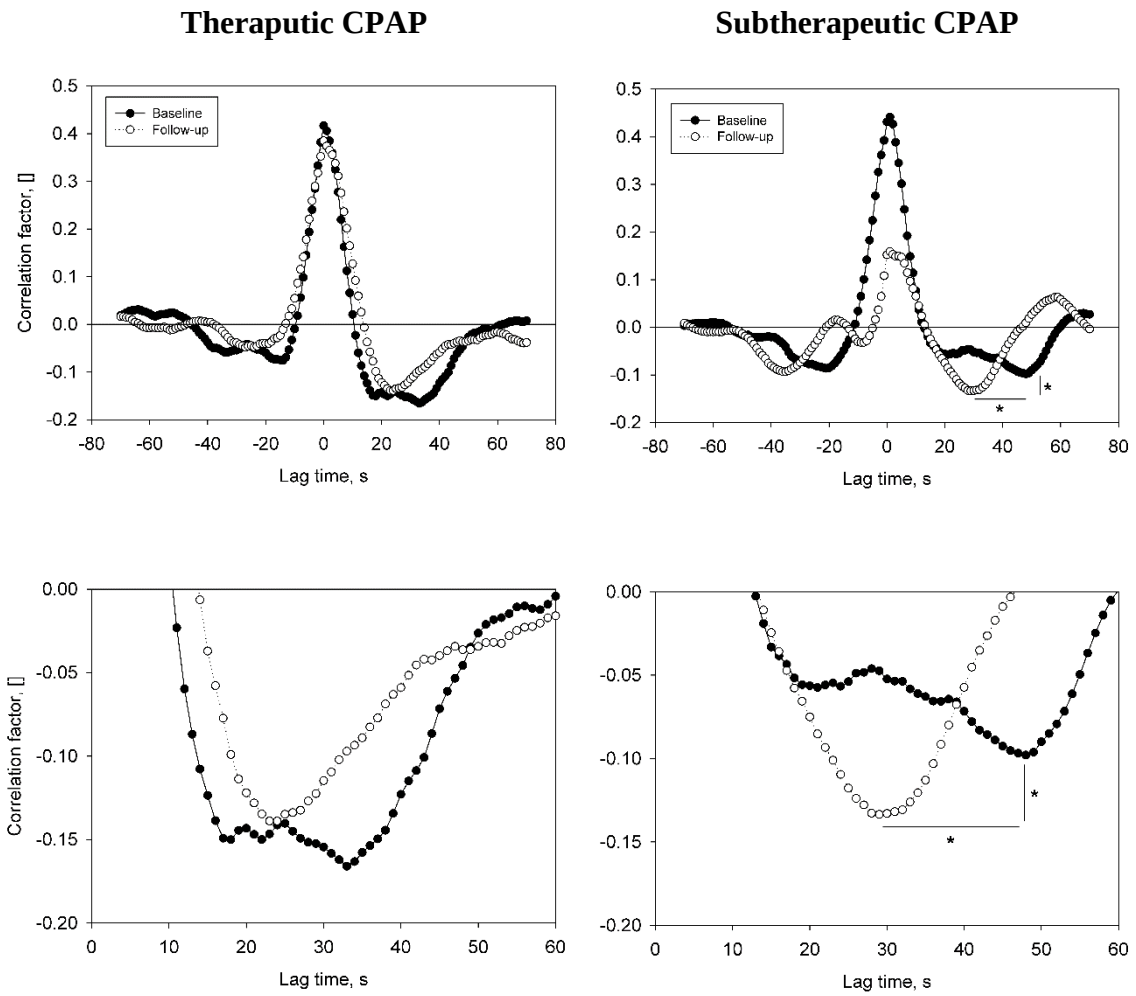

Figure S2. Cross-correlation of CTO and cerebral total haemoglobin (tHb) derived from NIRS. Group-means of cross-correlation coefficients are displayed as a function of lag time. Analyses were performed for three nocturnal intervals of 400 to 1000 sec duration for patients on therapeutic CPAP (left panels) 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.

REFERENCES

1. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J, Jr., Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Loube DL, Owens J, Pancer JP, Wise M. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005: 28(4): 499-521.

2. Ulrich S, Nussbaumer-Ochsner Y, Vasic I, Hasler E, Latshang TD, Kohler M, Muehlemann T, Wolf M, Bloch KE. Cerebral oxygenation in patients with OSA: effects of hypoxia at altitude and impact of acetazolamide. *Chest* 2014: 146(2): 299-308.

3. Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke* 2006: 37(11): 2720-2725.

4. Olopade CO, Mensah E, Gupta R, Huo D, Picchietti DL, Gratton E, Michalos A. Noninvasive determination of brain tissue oxygenation during sleep in obstructive sleep apnea: a near-infrared spectroscopic approach. *Sleep* 2007: 30(12): 1747-1755.