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RESEARCH LETTER

Salivary Cortisol in Obstructive Sleep Apnea: The Effect of CPAP

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Introduction

Sleep apnea and sleep-disordered breathing may affect the hypothalamic-pituitary-adrenal axis (HPA) due to hypoxic episodes and sleep disruption [1, 2]. Salivary cortisol is a simple and reliable surrogate for free, biologically active cortisol in the plasma [3]. This study evaluated the effect of continuous positive airway pressure (CPAP) on salivary cortisol as an index of physiologic stress related to sleepiness and obstructive sleep apnea (OSA).

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Materials and methods

Subjects

After obtaining Institutional Review Board approval, we recruited, and obtained written consent from new, untreated patients with clinical symptoms and signs suggestive of sleep disordered breathing; this included snorers and those with mild/moderate/severe sleep apnea. Subjects were recruited from sleep clinic patients scheduled for polysomnography (adult male or female, age 18–90, without prior treatment of OSA, or overt airway structural pathology that would interfere with CPAP use). Eighteen subjects were enrolled in a placebo (mucolytic) versus active treatment (auto-adjusting CPAP) outpatient trial. Salivary samples were obtained and the Epworth sleepiness scale (ESS) questionnaire [4] was completed at four time points during two separate 2-week trials.

Study protocol details

For the two-week placebo trial, subjects were given guaifenesin (Mucinex, Adams Respiratory Therapeutics, Dallas, TX) 600 mg twice a day. The saliva samples were obtained (Salivette, Sarstedt, Inc., Newton, NC) at bedtime ($\approx$11 pm), and the next morning ($\approx$7 am) on day 0 (before starting mucolytic), and days 1, 7, and 14 of mucolytic. After 1–2 weeks, the 2-week CPAP trial started with the same days and times of saliva collection as in the placebo trial. Each subject underwent individualized education and mask fitting as well as objective adherence and effectiveness data collection (Autoset, ResMed, San Diego, CA). Salivary cortisol was measured by enzyme-linked immunosorbent assay [5].

Statistical analysis

The data were analyzed after log transformation, and test a hypothesis of proportional difference between groups; results are given on the original scale. A repeated measures mixed model with compound symmetric covariance was used to test hypotheses of differences in average treatment effect (placebo versus CPAP), and difference in linear trends between the treatments, using the day of the study period as the linear measure. Separate analyses were performed for morning and evening cortisol measurements, as well as sub-analyses of only those that actually used CPAP (SAS 9.1). The Wilcoxon Rank Sum test was used to compare day 0 evening cortisol in CPAP versus placebo arm. Spearman Rank correlation was used to analyze the association between salivary cortisol and apnea-hypopnea index (AHI; an index of OSA severity). The Mann–Whitney Rank Sum Test was used to compare salivary cortisol results partitioned by ESS score (SigmaStat 3.0). Results were considered significant at $P = 0.05$.

Results

There were nine men and nine women (age 47 ± SD 9 years). Height was 170.5 ± 8.5 cm and weight was 102.2 ± 19.0 kg. BMI (kg/m^2) was 33.8 ± 6.2 and AHI was 30.8 ± 32.1. Nine subjects used CPAP ≥3 h per night throughout the study, and their results are the focus of the analysis. The average nightly CPAP use in the group using CPAP for ≥3 h (N=9) was 311 (180–444) min. In the group using CPAP for <3 h (N=9), it was 33 (2–85) min. There were no differences in baseline characteristics between the groups partitioned by CPAP use. No subjects had an 11PM salivary cortisol level above the reference range for healthy subject (>4.2 nmol/l) at time 0 in the Placebo arm. Four of 18 had an 11PM salivary cortisol above the reference range at time 0 in the CPAP arm.

In the subjects who used CPAP ≥3 h, salivary cortisol in the morning was significantly lower in the CPAP-treated arm compared to placebo at day 1 of treatment and close to significantly lower on day 14 (Table 1). The only significant finding in the evening was that the salivary cortisol at day 0 (the day before starting CPAP) was significantly increased compared to the placebo arm. There was no significant correlation between AHI (measure of severity of OSA) and either morning or evening salivary cortisol at day 0 of placebo (morning $\rho = -0.11$, $P = 0.68$; evening $\rho = -0.03$, $P = 0.91$, $N = 17$; $N = 1$ missing sample). Average ESS with Placebo treatment in all subjects was higher than CPAP (10.7 [CI 8.5–12.9] versus 8.9 [CI 6.8–11.2) ($N = 18$; $P = 0.0009$). Average ESS score for the nine subjects who used CPAP ≥3 h was 10.7 (6.8–14.6) for the placebo arm and 8.9 (4.9–12.8) during CPAP ($P = 0.0382$). In all subjects in the CPAP arm, baseline (at day 0) late night salivary cortisol (4.6 ± SD 2.0 nmol/l) was significantly lower ($P = 0.029$) in subjects who had a clinically meaningful decrease in sleepiness as measured by the ESS (decrease of ≥2 [6, 7], $N = 8$) compared to those that did not (8.9 ± SD 5.7 nmol/l; $N = 10$).

Discussion

The morning and evening salivary cortisol levels in the current study were remarkably normal compared to healthy subjects [3, 5]. CPAP use resulted in a significant but transient decrease in the morning, but not evening, salivary cortisol levels. Furthermore, it seems possible that the

Table 1 Salivary cortisol (nmol/l) in subjects ($N = 9$) who used CPAP ≥3 h/night

	Day	Placebo	CPAP	CPAP/Placebo (Ratio)	P value
Morning	0	12.1 (7.2, 20.5)	12.5 (7.6, 20.8)	1.0 (0.6, 1.7)	0.8938
	1	13.6 (8.1, 23.0)	7.4 (4.4, 12.2)	0.5 (0.3, 0.9)	0.0200
	7	13.3 (7.9, 22.3)	9.9 (6.0, 16.4)	0.8 (0.5, 1.2)	0.2490
	14	15.0 (8.9, 25.3)	9.2 (5.6, 15.3)	0.6 (0.4, 1.0)	0.0597
Evening	0	1.2 (0.6, 2.6)	3.2 (1.6, 6.4)	2.6 (1.2, 5.3)	0.014
	1	1.8 (0.9, 3.7)	2.2 (1.1, 4.4)	1.2 (0.6, 2.5)	[a]
	7	2.5 (1.2, 5.1)	3.0 (1.5, 6.1)	1.2 (0.6, 2.6)	[a]
	14	2.2 (1.0, 4.5)	1.9 (1.0, 4.0)	0.9 (0.4, 1.9)	[a]

Data are as mean (95% CI), after transformation to original scale. There was an overall treatment difference in the morning cortisol ($P = 0.0293$), but no difference between days ($P = 0.5263$) and no Treatment-by-Day interaction ($P = 0.2419$). Unadjusted P-values are reported for comparisons within each day. [a]There were no significant overall differences using the statistical model for evening cortisol for treatment ($P = 0.1321$), between days ($P = 0.5139$), or interaction ($P = 0.2134$); therefore, individual P values are not reported for days 1, 7, and 14. However, when analyzed by Wilcoxon rank test, evening salivary cortisol on day 0 was higher in the CPAP arm compared to the placebo arm ($P = 0.014$)

anticipation of CPAP use for the first time may have accounted for the increase in evening salivary cortisol the night before the CPAP trial started. Finally, subjects with an improvement in the ESS had significantly lower evening salivary cortisol levels before CPAP was started.

A recent study found that obese men with sleep apnea had slightly increased cortisol that returned to baseline after 3 months of CPAP use [8]. We found remarkably normal salivary cortisol in the morning and evening in the patients with OSA during the placebo trial in agreement with recent studies that compared obese subjects with OSA to those without OSA, and to normal subjects [9, 10]. Three months of consistent CPAP use resulted in lower evening salivary cortisol levels [9]. The study with only 2 weeks of CPAP treatment found lower morning cortisol levels compared to placebo. It could be that longer CPAP therapy is required to see a more consistent effect on the HPA axis. A post-hoc analysis found that a clinically meaningful decrease in ESS-measured sleepiness [6, 7] while using CPAP was associated with lower levels of late-night cortisol at the beginning of the CPAP arm of the study. We speculate that a failure to observe a reduction in ESS reflects patients with a tendency for hyper-arousal and poor sleep that overrides the benefits of CPAP treatment. Prior studies have shown that an increase in ESS >2 units is associated with active treatment and not placebo treatment arms [11].

In conclusion, patients with significant sleep disordered breathing appear to be able to maintain overall normal HPA axis function. Although a larger study is required to confirm these preliminary findings, morning but not evening cortisol was transiently reduced with active treatment in CPAP users. Evening cortisol levels were not affected and instead, higher salivary cortisol levels may predict an inadequate decrease in sleepiness during CPAP treatment.

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References

1. G. Carneiro, S.M. Togeiro, L.F. Hayashi, F.F. Ribeiro-Filho, A.B. Ribeiro, S. Tufik, M.T. Zanella, Effect of continuous positive airway pressure therapy on hypothalamic-pituitary-adrenal axis function and 24-h blood pressure profile in obese men with obstructive sleep apnea syndrome. Am. J. Physiol. Endocrinol. Metab. **295**, E380–E384 (2008)
2. N. Meston, R.J.O. Davies, R. Mullins, C. Jenkinson, J.A. Wass, J.R. Stradling, Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnea. J. Int. Med. **254**, 447–454 (2003)
3. H. Raff, Utility of salivary cortisol measurements in Cushing's syndrome and adrenal insufficiency. J. Clin. Endocrinol. Metab. **94**, 3647–3655 (2009)
4. M.W. Johns, A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep **14**, 540–549 (1991)
5. H. Raff, P. Homar, D.P. Skoner, New enzyme immunoassay for salivary cortisol. Clin. Chem. **49**, 203–204 (2003)
6. D.L. Steward, T.C. Huntley, B.T. Woodson, V. Surdulescu, Palate implants for obstructive sleep apnea: multi-institution, randomized, placebo-controlled study. Otolaryngol. Head Neck Surg. **139**, 506–510 (2008)
7. L.M. Tomfohr, S. Ancoli-Israel, J.S. Loredo, J.E. Dimsdale, Effects of continuous positive airway pressure on fatigue and sleepiness in patients with obstructive sleep apnea: data from a randomized controlled trial. Sleep **34**, 121–126 (2011)
8. A.N. Vgontzas, S. Pejovic, E. Zoumakis, H.M. Lin, C.M. Bentley, E.O. Bixler, A. Sarrigiannidis, M. Basta, G.P. Chrousos, Hypothalamic-pituitary-adrenal axis activity in obese men with and without sleep apnea: Effects of continuous positive airway pressure therapy. J. Clin. Endocrinol. Metab. **92**, 4199–4207 (2007)
9. A. Schmoller, F. Eberhardt, K. Jauch-Chara, U. Schweiger, P. Zabel, A. Peters, B. Schultes, K.M. Oltmanns, Continuous positive airway pressure therapy decreases evening cortisol concentrations in patients with severe obstructive sleep apnea. Metab. Clin. Exp. **58**, 848–853 (2009)
10. F. Dadoun, P. Darmon, V. Achard, S. Boullu-Ciocca, F. Philip-Joet, M.C. Alessi, M. Rey, M. Grino, A. Dutour, Effect of sleep apnea syndrome on the circadian profile of cortisol in obese men. Am. J. Physiol. Endocrinol. Metab. **293**, E466–E474 (2007)
11. A.N. Vgontzas, E.O. Bixler, H.-M. Lin, P. Prolo, Vela.-Bueno.A. Mastorakos, A. Kales, G.P. Chrousos, Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J. Clin. Endocrinol. Metab. **86**, 2787–2794 (2001)