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Continuous positive airway pressure therapy decreases evening cortisol concentrations in patients with severe obstructive sleep apnea

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Abstract

Patients with obstructive sleep apnea syndrome (OSAS) show recurrent episodes of nightly hypoxic stress. The purpose of this study is the detection of alterations of the hypothalamic-pituitary-adrenal stress axis in OSAS patients before and after continuous positive airway pressure (CPAP) therapy. An activation of the hypothalamic-pituitary-adrenal axis was proposed because of the nightly hypoxic stress in these patients, but previous studies were not conclusive. Here we hypothesize that CPAP therapy decreases salivary cortisol concentrations in patients with severe OSAS. We performed a clinical within-subject study including 50 patients with newly diagnosed OSAS and an apnea-hypopnea index greater than or equal to 40 h^{-1}. Diurnal profiles of salivary cortisol concentrations were compiled before and after 3 months of treatment with CPAP. Therefore, 6 cortisol samples were collected: before and after lunch, in the evening, the next morning after awakening, and before and after breakfast. Thirty-eight patients returned after 3 months of CPAP therapy for follow-up. According to the reference range for healthy subjects, cortisol values were not pathologically increased. Analysis of variance revealed a significant effect of CPAP therapy on diurnal cortisol profiles ($P = .048$). Subjects with severe OSAS showed a decrease (3.04 ± 0.55 nmol L^{-1} pre-CPAP vs 2.48 ± 0.78 nmol L^{-1} post-CPAP, $P = .038$) of evening cortisol levels after CPAP treatment, whereas prelunch levels were increased after CPAP therapy (7.18 ± 0.83 nmol L^{-1} pre-CPAP vs 10.22 ± 1.10 nmol L^{-1} post-CPAP, $P = .044$). Our results show that CPAP therapy decreases evening cortisol concentrations in patients with severe OSAS. These data suggest that OSAS may increase the cortisol nadir that is reversed after CPAP therapy.
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1. Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive loss of muscle tone in the upper airways and consecutive oxidative stress with decreased blood oxygen saturation [1] and fragmentation of sleep [2]. The criterion standard in OSAS therapy is continuous positive airway pressure (CPAP) [3], by which the apnea-hypopnea index (AHI) as the most common marker for severity of OSAS can be normalized.

Stress generally activates the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system (SNS); it is a known fact that hypoxic stress leads to an activation of both the SNS and the HPA axis [4]. In OSAS, an activation of the SNS with elevated catecholamine concentrations was found, which was tightly correlated to the severity of nightly hypoxias and normalized by eliminating hypoxias with CPAP therapy [5]. Accordingly, an activation of the HPA axis is assumable; but as yet, this effect has not been demonstrated in OSAS. Moreover, a fragmentation of sleep with microarousals as present in OSAS is associated with an activation of the HPA axis [2]. Previous studies did not find any OSAS-

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related changes in cortisol concentrations as compared with healthy subjects. Furthermore, CPAP therapy did not seem to affect HPA axis activity [6-8]. In contrast, Bratel et al [9] found a significant increase of fasting serum cortisol concentrations in patients with OSAS as compared with healthy controls. However, the metabolic syndrome [10], which is a frequent comorbidity in OSAS [11], induces independently an activation of the HPA axis with increased concentrations of cortisol [12-14], which was not sufficiently considered in the study of Bratel et al. Moreover, cortisol measurement at single time points without considering diurnal rhythm may be a methodological constriction curtailing the information gained from most investigations of the HPA axis [15].

In the present study, we hypothesized that patients with severe OSAS show an activated HPA axis reflected by increased daytime cortisol concentrations that are reversed after CPAP treatment. We examined 38 patients with severe OSAS and AHI greater than or equal to 40 h^{-1}, comparing diurnal salivary cortisol profiles in a within-subject design before and after 3 months of effective therapy with CPAP. Because of sources of error by matching for age, sex, body mass index (BMI), and possible comorbidities within a clinical trial, we passed on the implementation of a control group. In addition, we monitored fasting plasma lactate concentrations as a known parameter for anaerobic metabolism. Because lactate level is a marker of stress, we hypothesized that plasma lactate may be a marker for severity of the disease in OSAS patients [16,17].

2. Patients and methods

2.1. Participants

We included 50 patients of both sexes with severe OSAS and an AHI greater than or equal to 40 h^{-1} in the study to examine a highly homogeneous group of seriously diseased subjects. As our study was performed within the scope of a regularly scheduled admission of patients for OSAS diagnostics, all subjects underwent the same routine procedure comprising medical history and physical examination. During the primary examination in hospital, patients were screened for previous or actual psychiatric illness and were excluded in case of a positive result. Patients with severe internal or neurologic diseases, a suspected or verified endocrine disorder in their medical history, corticoid medication, renal insufficiency (excretion of metabolites), and manifest diabetes mellitus with antidiabetic medication were also excluded. Likewise, we did not include patients with a mechanical cause of OSAS, such as pharyngeal surgery or long-term intubation, and those with changes in medication during the study. Each participant gave written informed consent, and the study was approved by the local ethics committee.

Table 1
Polysomnographic data from patients with severe OSAS (AHI ≥40 h^{-1}) before and after 3 month of CPAP therapy

	Pre–CPAP treatment	Post–CPAP treatment
	Mean ± SEM	Mean ± SEM
AHI, h^{-1}	59.6 ± 2.0	5.8* ± 1.4
ODI, h^{-1}	49.5 ± 2.8	2.7* ± 0.4
MOS, %	92.2 ± 0.4	95.5* ± 0.3
Mean minimal O_2 saturation, %	75.4 ± 1.2	89.0* ± 1.0
Mean desaturation time, s	32.8 ± 4.9	33.8 ± 1.9
Mean maximal desaturation time, s	151.3 ± 9.6	78.9* ± 8.0
No. of desaturations, $night^{-1}$	352.9 ± 21.9	19.9* ± 2.7
Mean CPAP use, h $night^{-1}$		5.9 ± 0.4

Data are presented as mean values ± SEM.

* Statistically significant, with P less than .001 (based on paired Student t tests) by comparing parameters pre– and post–CPAP therapy.

2.2. Subject specifications

Fifty patients were included in the first study period. Thirty-eight patients returned to the second study period after 3 months of CPAP therapy, whereas 12 patients did not come to the control session because of therapy abort or without giving any reasons (rates of 30% therapy aborts have been reported before [18]). Patients with severe OSAS showed a mean AHI of 59.6 ± 2.0 h^{-1} (Table 1). After CPAP therapy, AHI was decreased to 5.8 ± 1.4 h^{-1}. The mean oxygen saturation (MOS) pre–CPAP therapy was 92.2% ± 0.4%. Mean use of the CPAP mask was 5.9 ± 0.4 hours per night. Four patients had fasting blood glucose levels greater than or equal to 7 mmol L^{-1}. The mean age was 55.1 ± 1.6 years, mean BMI was 35.4 ± 0.9 kg m^{-2}, and mean fasting blood glucose was 5.71 ± 0.16 mmol L^{-1}. Distribution between the sexes was 47 male and 3 female subjects. Twenty-six patients fulfilled the National Cholesterol Education Program–Adult Treatment Panel III criteria for a metabolic syndrome.

2.3. Procedure

Participants came to the Medical Clinic at the Research Center Borstel within the scope of their OSAS diagnostic procedure and were recruited after diagnosis of OSAS. At admission to the hospital, patients were examined including the assessment of BMI. Patients received a schedule and an introduction for sampling salivary cortisol by Salivette sampling devices (Sarstedt, Rommelsdorf, Germany). In contrast to blood analyses, the determination of salivary cortisol reflects free cortisol concentrations exclusively without the matrix effect of the binding protein (corticosteroid binding globulin [CBG]). Another advantage of salivary sample is the fact that this is a noninvasive method and thereby well tolerated by participating subjects. Therefore, the measurement of cortisol by saliva is a well-established method for clinical studies including patients [14,19,20]. Free saliva cortisol is highly correlated with free plasma cortisol [21]. Six saliva samples were collected at defined

time points: in the evening before going to bed, the next morning after awakening (supine), before and 1 hour after breakfast, and before and 1 hour after lunch. Meal times were standardized for all participants, and diurnal activity was largely determined by stationary routine. Saliva sampling was precisely timed by the daily clinical routine and, especially at noon, very tightly linked to meal delivery. The exact time of saliva sampling was recorded. The participants were explicitly advised not to collect the sample beyond the mentioned time points. If they missed a time point, they were told to omit this sample. Saliva samples were centrifuged at 2000*g* for 10 minutes and then frozen at −80°C.

All participants underwent an overnight polysomnography measurement, including monitoring of AHI, oxygen desaturation index (ODI), and MOS. Concentrations of fasting plasma glucose and lactate were determined from blood samples after the first night in the hospital.

After 3 months of CPAP therapy, patients returned for therapy checkup and underwent an overnight polysomnography using their CPAP device. The procedure for blood and saliva sampling was analogous to the first session.

2.4. Hormone assays

All salivary cortisol samples were measured by the same luminescence immunoassay (IBL, Hamburg, Germany; intraassay coefficient of variation, <8%; interassay coefficient of variation, <12%).

Plasma samples for determination of lactate concentrations were centrifuged at 1500*g* for 10 minutes; the supernatants were frozen at −80°C. Lactate was assessed by photometric lactate oxidase method (Lactic Acid, Abbott 9D89-20) on the Aeroset Clinical Chemistry Analyzer (Abbott, Chicago, IL). Fasting blood glucose was assessed within the routine laboratory diagnostics.

2.5. Statistical analysis

Statistical analysis was performed by SPSS for Windows, version 12.0.0 (SPSS, Chicago, IL). Variability values are expressed as standard error of means (SEM). *P* values less than .05 were considered significant. Analysis of variance for repeated measurements, corrected according to the Greenhouse-Geisser procedure and including the factor "treatment" (untreated vs CPAP treated), was implemented for patients who participated in the study before and after CPAP therapy (n = 38). In addition, cortisol concentrations were compared by paired Student *t* tests. To rule out any bias resulting from time variances of cortisol sampling, we repeated our analysis using unstandardized residuals of the cortisol concentrations after partialling out the variations in actual sampling time. However, the reported effects of CPAP on HPA axis activation remained unchanged. The area under the curve was calculated from diurnal cortisol profiles to determine overall differences in cortisol concentrations before and after CPAP treatment. Correlation analyses between ODI, MOS, and the area under the cortisol curve (AUC) were performed by Pearson correlation.

3. Results

3.1. Salivary cortisol

According to the reference range for healthy subjects given by our laboratory, cortisol values were not pathologically increased. Analysis of variance for repeated measures revealed a significant effect of CPAP therapy on diurnal cortisol profiles (effect of the factor "treatment," $P = .048$). Paired *t* test comparison of the different time points detected a decrease of evening cortisol levels (3.04 ± 0.55 nmol L^{-1} pre-CPAP vs 2.48 ± 0.78 nmol L^{-1} post-CPAP, $P = .038$, Figs. 1 and 2). Elapsed time between waking up and the first morning saliva sampling was 29.9 ± 3.6 minutes before and 33.1 ± 5.3 minutes after CPAP therapy. Surprisingly, cortisol levels at the time point before lunch were increased after CPAP therapy (7.18 ± 0.83 nmol L^{-1} pre-CPAP vs 10.22 ± 1.10 nmol L^{-1} post-CPAP, $P = .044$, Figs. 1 and 2). The maximum excursion of the diurnal cortisol curve between peak and nadir (13.80 ± 1.66 nmol L^{-1} pre-CPAP vs 16.84 ± 2.48 nmol L^{-1} post-CPAP, $P = .065$) as well as the AUC (3651.48 ± 321.84 nmol L^{-1} h pre-CPAP vs 4266.96 ± 306.36 nmol L^{-1} h post-CPAP, $P = .070$, Fig. 2) showed a trend toward a greater value after CPAP therapy. Cortisol concentrations at other time points were unchanged after CPAP therapy as revealed by paired *t* test. To rule out any bias resulting from time variances of cortisol sampling, we repeated our analysis using unstandardized residuals of the cortisol concentrations after partialling out the variations in actual sampling time. However, the reported effects of CPAP on HPA axis activation remained unchanged. However, a

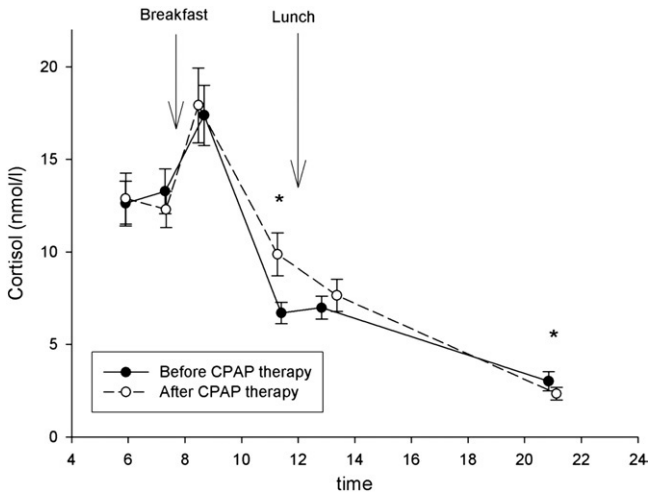

Fig. 1. Mean values of salivary cortisol concentrations (±SEM) before (black circles, solid line) and after (white circles, broken line) CPAP therapy. Asterisks denote statistical significance in paired Students *t* test with *P* less than .05.

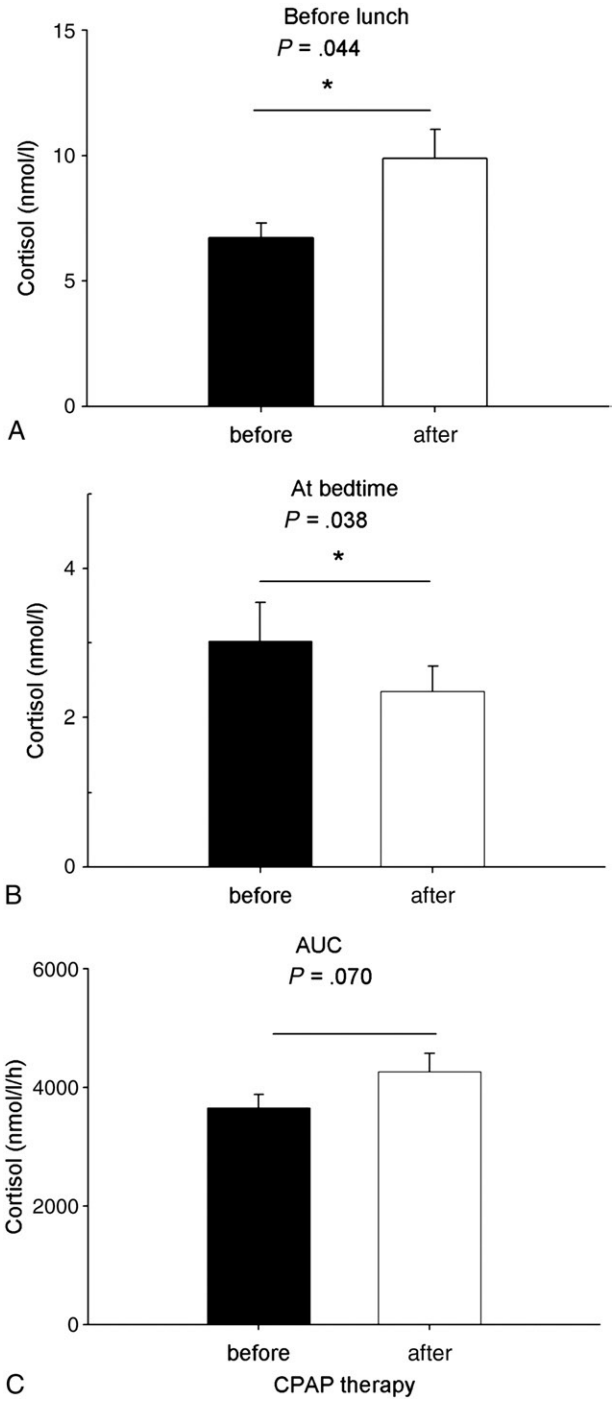

Fig. 2. Saliva cortisol concentrations (mean ± SEM) before lunch (A) and at bedtime (B), and cortisol AUC of diurnal profiles (C) before (white bars) and after (black bars) CPAP therapy. Asterisks denote statistical significance in paired Students *t* test with *P* less than .05.

negative correlation between cortisol concentrations after awakening and the MOS before treatment was observed ($r = -0.335$, $P = .023$). Cortisol AUC before treatment did not correlate with AHI ($r = -0.051$, $P = .735$) or ODI ($r = -0.008$, $P = .959$), and cortisol concentrations at single time points also did not correlate with AHI or ODI.

3.2. Plasma lactate

Mean plasma lactate concentrations were 1.09 ± 0.08 mmol L^{-1} before and 1.39 ± 0.16 mmol L^{-1} after CPAP therapy ($P = .145$) and were thereby within the reference range in all participants (>0.63 and <2.44 mmol L^{-1}). There were no correlations between lactate concentrations and AHI, ODI, or MOS before and after induction of CPAP therapy.

4. Discussion

Our data show that 3 months of CPAP therapy significantly affects cortisol concentrations in patients with severe OSAS, as reflected by decreased cortisol concentrations at bedtime. We further found an increase of preprandial saliva cortisol concentrations at lunchtime. Cortisol concentrations after awakening correlated negatively with the MOS before CPAP therapy was induced.

Recent studies give contradicting evidence in the context of obesity, sleep apnea, and HPA axis relationships. Our findings are in line with those of Vgontzas et al [22] who showed increased nightly cortisol concentrations in obese apneic patients as compared with obese controls and a trend to reduced cortisol concentrations after CPAP therapy. In contrast, Dadoun et al [23] found no significant differences in cortisol concentrations between obese OSAS patients and obese controls, which may possibly be because of a small number of participants and a distinctly lower mean AHI as compared with that of our study. Other studies focused at single time points in the morning and found no changes in cortisol concentrations upon CPAP therapy [24-26]. Only 1 study reported elevated cortisol concentrations in OSAS patients as compared with healthy controls [9]. In agreement with most of these previous results, in the present study, morning cortisol concentrations were found unchanged after CPAP therapy.

Point of major interest in our study is the change of cortisol concentration at bedtime after CPAP therapy. In salivary cortisol sampling, bedtime fits best to the plasma cortisol nadir [27]. In healthy humans, the plasma cortisol nadir is timed in the early hours of nighttime sleep; and the maximum concentration of cortisol is reached at about awakening time [8,28,29]. Our data indicate that OSAS patients display decreased nadir cortisol concentrations after CPAP therapy. Because it has been suggested that an elevation in cortisol nadir values plays a pathogenetic role in the development of glucose intolerance [30] as well as in depression [31], both of which are associated with OSAS, our data may shed new light on the relationship between OSAS and these comorbid diseases.

Against our first hypothesis, CPAP therapy does not generally decrease HPA axis activity and cortisol concentrations. In fact, cortisol concentrations before lunch were even slightly higher under CPAP therapy as compared with the

untreated state. This finding may appear to be paradoxical to the decreased cortisol levels at bedtime. We interpret the cortisol rise at lunchtime by a possible resistance against food-anticipated HPA axis stimulation in analogy to the known lacking cortisol rise upon corticotropin-releasing hormone stimulation in OSAS [24]. Physiologically, a cortisol peak occurs after food intake, which is especially prominent at noontime [32] and which also was found without food intake at the time of anticipated lunch mealtime [33]. Our data indicate that OSAS patients present a potential resistance against this food anticipation stimulus, which may be restored after CPAP therapy. This effect, however, does not seem to be related to the drop in bedtime cortisol levels after CPAP therapy that is not meal associated.

Overall, OSAS does not appear to have a generally increasing or decreasing effect on HPA axis, as revealed by cortisol concentrations close to the salivary cortisol levels for unstressed healthy subjects [20]. Nevertheless, changes in cortisol concentrations within the physiologic range have to be regarded, as cortisol concentrations within the reference range correlated with metabolic disturbances in patients with type 2 diabetes mellitus [14].

Potentially, OSAS dampens the diurnal oscillation between peak and nadir cortisol concentration. In the present study, we found a trend for a broader variation between cortisol peak after breakfast and nadir at bedtime after effective therapy for OSAS with CPAP, although this effect failed to attain significance.

In addition, the cortisol AUC, taken from 6 salivary samples, showed a trend to be elevated after CPAP treatment. Here, repeated salivary sampling remains just an approximation of total secretion for a period, which may be a limitation of this study. Entzian et al [8] implicated previously that healthy subjects, as compared with OSAS patients, exhibit a wider oscillation in their diurnal cortisol profile reflected by higher cortisol concentrations in the morning and lower cortisol nadir concentrations in the early night, although this effect did not reach statistical significance. Taken together, these findings may indicate a dampened HPA axis oscillation in patients with OSAS, which could be reversed by CPAP treatment.

Obstructive sleep apnea syndrome has also been shown to increase inflammatory markers, as revealed by increased interleukin-6 and tumor necrosis factor–α concentrations in patients with OSAS, which can be reversed by treatment with CPAP [8,34]. Vgontzas et al [35,36] could demonstrate a relationship between proinflammatory cytokines and cortisol secretion. Therefore, the decrease of cortisol concentrations in the evening may potentially be due to the reduction of the plasma cytokines interleukin-6 and tumor necrosis factor–α.

However, all changes in cortisol values found in this study occur within the reference range. Because most previous studies could not show any altered cortisol concentrations either at baseline as compared with healthy controls or upon CPAP therapy, we assumed that the expected effects in our study would not exceed the reference range. Therefore, we included a comparatively high number of participants into this study. This gain possibly accounts for the significant differences in cortisol concentrations after CPAP therapy in our study, where other studies showed trends or failed significance [22,23]. As previously shown, small changes in HPA axis activation within the reference range are also considered to be crucial and are known to be related to, for example, the metabolic syndrome [14,37,38]. A possible limitation of this study is the lack of a control group. Here, we did not include a non–sleep-disordered control group because a within-subject design with all participants being their own control is appropriate in this case. Moreover, CPAP application would have no effect on oxygenation levels in healthy subjects.

The second finding of our study is that fasting lactate concentrations in resting condition do not correlate with any of the parameters for severity of OSAS, that is, AHI, ODI, or MOS. In the literature, there are just a few data about the effect of OSAS on lactate metabolism. When lactate concentrations in resting conditions before and after 1 night with CPAP therapy were compared, there was no difference in lactate concentrations in patients with OSAS [39]. Vanuxem et al [40] found no difference in lactate concentrations between OSAS patients and controls, but a lower peak lactate level during maximal exercise in OSAS patients. In contrast, Bonanni et al [41] found higher lactate production during exercise and a lower lactate threshold in patients with OSAS as compared with controls. However, our data do not indicate any effect of OSAS or CPAP therapy on lactate metabolism, although a hypoxic stress-induced increase was expected, which should be reversed after CPAP therapy. Therefore, it is unlikely that lactate concentration is a parameter for severity of OSAS.

Our findings suggest that OSAS affects HPA axis function by elevating evening cortisol concentrations and dampening the activation before lunch. Continuous positive airway pressure therapy reverses these effects.

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