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Obstructive Sleep Apnea Treatment: Peripheral and Central Effects on Plasma Renin Activity and Aldosterone

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Summary: To assess the effect of obstructive sleep apnea treatment on plasma renin activity (PRA) and plasma aldosterone seven male patients were studied under two conditions: untreated and treated with nasal continuous positive airways pressure (CPAP). PRA and plasma aldosterone were measured at 10-min intervals for both nights. CPAP treatment diminished the urinary and Na^+ excretion, whereas plasma volume increased. The mean levels of PRA and aldosterone were significantly enhanced by the treatment, increasing respectively from 1.5 ± 0.3 to 3.0 ± 0.7 ngAI $ml^{-1} \cdot hr^{-1}$ ($p < 0.05$) and from 8.0 ± 1.0 to 12.0 ± 1.7 ng·100 ml^{-1} ($p < 0.05$). PRA curves reflected the overall sleep structure as similarly described in normal subjects. The apnea-induced sleep disturbance led to flat PRA profiles and the restoration of a normal sleep pattern by treatment restored the PRA oscillations related to the sleep cycles and consequently restored aldosterone oscillations. The mean amplitude of these oscillations increased respectively from 1.0 ± 0.1 to 1.8 ± 0.4 ngAI $ml^{-1} \cdot hr^{-1}$ and from 5.4 ± 1.2 to 10.9 ± 1.9 ng·100 ml^{-1}. These results suggest that CPAP treatment modifies the nocturnal patterns of PRA and aldosterone by increasing their mean levels and their oscillation amplitude. This indicates increased secretion, which contributes to the normalization of urine and Na output. **Key Words:** Sleep apnea—Plasma renin activity—Aldosterone.

Sleep apnea is a disorder characterized by repetitive upper airway occlusion inducing progressive hypoxemia, which leads to arousal and termination of the obstruction. It is thus associated with marked sleep fragmentation. As recently reported, patients with obstructive sleep apnea (OSA) have increased urine and sodium output during the hours of sleep (1,2). Medical treatment with nocturnal nasal continuous positive airway pressure (CPAP) reverses this feature (1). Increased atrial natriuretic peptide (ANP) release during sleep in patients with OSA and its normalization by CPAP treatment explains in part these changes in water and Na^+ excretion (3,4). However, it is unclear whether the renin–angiotensin–aldosterone axis, known to play an important role in body fluid and salt regulation, is involved. Previous analyses did not show any difference in urinary excretion of aldosterone or in morning plasma active renin concentration between untreated and CPAP-treated patients (5), but an increase of mean hourly plasma renin activity was found when patients were treated (6).

In normal humans with acute increases in plasma atrial natriuretic peptide (ANP) either endogenous (7) or exogenous (8,9) parallel decreases in plasma renin activity (PRA) and plasma aldosterone have been observed, supporting the view that ANP has anti-renin–angiotensin–aldosterone system actions. ANP acts on aldosterone through a combination of two mechanisms: first by inhibiting renal renin release and so consequently decreasing aldosterone release due to a diminished influence of angiotensin II (10,11), and second by directly decreasing aldosterone synthesis at the adrenal level (12,13).

In OSA patients an action of this nature may interplay with the central nervous system action participating in the control of renin secretion. The nocturnal oscillations of PRA, an index of the renin–angiotensin system, have been shown to be closely related to the rapid eye movement (REM), nonREM (NREM) sleep

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cycles (14). NREM sleep is associated with increases in PRA levels and REM sleep linked to decreasing levels. Thus the sleep fragmentation observed in OSA patients could affect this sleep-dependent PRA profile. Aldosterone secretion, for which adrenocorticotropic hormone (ACTH) and angiotensin II are major controlling factors (15), could also reflect the disrupted sleep in OSA patients. It was therefore of interest to determine precisely the nocturnal PRA and aldosterone profiles in untreated and CPAP-treated patients together with their sleep structure. In addition plasma cortisol, reflecting ACTH secretion (16), was measured as an index of the physiological strain.

METHODS

Subjects and procedures

Seven male OSA patients were investigated following receipt of their informed consent. The selection criteria included absence of intrinsic renal or hepatic disorders, heart failure and chronic air-flow limitations and absence of any drug treatment. Patients were aged 40 ± 1 yr (mean ± SE) with a body mass index of 35.8 ± 2.9 $kg \cdot m^{-2}$ and had severe OSA (apnea index 91 ± 9 apneas/hr). They had moderate to severe hypoxemia during sleep (mean lowest SaO_2 = 84.2 ± 3.6%). Daytime hypoxemia was absent to moderate (PaO_2 while awake breathing room air: 75 ± 5 mm Hg) without CO_2 retention. Their mean resting blood pressure was 141 ± 8/92 ± 8 mm Hg.

Each patient was studied during two nights with a 7-day interval between the studies. For one of the nights they were untreated and the other treated with CPAP. Sleep was polygraphically monitored using standard measurements. Urine was collected from 2100 hr until 0700 hr. Patients had standard hospital meals on the day before the study night, Na^+ intake averaging 175 mEq/day.

In addition mean nocturnal aldosterone and PRA levels were calculated in six normal subjects (41.6 ± 3.5 yr and body mass index of 25.9 ± 1.7 $kg \cdot m^{-2}$) from blood collected every 10 min throughout the night.

Blood sampling

On the study-nights patients were placed in a supine position after insertion of an indwelling catheter into a forearm vein 2 hr before blood sampling. Blood was collected continuously in an adjoining room and sampled at 10-min intervals. Lights were switched off at 2200 hr and turned on again at 0630 hr. For the treatment night the patients were put on nasal CPAP after the catheter had been inserted. Blood samples were collected in plastic tubes containing EDTA-Na_2 (1 $mg \cdot ml^{-1}$) and aprotinin (500 $KIU \cdot ml^{-1}$) and kept on ice. Plasma was separated rapidly at 4°C and stored at −25°C for later analysis. A maximum of 250 ml blood was removed during each night.

Assays

PRA was measured by radioimmunoassay (RIA) of the angiotensin I (AI) generated after plasma incubation at pH 6. The detection limit was 0.18 $ngAI \cdot ml^{-1} \cdot hr^{-1}$. The intra-assay coefficient of variation for duplicates was 6.0% for levels comprised between 2 and 10 $ngAI \cdot ml^{-1} \cdot hr^{-1}$; 10% for levels between 1 and 2 $ngAI \cdot ml^{-1} \cdot hr^{-1}$ and 30% for levels less than 1 $ngAI \cdot ml^{-1} \cdot hr^{-1}$.

Plasma aldosterone and cortisol were measured by RIA using antisera prepared against carboxymethyloxime conjugates. The detection limits were, respectively, 0.5 $ng \cdot 100\ ml^{-1}$ and 0.5 $\mu g \cdot 100\ ml^{-1}$. The intra-assay coefficients of variation for duplicates were 7.5% for aldosterone levels above 10 $ng \cdot 100\ ml^{-1}$ and 10% for levels less than 10 $ng \cdot 100\ ml^{-1}$. For cortisol they were 2% above 15 $\mu g \cdot 100\ ml^{-1}$, 4% between 5 and 15 $\mu g \cdot 100\ ml^{-1}$ and 10% for levels less than 5 $\mu g \cdot 100\ ml^{-1}$.

At 600 hr blood hematocrit (Hct) and hemoglobin (Hb) were measured in triplicate. Relative changes in plasma volume (PV), between the treatment and the nontreatment night, were calculated according to Dill and Costill (17).

Plasma K^+ was measured on the last night-sample collected and urinary Na^+ on the pooled nocturnal urines. Both were assayed by flame photometry.

Data analysis

Polysomnographic recordings were scored at 30-sec intervals using standardized criteria (18). The data were grouped into consecutive 10-min periods for a comparative analysis with the hormone results obtained from the 10-min-interval plasma samples. For each period, the percentage of wakefulness and of each sleep stage was determined.

For between hormone comparisons of mean profiles, values were expressed as a percentage of the nocturnal mean. The nocturnal trends for PRA, plasma aldosterone and cortisol were determined using an algorithm calculating polynomial regression line of the third degree.

Individual PRA and aldosterone profiles were analyzed using the pulse detection program ULTRA at a threshold of three times the coefficients of variation (19). The significant oscillations were then analyzed peak by peak for aldosterone in relation to PRA. For each significant peak the duration and magnitude were quantified. The effects of CPAP treatment were as-

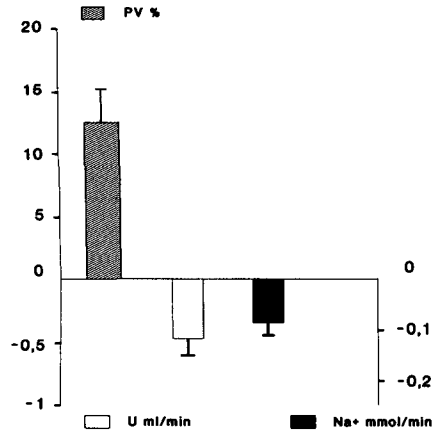

FIG. 1. The effect of treatment on plasma volume (PV) and nocturnal urinary (U) and Na excretion (mean ± SE).

sessed by comparing individual mean levels obtained for the treatment and nontreatment nights using a paired Student's *t* test. Results are expressed as means ± SE (n = 7).

RESULTS

Urinary volume and sodium excretion

The urine flow during the night with CPAP treatment was significantly reduced compared to the night without treatment (0.56 ± 0.06 ml·min^{-1} vs. 1.05 ± 0.13 ml·min^{-1}, $p < 0.02$). Treatment also significantly reduced urinary Na^+ excretion ($p < 0.01$), which declined from 0.16 ± 0.02 mmol·min^{-1} for the nontreatment night to 0.08 ± 0.01 mmol·min^{-1} for the treatment night. These urinary volume and Na^+ changes are illustrated in Fig. 1.

Plasma volume changes and plasma potassium

Blood samples obtained at 0600 hr were analyzed for Hct and Hb for the treatment and nontreatment nights. The mean PV increase (ΔPV) induced by the treatment and calculated from these Hct and Hb values was 12.7 ± 2.8% ($p < 0.01$) (Fig. 1).

Plasma K^+ values measured in the early morning did not differ significantly for both nights (4.8 ± 0.1 vs. 4.9 ± 0.1 mEq·l^{-1}).

Mean nocturnal hormone profiles

The mean levels of both PRA and plasma aldosterone of the patients were significantly enhanced by the CPAP treatment ($p < 0.05$). They increased from 1.5 ± 0.3 (nontreatment night) to 3.0 ± 0.7 ngAI·ml^{-1}·hr^{-1} (treatment night) for PRA and from 8.0 ± 1.0 to 12.0 ± 1.7 ng·100 ml^{-1} for aldosterone. Mean nocturnal levels obtained in the group of normal subjects were 2.2 ± 0.4 ngAI·ml^{-1}·hr^{-1} for PRA and 8.9 ± 1.2 ng·100 ml^{-1} for aldosterone. No statistical difference could be found between the groups, neither for the treatment night nor for the nontreatment night of the patients. This may be attributed to the large interindividual differences observed for the mean values. The mean patient's plasma cortisol level did not differ significantly between the nights with or without treatment (8.7 ± 0.8 vs. 7.8 ± 0.6 μg·100 ml^{-1}).

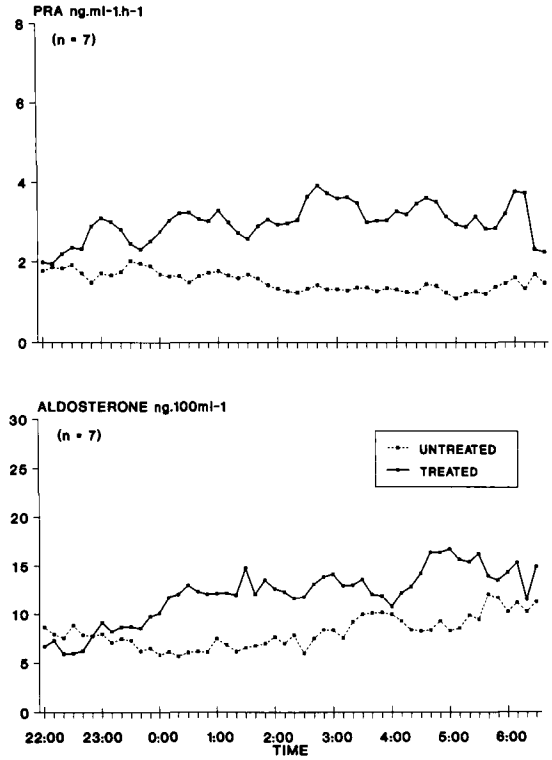

FIG. 2. Mean plasma renin activity (PRA) and aldosterone profiles from seven OSA patients during the night without and the night with treatment.

The mean nocturnal PRA and aldosterone curves calculated across subjects (n = 7) are illustrated in Fig. 2. They give clear evidence of the treatment-related increases throughout the nights. Flat mean profiles at low levels were obtained for PRA during the nights without treatment and more fluctuating profiles at higher levels during the nights with treatment. A smaller relative difference was observed between the aldosterone profiles.

PRA and aldosterone profiles also differed in their general trend, especially during the early morning hours. Under both conditions the nocturnal mean curves of aldosterone were compared with the PRA and cortisol curves (Fig. 3). For each individual, values were expressed as a percentage of the mean nocturnal level. This allows the comparison between the hormones and prevents giving too much emphasis to some individual

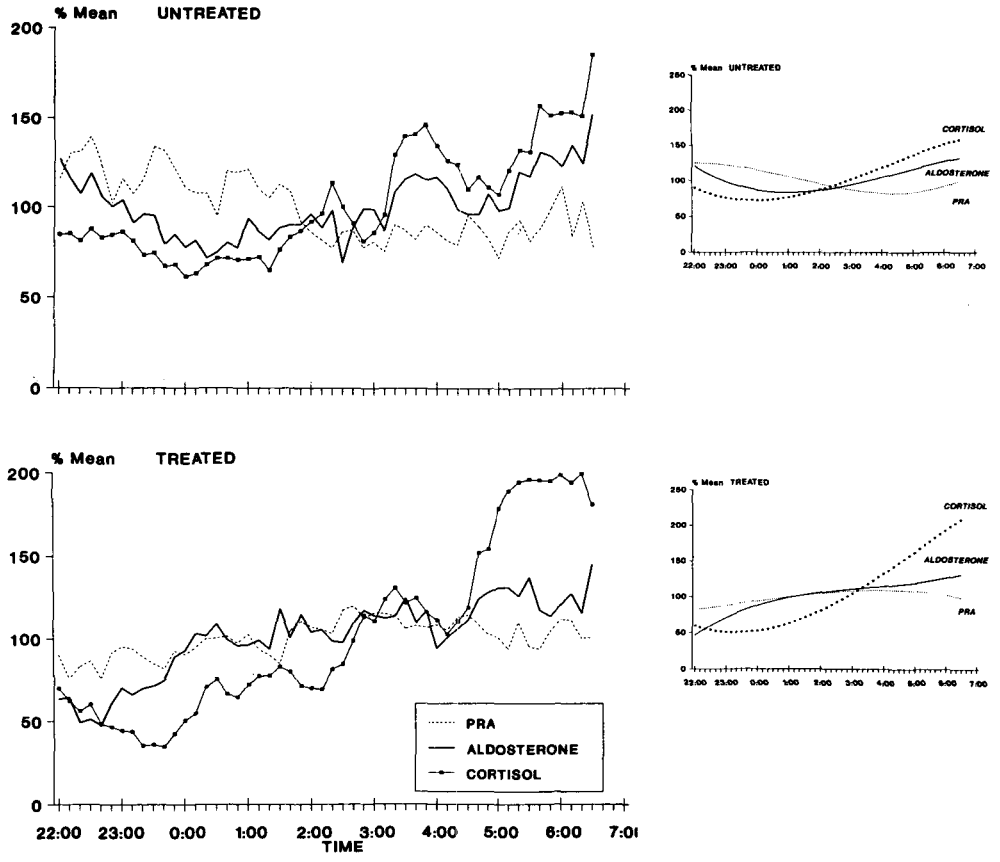

FIG. 3. Nocturnal mean curves of PRA, aldosterone and cortisol expressed as percent of the mean levels and overall nocturnal trends of seven untreated and treated patients.

values. The cortisol profile reflects that of ACTH, one of the stimulating hormones of aldosterone. During the night without treatment, the aldosterone profile resembled that of cortisol, with low values at the beginning of the night and an increase in early morning hours. However, the relative amplitude of the morning increase was lower for aldosterone than for cortisol. The overall similarity of the nocturnal trends of aldosterone and cortisol in untreated patients was not evident with treatment. Treatment enhanced renin secretion and also its influence on aldosterone secretion. Under these conditions the aldosterone profile showed a closer resemblance to that of PRA, except in the early morning when ACTH still appeared to dominate aldosterone as well as cortisol secretion. The overall nocturnal trends clearly illustrate these relationships.

Individual PRA and aldosterone profiles and sleep cycles

Figure 4 shows the nocturnal PRA and aldosterone profiles with the corresponding sleep stage patterns in two representative apnea patients with and without treatment.

Sleep pattern

In all patients, when untreated, the sleep stage pattern gives evidence of frequent awakenings, absence of deep sleep and few and short REM sleep periods. The treatment led to improvements in sleep depth and REM sleep, and it diminished the time spent in stages 1 and 2 and wakening periods. In some treated patients regular REM–NREM sleep cycles occurred, which were similar to those observed in normal subjects (Fig. 4: left panel). In others, although deep sleep and REM sleep were reestablished, the sleep structure remained irregular with shorter REM–NREM sleep cycles (Fig. 4: right panel).

PRA

PRA curves reflected the patterns of sleep stage distribution. Increasing PRA levels coincided with NREM sleep phases and declining levels with REM sleep. This relationship has been previously demonstrated in normal subjects (14). When sleep cycles were regular such as in several of the treated patients the oscillating PRA levels also became regular (Fig. 3: left panel). Irregu-

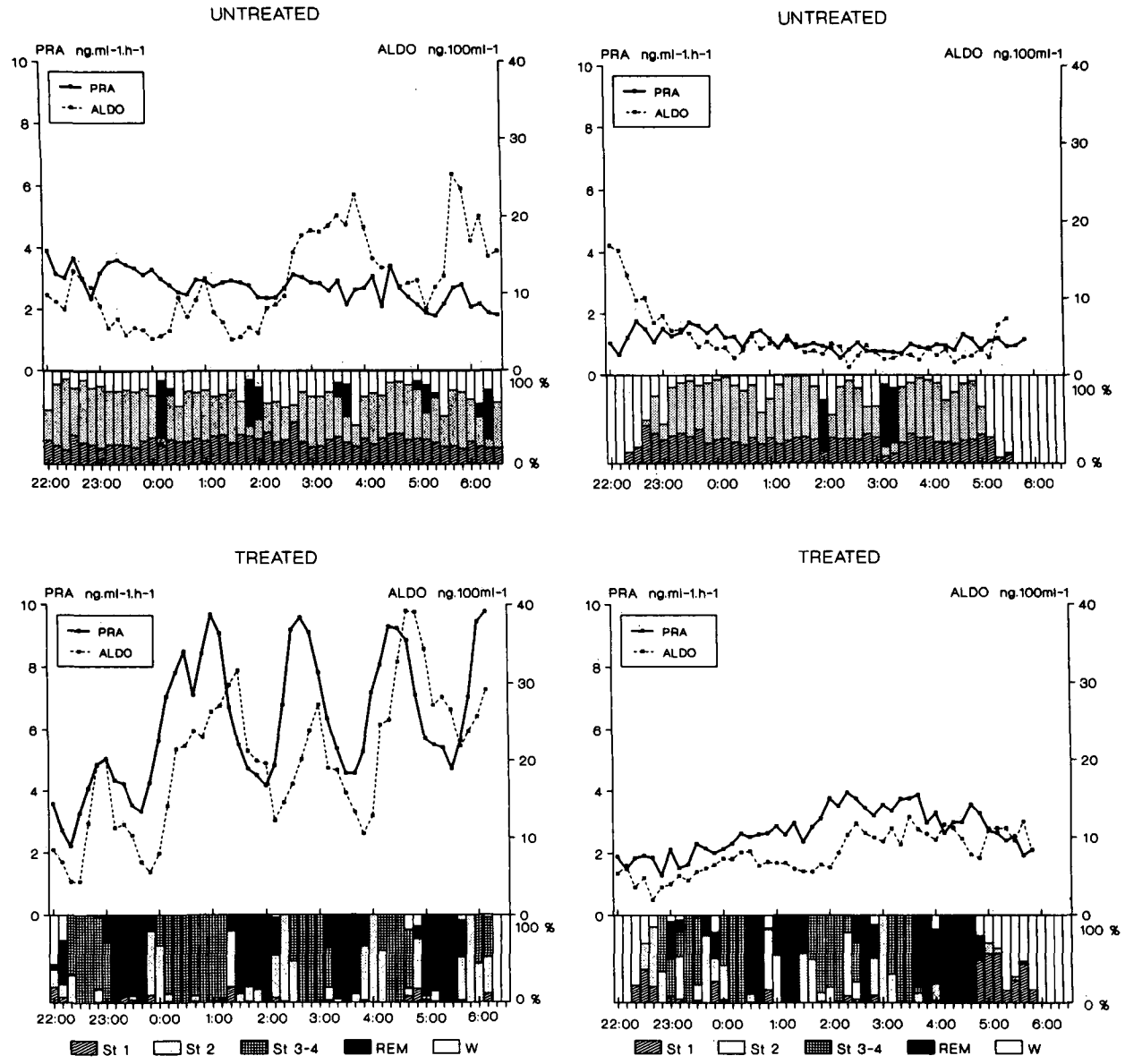

FIG. 4. Individual nocturnal PRA and aldosterone profiles and corresponding sleep stage patterns from two subjects during the nights without and with treatment.

larities in the sleep structure such as short sleep cycles and varying length of sleep stage duration led to fluctuations of smaller amplitude and a general nonoscillatory PRA pattern (Fig. 3: right panel). The numerous awakenings and the very shallow sleep, observed in the untreated patients, blunted the PRA increases normally associated with an increase in sleep depth, resulting in flat PRA profiles. The mean amplitude of the PRA peaks was 1.0 ± 0.1 ngAI·ml^{-1}·hr^{-1} for the nontreatment night and 1.8 ± 0.4 ngAI·ml^{-1}·hr^{-1} for the treatment night. Thus the sleep quality strongly influenced the PRA profiles, the peak amplitude as well as the mean levels.

Aldosterone

For each patient, treatment enhanced the amplitude of the plasma aldosterone fluctuations concomitantly with a rise in the mean level. The overall mean amplitudes of the fluctuations were 5.4 ± 1.2 ng·100 ml^{-1} for the nontreatment night and 10.9 ± 1.9 ng·100 ml^{-1} for the treatment night, respectively.

The ULTRA peak detection program was used to identify significant aldosterone and concomitant PRA fluctuations. This enabled the relative influence of the renin–angiotensin system on aldosterone secretion in both conditions to be established. The analysis re-

vealed that for the night without treatment, 11% of aldosterone peaks were preceded by PRA peaks with a time lag, as previously established, of between 10 and 20 min (15). Treatment enhanced the number of significant peaks to 38%, which were preceded by PRA peaks. This suggests that under treatment conditions the renin–angiotensin system has an increased influence on aldosterone secretion and as a consequence the association of aldosterone to sleep cycles becomes closer. An overall picture of this more or less pronounced relationship is given by the nocturnal mean trends illustrated in Fig. 3.

DISCUSSION

The results from this study demonstrate that in OSA patients both the mean levels and amplitude of the PRA and aldosterone oscillations increased with treatment, plasma K^+ remained unchanged and urine excretion diminished. This observation is in line with the role that the renin–angiotensin–aldosterone system is known to play in body fluid and salt regulation. In addition to these peripheral effects of OSA, PRA and plasma aldosterone profiles also reflected a disturbed central control mechanism, which is manifested by the marked sleep fragmentation characteristic of these patients. CPAP treatment tended to normalize the sleep pattern restoring deep sleep and REM sleep and also the PRA rises normally associated with NREM sleep (14).

From this study it is difficult to assess whether CPAP treatment actually normalizes renin and aldosterone release, as the overall mean values were in the normal range for both nights. Nevertheless the nocturnal PRA and aldosterone profiles of the patients, which, without treatment, differed considerably from those of the control subjects, showed a strong resemblance with treatment, suggesting a normalizing effect of CPAP treatment on hormone secretion.

The effect of CPAP treatment on nocturnal water and Na^+ excretion could be in part attributed to alterations in ANP levels (4). It has been demonstrated that patients with OSA have raised plasma ANP levels during periods of obstructive apnea compared with the awake state, and plasma ANP levels were reduced with CPAP treatment. Such an increase is possibly due to hypoxemia-induced vasoconstriction, as this is in accordance with conclusions from animal (20) and human studies (21,22) in which hypoxemia has been experimentally induced. The inhibitory role of ANP on the renin–angiotensin–aldosterone system may be an important factor in the salt and water balance of OSA patients as increased ANP release and a decreased activity of this system concur to increase urine and Na^+ excretion and decrease vascular resistance. The lower plasma volume in the untreated compared with treated patients possibly results from these combined effects.

In the untreated state a dissociation between PRA and plasma aldosterone profiles was observed suggesting that the renin–angiotensin system was not the main factor stimulating aldosterone secretion. Evidence that ACTH plays a role in the regulation of aldosterone was demonstrated by the marked similarity of the plasma cortisol and aldosterone profiles. The possibility of an inhibitory effect of ANP must also be considered when discussing aldosterone regulation in the untreated OSA patients. ANP has been shown to act directly on adrenal zona glomerulosa cells (12,13), and as acute hypoxemia is a potent stimulus for ANP release (22,23), it is possibly an important factor responsible for the dissociation of aldosterone from the renin–angiotensin system under these conditions.

The close association between renin release and the REM–NREM sleep cycles, previously demonstrated in normal subjects (14), was persistent in OSA patients. Disturbed sleep was accompanied by almost flat PRA profiles with very small oscillations, whereas treatment, improving sleep, amplified the oscillations, which gave clear evidence of their relationship to sleep stages. In the treated patients, where a normalized sleep pattern was achieved, 38% of plasma aldosterone oscillations were in synchrony with those of PRA and, like PRA, showed a temporal relationship to sleep stages, which was similar to that previously described in normal subjects (15). In contrast in untreated patients the nocturnal aldosterone profiles demonstrate the lack of influence of the renin–angiotensin system due to reduced activity as indicated by the damped PRA oscillations. In this case the aldosterone profiles did not appear to relate closely to sleep stages and the relationship between aldosterone and sleep stages probably reflected that of ACTH and sleep stages (24).

In conclusion the results demonstrate that CPAP treatment of OSA patients, which diminished diuresis and natriuresis and increased plasma volume, is accompanied by increased renin and aldosterone release. These observations suggest that ANP may be in part responsible for the diminished activity of the renin–angiotensin–aldosterone system in untreated patients. The combined effects of these hormonal systems should result in a lower blood volume and lower blood pressure and appear as a protective mechanism against blood pressure rise in OSA patients. But in addition to these peripheral mechanisms controlling renin and aldosterone release, the activity of the juxtaglomerular cells depends on the processes governing sleep stage alternation, which consequently also influences aldosterone secretion.

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