ERJ Express. **Published on September 1, 2011 as doi: 10.1183/09031936.00052611**

Influence of nasal continuous positive airway pressure treatment on digital volume pulse in patients with obstructive sleep apnea

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Short title: Digital volume pulse in patients with obstructive sleep apnea

Keywords: digital volume pulse wave, nasal continuous positive airway pressure, obstructive sleep apnea, vasoconstriction

Word count of abstract: 193 words

Word count of text: 3376 words

Number of figures: 4

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ABSTRACT

Obstructive sleep apnea (OSA) is linked to increased cardiovascular risk. This risk can be reduced by nasal continuous positive airway pressure (nCPAP) treatment. Since OSA is associated with an increase of several vasoconstrictive factors we investigated whether nCPAP influences digital volume pulse wave .

We performed digital photoplethysmography during sleep at night in 94 consecutive patients who underwent polysomnography and 29 patients treated with nCPAP. Digital volume pulse waves were obtained investigator-independent and quantified using an algorithm for continuous automated analysis.

In patients with OSA and an apnea-hypopnea index of more than 10 per hour a significant vasoconstriction during the night was observed ($p<0.0001$ by Friedman test). A significant positive correlation existed between vasoconstriction and apnea-hypopnea index (Spearman correlation, $r=0.27$; $p<0.01$; $n=94$) and arousal index (Spearman correlation, $r=0.21$, $p<0.05$, $n=94$). After 6 month of nCPAP treatment the apnea-hypopnea index was significantly reduced from 27±3 per hour to 4±2 per hour (each $n=29$; $p<0.001$) and vasoconstriction during the night was significantly reduced from 10±3% to 3±1% ($p<0.01$).

We show changes in the reflective index during the night consistent with vasoconstriction in patients with OSA, which are significantly reduced after six month of nCPAP treatment.

Patients with symptomatic obstructive sleep apnea (OSA) are characterized by repeated episodes of upper-airway occlusion during sleep, with consequent excessive daytime sleepiness and impairment of quality of life [1,2]. Patients with untreated OSA have increased cardiovascular morbidity and mortality, whereas treatment with nasal continuous positive airway pressure (nCPAP) reduces cardiovascular risk in these patients [3,4]. The pathophysiology of OSA and its adverse effects on the cardiovascular system remain complex. Apnea and hypopnea cause temporary elevations in blood pressure in association with hypoxia and sympathetic activation. Intermittent hypoxia causes sympathetic nervous system overactivity, activation of the renin-angiotensin system, oxidative stress and endothelial dysfunction [5-7]. The digital volume pulse provides additional information to peripheral pressure pulse. Its contour is determined mainly by characteristics of the systemic circulation, including pressure wave reflection. Increased pulse wave reflection contributes to disturbances of heart-vessel coupling and finally to the development of cardiovascular disease [8,9].

Treatment of OSA is aimed mainly at preventing the collapse of upper airways, reducing the number of episodes of apnea and hypopnea, and reducing the number of oxyhemoglobin desaturation during sleep. Treatment using nCPAP reduces the episodes of apnea and hypopnea. Several, but not all, investigators showed that nCPAP reduces elevated blood pressure [10-12]. Beneficial effects of nCPAP treatment also include reduced activation of sympathetic nervous system [13,14]. However, there are very limited data on arterial vascular behavior during nCPAP treatment. We therefore performed non-invasive monitoring of digital volume pulse wave during the night in OSA with and without nCPAP treatment.

METHODS

Patients

We prospectively investigated digital volume pulse in 94 consecutive patients with suspected obstructive sleep–related breathing disorders admitted to our sleep laboratory through unselected referral from primary or secondary care physicians. Information about sleep history was recorded at baseline and at the time of the final polysomnographic studies. Subjects were studied in a quiet, temperature-controlled room.

The study protocol was approved by the local ethics committee. Written informed consent was obtained from all patients before entry into the study.

Polysomnography

94 consecutive patients underwent overnight polysomnography for screening for obstructive sleep apnea syndrome according to standardized methods [15-17]. According to the patients bedtime behavior polysomnography and digital photoplethysmography were individually started and finished to allow undisturbed sleep. Baseline measurements were performed with patients awake lying in the supine position before the start of the polysomnography.

An 18-channel polysomnographic recording system (Somnolab, Weinmann, Germany) was used to assess sleep state and respiratory and cardiac variables. Continuous recordings included electroencephalography, electrooculography, electrocardiography, submental and leg electromyography. The thoracic/abdominal respiratory movements were detected by according standard belts with piezoelectric sensors by Weinmann's Somnolab equipment (Weinmann, Germany).

Sleep was staged manually using standard methods [15]. Arterial oxyhemoglobin saturation, oral and nasal airflow, tracheal sounds, and rib-cage and abdominal respiratory motion were used to assess episodes of sleep-disordered breathing. Polysomnography records were inspected visually in 30-second periods for episodes of abnormal sleep, breathing, and oxygenation. According to the commonly used clinical criteria, a breathing event during objectively measured sleep was defined as abnormal if either a complete cessation of airflow lasting 10 seconds or more took place (apnea) or a reduction in respiratory airflow of 50% or more of the airflow lasting longer than 10 seconds associated with either an arousal or a desaturation of > 4% could be discerned (hypopnea). For the detection of apneas/hypopneas respiratory flow nasal cannulas were used.

Obstructive apnea was defined as absence of airflow in the presence of paradoxical chest-wall motion. The apnea-hypopnea index was defined as the average number of episodes of apnea and hypopnea per hour of objectively measured sleep and was the summary measurement of the occurrence of sleep-disordered breathing. The oxygen desaturation index (ODI) was calculated by dividing the total number of oxygen desaturations by the total sleep time, with desaturation defined as a ≥10s reduction in oxygen saturation ≥4% of baseline.

In 29 patients with symptomatic OSA nCPAP treatment was started. Patients were advised to retain their usual behaviors, including diet and daily activity. Patients were educated by trained personal to use their CPAP device as recommended.

CPAP treatment was performed using devices from Respironics (Murrysville, PA, USA) and Weinmann (Hamburg, Germany). Commercially available masks were used and the optimum size was determined individually before treatment. All CPAP titrations were performed in hospital during a second attended laboratory polysomnography night by trained personal. The

majority of patients (n=23) received conventional CPAP with a fixed pressure, four patients received CPAP with expiratory pressure relief technology and two patients received auto-PAP. Conventional CPAP titration was performed manually, started at 4 cm H_2O and increased in steps of 1 cm H_2O until removal of apneas, hypopneas, flow limitations, oxygen desaturations, and snoring in all sleep stages and body positions**.** The pressure obtained thereby was considered to be the optimal. Using the expiratory relief technology expiratory PAP applied is kept below the CPAP. For auto-PAP the minimal pressure was kept at 5 cm H_2O, the pressure range was 5-14 cm H_2O. The pressure was set to start automatically after 20 min of adaptation. The devices used monitored snoring, flow and impedance. These parameters are used to detect respiratory events and the pressure is adjusted automatically. The automatic pressure profiles of the devices were considered acceptable if the recording period of the autoPAP device was at least 6 hours, the mean leak was lower than 0.4L/second, and the total sleep time was at least 5 hours. Patients reported proper adherence to CPAP therapy. None of the patients interrupted CPAP therapy during the 6-months interval. Another polysomnographic evaluation was performed 6 months after starting nCPAP treatment.

Digital photoplethysmography

Digital volume pulse waves were continuously quantified by the reflective index obtained by non-invasive digital photoplethysmography and an algorithm for continuous, investigator-independent, automatic analysis. The reflective index was determined according to Scholze et al. with minor modifications [18]. Digital volume pulse waves were measured by the transmission of red and infrared light through the finger pulp of the third digit using a conventional pulse oximeter with a sampling frequency 300Hz which is further processed by the internal software at a frequency of 25Hz. The pulsatile component results in a reduction of transmitted light due to the accompanying increase of optical density and path length of the illuminated tissue. The changes in light intensity are measured by the photodetector and correlate to the digital volume pulse wave. The maximum of each digital volume pulse wave is determined automatically and set to 100. The reflective index was calculated from the mean of the 5th to the 10th data point after the maximum of the digital volume pulse wave. This area covers the diastolic shoulder region to the dicrotic wave which is in part formed by pulse waves reflected back from peripheral vascular sites of impedance mismatch. As indicated in our previous studies short-term changes of the reflective index reflect vasoconstriction or vasodilatation [18,19]. Earlier studies from our group indicated that the reflective index shows a significant positive correlation with invasively determined systemic vascular resistance by

pulmonary artery catheter (Spearman correlation, $r = 0.64$, $p < 0.01$, $n = 20$). In mechanically ventilated ICU patients under anesthesia with midazolam and fentanyl there was a significant correlation between lower pH in the arterial blood gas analysis and vasodilation indicated by a lower reflective index (Spearman correlation, $r = 0.22$, $p < 0.05$, $n = 102$) but not with PaO_2 or $PaCO_2$.

Data of the reflective index obtained from all digital volume pulse waves were averaged every 2.5 minutes. The reflective index values shown in the figures and used for the statistical analyses were obtained at every full hour between midnight and 5 AM in all patients and therefore give the respective reflective indices at time of day.

Statistics

Descriptive statistics for continuous variables are given as mean ± SEM. Differences between groups were analyzed by non-parametric Mann-Whitney-test. Relations between parameters were assessed using non-parametric partial Spearman correlations. Reproducibility data are given as Bland-Altman plots that depict percentage differences between 2 measurements plotted against the mean of 2 measurements. Bias and 95% limit of agreement are given. Changes of the reflective index during the night were analyzed by non-parametric Friedman test with Dunn's Multiple Comparison post-hoc test. Analyses were performed with GraphPad prism software (version 5.0, GraphPad Software, San Diego, CA). All statistical tests were two-sided. A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Digital volume pulse waves and the diastolic shoulder region used for the determination of the reflective index are depicted in **Figure 1A and B**. To demonstrate the reliability of reflective index measurements repeated determinations were performed (**Figure 1C and D**). There was a good agreement between the first and the second determination of the reflective index ($n = 30$; $r = 0.92$; $p < 0.001$). Analyzing the data according to Bland-Altman confirmed a good reproducibility of measurements (bias, -0.1%; 95% limit of agreement, -5.5% to 5.4%). To illustrate how vasoconstriction results in an increased reflective index, digital volume pulse waves were measured using photoplethysmography during systemic vasoconstriction induced by cold-pressure tests in healthy subjects. As shown in **Figure 1E** the reflective index significantly increased during cold-pressure tests from 100 ± 1% to 112 ± 1% arbitrary units ($n = 3$; $p < 0.05$) indicating vasoconstriction. In healthy subjects voluntary apnea significantly

increased the reflective index from 100 ± 4% to 114 ± 5% arbitrary units ($p < 0.05$) consistent with vasoconstriction during apnea. During apnea there was also an increase of muscle sympathetic nerve activity (18) from 9 bursts/Min to 28 bursts/Min.

The clinical, biochemical and polysomnographic characteristics of 94 patients that underwent polysomnography for screening of OSA are shown in **Table 1**. The changes of the reflective index during the night for all 94 patients are summarized in **Figure 2A**. The baseline reflective index (100%) was obtained when patients were awake lying in the supine position at the start of the polysomnography. In patients with an apnea-hypopnea index <10 no significant change of the reflective index was observed during the night ($n = 29$; $p > 0.05$; Figure 2B). After the exclusion of females the results remained unchanged ($n = 20$; $p > 0.05$). In contrast, 65 patients had OSA with an apnea-hypopnea index more than 10 per hour. In these patients the reflective index significantly increased to 109 ± 2% during the night ($n = 65$; $p < 0.0001$; Figure 2B). In the subgroup of males with AHI > 10 the reflective index significantly increased to 109 ± 2% ($n = 50$; $p < 0.0001$). We observed a significant correlation between the apnea-hypopnea index and the change of the reflective index during the night ($r = 0.27$; $p = 0.01$; $n = 94$). After the exclusion of females this correlation remained significant ($r = 0.29$; $p = 0.01$; $n = 70$). The arousal index was also significantly associated with the change of the reflective index during the night ($r = 0.21$, $p = 0.03$, $n = 94$; and $r = 0.27$, $p = 0.02$, $n = 70$ for males only). With increasing apnea-hypopnea index or arousal index an increased reflective index was observed, consistent with an increased vasoconstriction in more severe OSA.
From a cardiovascular point of view oxygen desaturation events >4% during sleep are of special interest. Therefore the oxygen desaturation index (ODI) >4% was also analyzed. There was a significant correlation between the ODI and the change of the reflective index during the night ($r = 0.22$; $p = 0.02$; $n = 119$). The same correlation was found in the subgroup of male patients ($r = 0.25$; $p = 0.02$; $n = 87$).

To get information about the influence of sleep stage on the reflective index we analyzed the reflective index in relation to sleep stage at 1.00 am. Sleep stages were determined visually according to Rechtschaffen und Kales [20]. Delta sleep comprises sleep stages 3 and 4. We found a significantly higher reflective index consistent with higher vasoconstriction in sleep stage 1 compared to REM sleep ($n = 94$; $p < 0.05$; Figure 3).

Of the 94 patients that underwent polysomnography 13 patients had an AHI < 5, 19 patients were found to have an AHI > 5 but were asymptomatic for OSA and 62 patients were symptomatic and in need of treatment. Asymptomatic patients reported no significant daytime sleepiness (ESS<10), insomnia, subjective sleep disturbances, snoring or other OSA associated symptoms.

Of the 62 patients for whom nCPAP treatment was recommended after the polysomnography screening only 29 patients were available to follow up due to administratively restrictions. Those patients and asymptomatic patients were compared and characterized in table 2.

In 29 patients with symptomatic OSA, nCPAP treatment was started, and polysomnography was repeated after 6 months. CPAP-adherence was measured as CPAP-hours per night recorded as machine run time from the time counter internal to the CPAP device. Mean CPAP adherence was 5.6 ± 0.4 hours per night. The clinical, biochemical and polysomnographic characteristics of CPAP treated patients are shown in **Table 3.** After nCPAP treatment, the apnea-hypopnea index was significantly reduced from 24 ± 4 per hour to 4 ± 2 per hour ($p < 0.001$). In the subgroup of male patients the apnea-hypopnea index was significantly reduced from 26 ± 4 per hour to 5 ± 3 per hour ($n = 20$, $p < 0.001$) after nCPAP treatment. The ODI >4% was reduced by nCPAP from 26 ± 3 in all treated patients and 27 ± 4 in male patients to 0 ± 0 respectively ($p < 0.0001$).

Before nCPAP treatment in 29 patients with symptomatic OSA the reflective index significantly increased during the night to 110 ± 3% at 05.00 in the morning indicating vasoconstriction ($n = 29$; $p < 0.001$; **Figure 4A**). In the subgroup of male patients with symptomatic OSA the reflective index significantly increased to 109 ± 2% ($n = 20$; $p < 0.01$).

After 6 month of nCPAP treatment the significant increase of the reflective index during the night could not be observed any longer ($n = 29$; $p > 0.05$; **Figure 4B**). The same result was obtained in the subgroup of male patients ($n = 20$; $p > 0.05$). These data are in line with the notion that the successful therapy of OSA by nCPAP was accompanied by a reduction of the reflective index consistent with reduced vasoconstriction during the night.

DISCUSSION

The present study shows that patients with symptomatic OSA exhibited a significantly increased reflective index consistent with vasoconstriction during sleep at night. The severity of OSA as quantified by the apnea-hypopnea index was directly associated with the increase in vasoconstriction. The successful treatment of OSA using nCPAP significantly reduced

vasoconstriction, providing one possible explanation for beneficial effects of nCPAP therapy on cardiovascular morbidity in patients with OSA.

In previous investigations it was shown that an oxygen desaturation index (ODI) ≥4% was associated with prevalent cardiovascular disease in a large community sample of middle-aged and older subjects [21]. In our study population with a high prevalence of sleep-disordered breathing we found a significant correlation between the ODI >4% and the change of the reflective index during the night. Higher oxygen desaturation indices were associated with a more pronounced increase of the reflective index consistent with more pronounced vasoconstriction during the night. These findings suggest that changes of the reflective index during the night may add information for the assessment of cardiovascular risk in these patients.

Several mechanisms have been described in patients with OSA that can result in increased vasoconstriction finally leading to progression of cardiovascular disease. First, increased sympathetic activation induced by nocturnal hypoxia has been reported in normal volunteers and in patients with OSA [22,23]. In these studies sympathetic activity was derived from measurements of muscle sympathetic nerve activity. Previous experimental studies from our group already indicated that an elevated sympathetic nerve activity measured by microneurography from the peroneal nerve results in an increased reflective index [18]. In the present study we confirmed that apnea increased the reflective index in a similar way as vasoconstriction induced by the cold pressure test. Therefore our present results of increased vasoconstriction are in line with previous findings of increased sympathetic activity in patients with OSA. Second, patients with OSA show endothelial dysfunction which predisposes to reduced vasodilatation and increased vasoconstriction. Studies showed that patients with OSA had lower endothelium-dependent flow-mediated dilation compared with control subjects [24,25]. Third, patients with OSA had significantly higher plasma levels of potent vasoconstrictors, including endothelin-1 and angiotensin II compared with healthy controls. Furthermore, the endothelin-1 level was significantly correlated with the apnea-hypopnea index [26,27]. Forth, patients with OSA had significantly higher markers of oxidative stress and inflammation, finally leading to hypertension [28]. Increased reactive oxygen species had also been reported in patients with OSA [29]. Increased serum concentrations of high sensitivity C-reactive protein, interleukin 6, tumor necrosis factor-alpha, and malondialdehyde could be reduced during successful nCPAP treatment [30].

We found a significant influence of sleep stage on the reflective index with lower reflective index values consistent with less vasoconstriction in deep (delta) sleep and significantly lower

reflective index in REM sleep compared to sleep stage 1. This might be explained by an increase of vagal tone in deep sleep compared to stage 1 sleep and in components of REM sleep [31,32]. A significant decrease of blood catecholamine concentration (epinephrine and norepinephrine) during REM sleep despite the well-known increase of muscle sympathetic activity during this stage was convincingly demonstrated and discussed by Dodt et al. [33]. According to recent guidelines nCPAP devices are recommended to treat patients with symptomatic OSA to reduce their cardiovascular risk [2,34]. The mean CPAP adherence in our study is in the same range or above the values reached in comparable investigations [35-37). According to recent literature mean nCPAP duration of 5 to 6 hours predictes normalization of the Functional Outcomes of Sleep Questionaire in 68% of patients [35]. CPAP use of 5.6 hours per night constitutes the threshold for positive effects on blood pressure in nonsleepy hypertensive patients reported by Barbé et al. [36] and was shown to reduce blood pressure and nocturnal sympathetic activity [37].

The present study shows that successful treatment of OSA using nCPAP significantly reduces vasoconstriction during the night. Treatment with nCPAP significantly reduced sympathetic nerve activity and norepinephrine plasma levels in patients with OSA [38,39]. The reduction of sympathetic nerve activity could contribute to the reduced vasoconstriction observed in the present study. Furthermore, previous studies showed that effective treatment using nCPAP significantly reduced leptin in patients with OSA [40]. Since leptin is able to stimulate sympathetic mechanisms that produce vasoconstriction, the reduced leptin concentrations during nCPAP treatment may ameliorate vasoconstriction [41]. Decreased sympathetic nerve activity and decreased concentrations of vasoconstrictive mediators are probably the underlying mechanisms which finally result in the reduced vasoconstriction we observed 6 month after starting the nCPAP therapy but our study did not investigate the underlying mechanisms or mediators. The reduction of nocturnal vasoconstriction causes shifting of the pulse wave reflecting sites to more peripheral areas. As outlined by Safar et al., shifting of the pulse wave reflecting sites to more peripheral areas improves heart-vessel coupling and finally results in a reduced cardiovascular risk [9]. We used an analytical method that allows non-invasive, investigator-independent, automatic analysis enabling monitoring of digital volume pulse during the night. Further studies should be performed to investigate if the observed vascular effects under nCPAP treatment can be used to predict cardiovascular risk reduction in individual nCPAP treated patients. Mean delta-sleep (sleep stage 3+4) in our cohort was over 20% in asymptomatic OSA whereas it was lower in patients with symptomatic OSA. Delta-sleep significantly increased with nCPAP treatment. These results

are in agreement with improved delta-sleep with CPAP therapy [42,43]. However, we cannot exclude an overestimation in our reports of delta-sleep. Inter-scorer reliability has been shown to range from 65 to 78% applying the criteria of Rechtschaffen and Kales [44]. All our sleep stage data were evaluated by one scorer.

Conclusion

In summary, using digital photoplethysmography we show a change in the reflective index consistent with increased vasoconstriction during the night in patients with OSA and an AHI>10. We show that a successful therapy of symptomatic OSA by nCPAP for six month is accompanied by a change in the reflective index consistent with reduced vasoconstriction during the night.

SUPPORT STATEMENT

None.

STATEMENT OF INTEREST

Dr. Sanner has served as a medical advisor and has received travel grants and honoraria for lectures from Weinmann, Germany.

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Table 1. Clinical and biochemical characteristics of 94 patients that underwent polysomnography. Patients were grouped according to their respective apnoe-hypopnoe index (AHI). CVD denotes presence of or a history of coronary artery disease, stroke or peripheral arterial vascular disease. ACE/AT denotes angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists. Continuous data are shown as mean ± SEM.

Characteristic	AHI<10 (n=29)	AHI>10 (n=65)	p value
Age (years)	57 ± 2	60 ± 2	0.26
Male (%)	20 (69%)	50 (77%)	0.45
Body mass index (kg/m²)	27.8 ± 1,0	29.1 (0,6)	0.31
Comorbidities			
Diabetes (%)	4 (14%)	9 (14%)	1.00
Hypertension (%)	14 (48%)	34 (52%)	0.82
CVD (%)	10 (35%)	18 (28%)	0.63
Smoking (%)	12 (41%)	18 (28%)	0.23
Systolic blood pressure (mmHg)	132 ± 5	136 ± 3	0.27
Diastolic blood pressure (mmHg)	84 ± 3	84 ± 2	0.67
Pulse pressure (mmHg)	48 ± 4	53 ± 2	0.21
Leukocytes (/nL)	7.9 ± 0.4	7.6 ± 0.3	0.63
Hemoglobin (g/dL)	14.8 ± 0.3	14.5 ± 0.2	0.51
Platelets (/nL)	263 ± 10	259 ± 9	0.53
Serum creatinine (mg/dL)	1.0 ± 0.0	1.0 ± 0.0	0.45
Serum sodium (mmol/L)	140 ± 1	140 ± 0	0.83
Serum potassium (mmol/L)	4,2 ± 0,1	4,1 ± 0,1	0.43
Serum calcium (mmol/L)	2.40 ± 0.03	2.35 ± 0.01	0.07
Glucose (mmol/l)	6.9 ± 0.6	7.6 ± 0.4	0.15
Total cholesterol (mg/dL)	212 ± 9	215 ± 6	0.94
Triglycerides (mg/dL)	152 ± 20	211 ± 20	0.09
C-reactive protein (mg/dL)	0.6 ± 0.3	0.4 ± 0.1	0.19
Medication			
ACE/AT (%)	11 (38%)	24 (37%)	1.00
Beta blockers (%)	8 (28%)	19 (29%)	1.00
Calcium channel inhibitors (%)	3 (10%)	10 (15%)	0.75
Diuretics (%)	8 (28%)	16 (25%)	0.80
Antiplatelet drugs (%)	7 (24%)	20 (31%)	0.62

Table 2. Characteristics of 19 asymptomatic and 29 symptomatic patients with obstructive sleep apnea (OSA). Continuous data are shown as mean ± SEM. SaO2 denotes arterial oxyhemoglobin saturation, REM denotes rapid eye movement. ESS denotes the value reached on the Epworth Sleepiness Scale to record daytime sleepiness. The apnea-hypopnea index (AHI) is the mean number of episodes of apnea and hypopnea per hour of sleep. The arousal index is the mean number of arousal reactions per hour of sleep. The reflective index at 5.00 a.m. is given as percentage of the reflective index of the patient awake in the lying position before the start of the polysomnography. ODI indicates the oxygen desaturation index.

Characteristic	Asymptomatic OSA (n=19)	Symptomatic OSA (n=29)	p value
Apnea-hypopnea index	14 ± 2	27 ± 3	<0.01
Arousal index	11± 1	14 ± 2	0.22
Sleep efficiency (%)	76 ± 3	76 ± 2	0.96
Stage wake (Min)	102 ± 16	103 ± 9	0.59
Total sleep time (Min)	301± 14	316 ± 8	0.43
Sleep stage 1 (% of total sleep time)	9.7 ± 2.4	10.9 ± 2.9	0.89
Sleep stage 2 (% of total sleep time)	53.5 ± 3.1	57.6 ± 3.2	0.25
Delta sleep (stage 3+4, % of total sleep time)	24.0 ± 2.7	19.9 ± 2.1	0.27
Sleep stage REM (% of total sleep time)	12.8 ± 1.5	11.6 ± 1.4	0.57
Minimum nocturnal SaO2 (%)	83 ± 1	77 ± 2	<0.05
Mean nocturnal SaO2 (%)	94 ± 0	93 ± 0	<0.05
SaO2<90% (%)	5 ± 2	19 ± 4	<0.05
ESS	5 ± 1	10 ± 2	0.08
ODI	12 ± 3	26 ± 3	<0.01
Change of Reflective index during the night (% of awake)	5 ± 2	10 ± 3	0.17

Table 3. Characteristics of 29 patients with obstructive sleep apnea (OSA) before and after nasal continuous positive airway pressure (nCPAP) treatment. Continuous data are shown as mean ± SEM. SaO2 denotes arterial oxyhemoglobin saturation, REM denotes rapid eye movement. The apnea-hypopnea index (AHI) is the mean number of episodes of apnea and hypopnea per hour of sleep. The arousal index is the mean number of arousal reactions per hour of sleep. ODI indicates the oxygen desaturation index.

Characteristic	Before nCPAP (n=29)	After nCPAP (n=29)	p value
Apnea-hypopnea index	27 ± 3	4 ± 2	<0.0001
Arousal index	14 ± 2	10 ± 1	<0.05
Sleep efficiency (%)	76 ± 2	81 ± 4	<0.05
Stage wake (Min)	103 ± 9	66 ± 9	<0.01
Total sleep time (Min)	316 ± 8	349 ± 17	<0.01
Sleep stage 1 (% of total sleep time)	10.9 ± 2.9	5.6 ± 1,7	0.16
Sleep stage 2 (% of total sleep time)	57.6 ± 3.2	52.6 ± 3.1	0.35
Delta sleep (stage 3+4, % of total sleep time)	19.9 ± 2.1	27.6 ± 2.8	<0.05
Sleep stage REM (% of total sleep time)	11.6 ± 1.4	14.2 ± 1.4	0.17
Minimum nocturnal SaO2 (%)	77 ± 2	86 ± 1	<0.0001
Mean nocturnal SaO2 (%)	93 ± 0	94 ± 0	<0.0001
SaO2<90% (%)	19 ± 4	4 ± 1	<0.0001
ODI	26 ± 3	0 ± 0	<0.0001
Change of Reflective index during the night (% of awake)	10 ± 3	6 ± 4	<0.05

FIGURE LEGENDS

Figure 1. Determination of the reflective index by fingertip photoplethysmography

A, Typical digital volume pulse waves obtained by photoplethysmography during 20 seconds are shown. Pulse waves were measured by the transmission of red and infrared light through the finger pulp.

B, One typical pulse wave is depicted. The maximum of the digital pulse wave was determined. The reflective index was calculated from the mean of the 5th to the 10th data point after the maximum of the digital pulse wave (shaded area) covering the typical "shoulder region" of the diastolic pulse wave decay.

C, Regression curve for first and second measurements of the reflective index. Spearman correlation, $n = 30$; $r = 0.92$; $p < 0.001$.

D, Bland-Altman plot. In the Bland-Altman plots, which quantify the average discrepancy between two measurements, the bias and 95% limit of agreement are indicated by lines.

E, Bar graph showing summary data of the reflective index under resting conditions and during cold pressure test in healthy subjects. Data are mean ± SEM, $n = 3$ $*p < 0.05$ compared to resting conditions.

F, Bar graph showing summary data of the reflective index under resting conditions and during apnoe in healthy subjects. $*p < 0.05$ compared to resting conditions.

Figure 2. Reflective index in patients that underwent polysomnography.

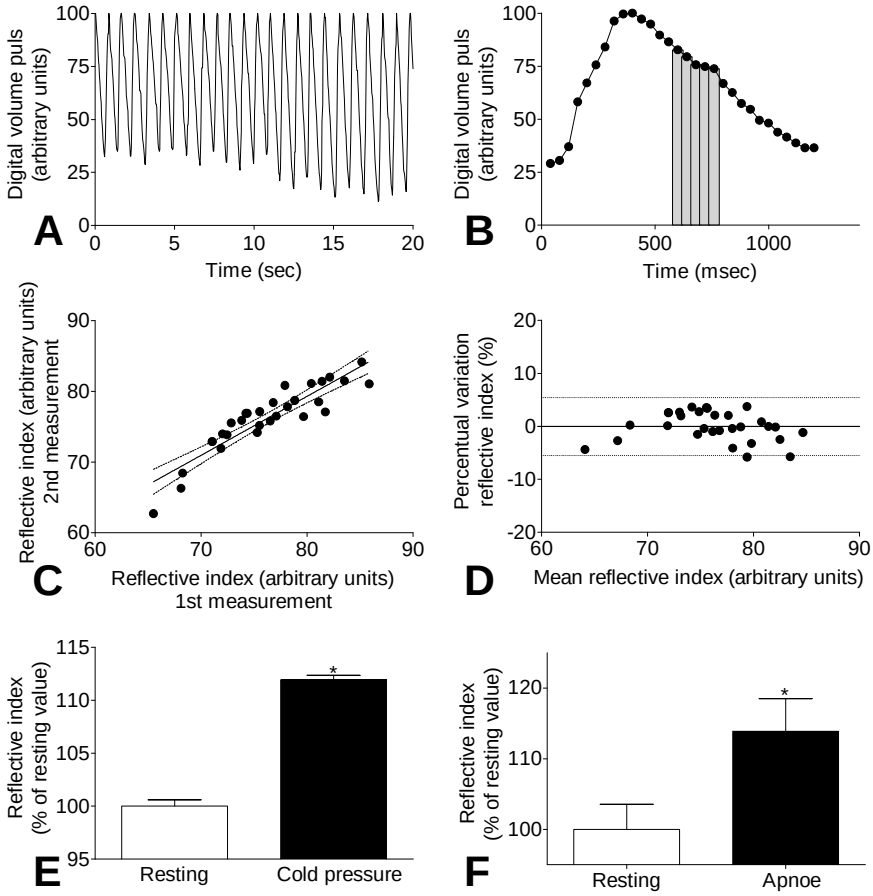
A, Bar graph showing the reflective index in all 94 patients that underwent polysomnography for screening of obstructive sleep apnea. $***p < 0.001$ by Friedman test with Dunn's Multiple Comparison post-hoc test compared with patients awake in the lying position before the start of the polysomnography.

B, Comparison of the reflective index in 29 patients with an apnea-hypopnea index (AHI) less than 10 per hour and 65 patients with an apnea-hypopnea index (AHI) more than 10 per hour during the night. $***p < 0.0001$ by Friedman test with Dunn's Multiple Comparison post-hoc test compared with patients awake in the lying position before the start of the polysomnography.

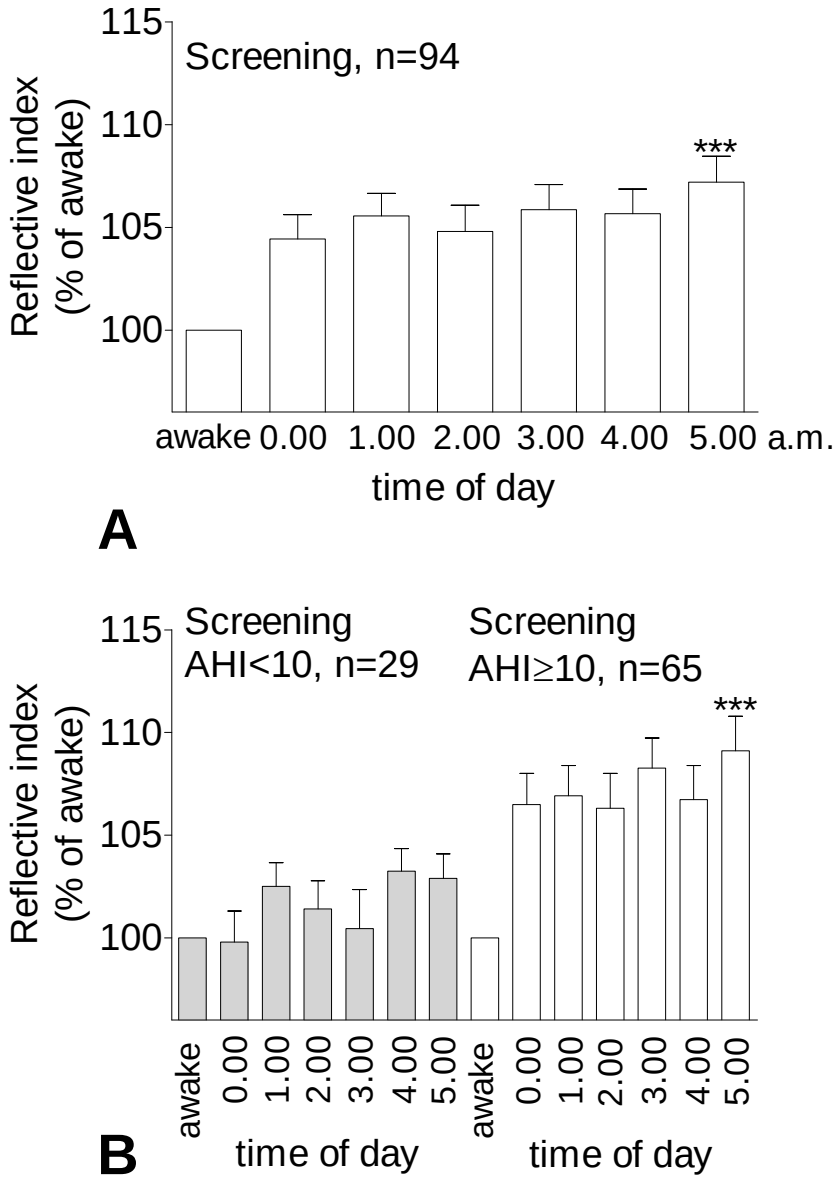
Figure 3. Reflective index values in relation to patients sleep stage at 1.00 am. Bar graph showing summary data for reflective indices at sleep stages W (awake), 1, 2, 3+4 (delta sleep) and REM in 94 patients that underwent polysomnography screening. Data are given as % of the reflective index of patients awake in the lying position before the start of the

polysomnography. *p<0.05 by Kruskal-Wallis test with Dunn's Multiple Comparison post-hoc test. Sleep stage 1 showed a significantly higher reflective index compared to REM sleep consistent with a higher vasoconstriction in sleep stage 1.

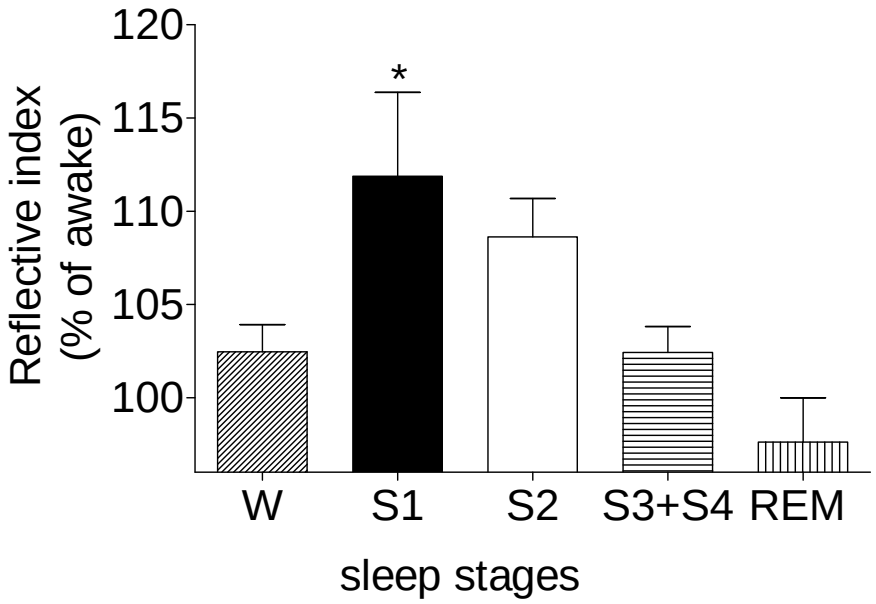
Figure 4. Reflective index in 29 patients with obstructive sleep apnea (OSA) before and 6 months after treatment with nasal continuous positive airway pressure (nCPAP).
A, Bar graph showing the reflective index during the night before nCPAP treatment. ***p < 0.001 by Friedman test with Dunn's Multiple Comparison post-hoc test compared with patients awake in the lying position before the start of the polysomnography.
B, Bar graph showing the reflective index during the night during nCPAP treatment.



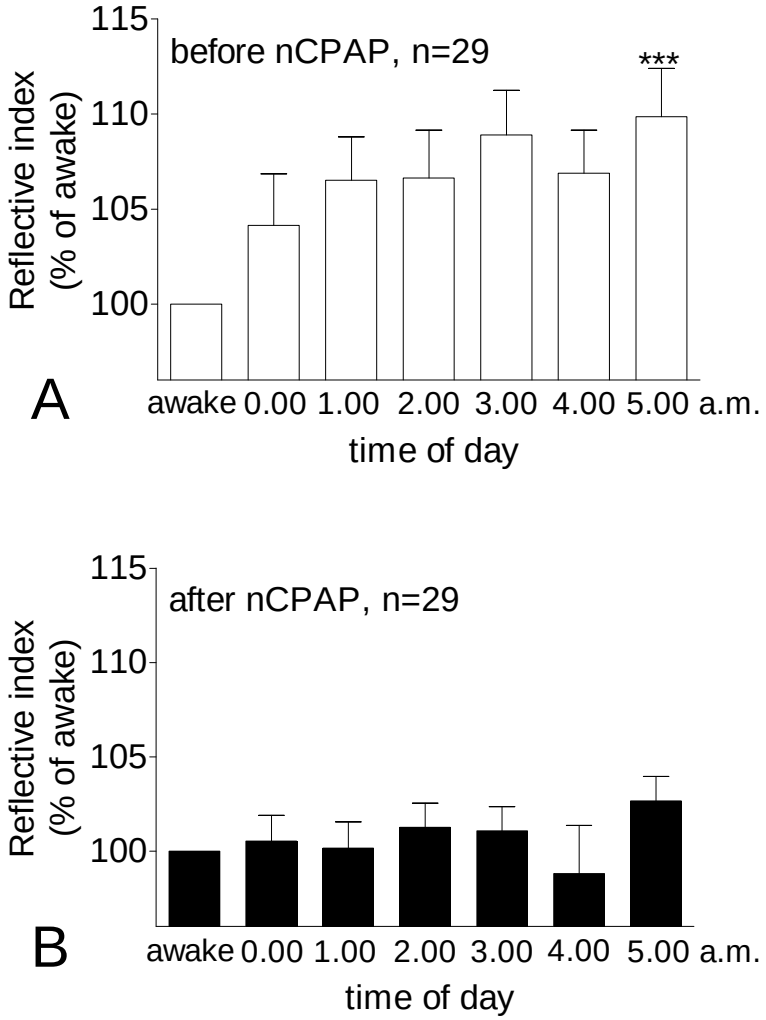
Scholze et al., Figure 1



Scholze et al., Figure 2



Scholze et al., Figure 3



Scholze et al., Figure 4