ORIGINAL ARTICLE

Evaluation of Continuous Positive Airway Pressure Therapy on Renin–Angiotensin System Activity in Obstructive Sleep Apnea

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Abstract

Rationale: Obstructive sleep apnea (OSA) has been associated with kidney function loss, which may be related to changes in the renin–angiotensin system (RAS).

Objectives: We sought to determine the effect of continuous positive airway pressure (CPAP) of patients with OSA on renal hemodynamics at baseline and in response to angiotensin II (AngII), which reflects RAS activity.

Methods: Twenty normotensive, nondiabetic, newly diagnosed OSA subjects (15 men, 5 women, 50 ± 2 yr, respiratory disturbance index [RDI] $> 15\ h^{-1}$) with nocturnal hypoxemia ($Sa_{O_2} < 90\%$ for >12% of the night) were studied in high-salt balance pre- and post-CPAP therapy (>4 h CPAP use/night for 1 mo). Glomerular filtration rate (GFR), renal plasma flow (RPF), and filtration fraction (FF) (a surrogate marker for intraglomerular pressure) were measured pre- and post-CPAP using inulin and para-aminohippurate clearance techniques at baseline and in response to graded AngII infusion (3 ng/kg/min × 30 min and 6 ng/kg/min × 30 min, respectively).

Measurements and Main Results: CPAP corrected OSA and hypoxemia (RDI: 42 ± 4 vs. 4 ± 1 h^{-1}, $P < 0.001$; duration $Sa_{O_2} < 90\%$: 36% ± 5% vs. 6 ± 2%, $P < 0.001$). CPAP reduced GFR (124 ± 8 ml/min vs. 110 ± 6 ml/min, $P = 0.014$), increased RPF (692 ± 36 ml/min vs. 749 ± 40 ml/min, $P = 0.059$), and reduced baseline FF (18.9 ± 1.6% vs. 15.3 ± 1.0%, $P = 0.004$). Post-CPAP demonstrated a blunted GFR response (−9 ± 3 ml/min vs. −2 ± 2 ml/min, $P = 0.033$) and augmented RPF response (−182 ± 22 ml/min vs. −219 ± 25 ml/min, $P = 0.024$) to AngII. FF response was maintained ($P = 0.4$). CPAP reduced baseline mean arterial pressure (94 ± 2 vs. 89 ± 2 mm Hg, $P = 0.002$), plasma aldosterone (149 ± 18 vs. 109 ± 10 pmol/L, $P = 0.003$), and urinary protein excretion (61 [39–341] mg/day vs. 56 [22–204] mg/d, $P = 0.003$).

Conclusions: CPAP therapy was associated with improved renal hemodynamics and down-regulation of renal RAS activity, suggesting a potential therapeutic benefit for kidney function.

Keywords: continuous positive airway pressure; nocturnal hypoxemia; obstructive sleep apnea; renal hemodynamics; renin–angiotensin system

Obstructive sleep apnea (OSA) is highly prevalent in chronic kidney disease (CKD), occurring in 25–54% of patients (1–5). Nocturnal hypoxemia has also been associated with loss of kidney function (3, 6, 7). Importantly, continuous positive airway pressure (CPAP) is an effective treatment for OSA (8). The mechanism underlying the loss of renal function

(Received in original form March 19, 2014; accepted in final form July 14, 2014)

Supported by an establishment grant from Alberta Innovates–Health Solutions; the Cosmopolitan International Club of Calgary Graduate Scholarship, an American Society of Nephrology Student Scholar Grant, and the Foothills Medical Centre Sleep Centre Development Fund (D.D.M.N.); and Alberta Innovates–Health Solutions, the Canadian Institute of Health Research, and a joint initiative of Alberta Health and Wellness, the University of Alberta, and the University of Calgary (S.B.A.). M.J.P. holds the Brenda Strafford Foundation Chair for Alzheimer Research. Funding sources had no role in the design, conduct, or reporting of this study.

Author Contributions: Concept and design of study: D.D.M.N., P.J.H., and S.B.A. Acquisition, analysis and interpretation of the data: D.D.M.N., P.J.H., M.J.P., G.B.H., B.R.H., D.Y.S., and S.B.A. Drafting of the manuscript: D.D.M.N. and S.B.A. Review of manuscript for important intellectual content: D.D.M.N., P.J.H., M.J.P., G.B.H., B.R.H., D.Y.S., and S.B.A. Final approval of manuscript: D.D.M.N., P.J.H., M.J.P., G.B.H., B.R.H., D.Y.S., and S.B.A. Study supervision: S.B.A.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 190, Iss 5, pp 572–580, Sep 1, 2014

Originally Published in Press as DOI: 10.1164/rccm.201403-0526OC on July 17, 2014
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea (OSA) has been associated with loss of kidney function, and limited studies suggest a role for the renin–angiotensin system (RAS) in mediating the pathophysiology. Continuous positive airway pressure (CPAP) is an effective treatment for OSA, but the effect on the RAS remains unknown.

What This Study Adds to the Field: To our knowledge, this is first study to examine the effect of CPAP treatment on renal hemodynamics and the intrarenal RAS. Treatment of OSA with CPAP resulted in (*1*) reduced filtration fraction, (*2*) decreased baseline aldosterone levels, and (*3*) reduced renal RAS activity as reflected by the greater decrease in renal plasma flow in response to angiotensin II post-CPAP therapy. These findings suggest not only that treatment of OSA with CPAP reduces glomerular pressure, a marker of renal risk, but that the mechanism by which this occurs involves down-regulation of renal RAS activity. These findings support a role for the RAS in mediating OSA-induced hypertension and kidney disease in humans.

associated with OSA is unclear, but limited studies suggest a prominent role of the renin–angiotensin system (RAS), activation of which results in a predisposition to kidney and vascular disease (9).

The mechanism underlying the loss of renal function associated with OSA is unclear, though recently the role of kidney tissue hypoxia in the development of nephropathy has been highlighted (10). Limited studies suggest a prominent role of the RAS in the setting of chronic intermittent hypoxia (11–13), activation of which results in a predisposition to kidney and vascular disease (9). Multiple lines of evidence have underscored the importance of up-regulated RAS activity in both initiation and progression of kidney disease (14, 15). However, reports on the association between OSA and the RAS in humans are conflicting (16–22). One study reported OSA patients to have increased filtration fraction compared with healthy controls and CPAP therapy for 1 week improved filtration fraction, a marker of glomerular hyperfiltration and risk of kidney function loss in OSA patients not receiving RAS blockade therapy (22). However, to our knowledge, there have been no studies conducted to date in which researchers examined activity of the renal RAS as a primary outcome.

The high prevalence of OSA in the CKD population, coupled with the uncertainty of the effects of CPAP on kidney function and renal RAS activity, prompted our examination of the relationship between CPAP and change in renal hemodynamics as well as RAS activity in a cohort of otherwise healthy OSA patients before and after initiation of CPAP therapy. At present, there is no readily available means of assessing intrarenal RAS activity in humans. However, the renal plasma flow (RPF) response to infused angiotensin II (AngII) is an indirect measure of the intrinsic activity of the intrarenal RAS and, in the setting of high sodium balance, is inversely correlated with endogenous RAS activity (23–25). We hypothesized that use of CPAP therapy would result in an increase in the RPF vasoconstrictor response to AngII, signifying a decrease in renal RAS activity. Some of the results of this study have previously been reported in the form of an abstract (26).

Methods

Subjects

Subjects with OSA were recruited from community patients referred for suspected OSA to the Foothills Medical Centre Sleep Centre and a respiratory home care company (Healthy Heart Sleep Co.), both in Calgary, Alberta, Canada, between June 2011 and May 2012. Men and women ages 18–70 years with moderate to severe OSA and significant nocturnal hypoxemia were eligible to participate in the study. All subjects underwent a medical history, physical examination, and laboratory screening. Exclusion criteria included cardiovascular, cerebrovascular, and kidney disease; uncontrolled hypertension (blood pressure [BP] >140/90 mm Hg despite maximal use of antihypertensive medications); diabetes mellitus; severe lung disease; current treatment for OSA; current smoking; pregnancy; and use of nonsteroidal anti-inflammatory medications or exogenous sex hormones. The study protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Written informed consent was obtained from all study subjects in accordance with the Declaration of Helsinki.

Sleep Apnea and Hypoxemia Assessment

Additional details on the method used to assess severity of OSA and hypoxemia status are provided in an online supplement. Briefly, subjects performed an unattended, overnight cardiopulmonary monitoring examination at home (Remmers Sleep Recorder Model 4.2; Saga Tech Electronic, Calgary, AB, Canada), which has been validated by comparison to attended polysomnography (27, 28). Sleep apnea was defined as a respiratory disturbance index (RDI) $\geqslant$ 15, as this reflects moderate to severe sleep apnea that is likely to be clinically significant (27, 28). Nocturnal hypoxemia was defined as in other studies (29) as a $Sa_{O_2} < 90\%$ for $\geqslant$12% of the duration of nocturnal monitoring.

Study Protocol

The study protocol we used for assessment of RAS activity is well-established (23, 25, 30, 31), and additional details are provided in an online supplement. Glomerular filtration rate (GFR), RPF, BP, and circulating RAS components (plasma renin activity [PRA] and aldosterone) were measured at baseline and in response to AngII challenge (3 ng/kg/min $\times$ 30 min, 6 ng/kg/min $\times$ 30 min, respectively) as an index of RAS activity (23, 25, 30, 31) followed by a 30-minute recovery period. Blood samples were collected at baseline and every 30 minutes thereafter throughout the study period. All subjects provided a second morning spot urine for determination of urinary sodium to verify compliance with the high-salt diet (32). Subjects on medications which interfere with RAS activity were switched to a calcium-channel blocker (amlodopine) to achieve adequate BP control 2 weeks prior to each study day, as these agents are considered to have a neutral effect on the RAS (33). BP was recorded every 15 minutes with an automatic recording device (Critikon DINAMAP ProCare Monitor; GE Medical Systems, Milwaukee, WI). Subjects were studied in the supine position using

a standard cuff placed on the right arm. The mean of two readings taken by the same registered nurse (D.Y.S.) were recorded. Mean arterial pressure (MAP) was calculated as one-third systolic BP (SBP) and two-thirds diastolic BP (DBP). Filtration fraction (FF), a surrogate marker of glomerular pressure, was calculated as the GFR/RPF ratio. Renal vascular resistance (RVR) was calculated as the MAP/RPF ratio. Details regarding laboratory measurements are provided in an online supplement.

CPAP Treatment

After completing the first study day, subjects were treated with CPAP therapy as per the guidelines for treatment of OSA (8). All subjects underwent an auto-CPAP trial to determine individual CPAP requirement. Initial auto-CPAP settings were 16/6 cm H_2O and were automatically titrated according to the CPAP unit titration algorithm to optimize therapy. If airflow limitation or nocturnal hypoxemia was not fully corrected, subjects were switched to fixed CPAP, which was estimated from the CPAP level at the 95th percentile. Adherence to CPAP therapy was monitored by electronic download from the unit each month. Once satisfactory CPAP adherence was achieved (defined as CPAP use for >4 h/night on >70% nights for 4 wk) (8) and correction of OSA and nocturnal hypoxemia was confirmed by a repeat Level 3 sleep test while using CPAP, subjects underwent reassessment of RAS activity and kidney function identical to the pre-CPAP assessment during a second study day.

Analysis

Data are reported as mean ± SE, number (percentage), or median (range) as appropriate. Our primary outcomes were the changes (Δ) in renal hemodynamics (GFR, RPF, FF, and RVR) at baseline and in response to AngII (3 ng/kg/min and 6 ng/kg/min, respectively) as a measure of renal RAS activity pre- and post-CPAP therapy. Secondary study outcomes were the changes in BP, PRA, and aldosterone at baseline and in response to AngII pre- and post-CPAP. Pre- and post-CPAP comparisons were made using the Wilcoxon signed-rank test. To examine the response to AngII on each study day, we conducted a repeated-measures analysis of variance with a Bonferroni correction for outcomes with multiple measurements.

Sensitivity analyses were conducted excluding subjects with controlled hypertension, female subjects, and subjects with persistent nocturnal hypoxemia while on CPAP. We sought to determine if the observed differences in our results were due to other variables known to affect the RAS by performing sensitivity analyses. All statistical analyses were performed with the statistical software package SPSS version 17.0 (SPSS, Chicago, IL) and were two-tailed with a significance level of 0.05.

Results

Study Enrollment

Twenty-nine OSA subjects were enrolled in the study and completed Study Day 1. Twenty OSA subjects completed the study and were included in the final analyses. Nine subjects discontinued CPAP and were lost to follow-up. Subjects who withdrew from the study did not differ from subjects who completed the study (*see* Table E1 in the online supplement). One subject ingested a single dose of the AngII receptor blocker (ARB) candesartan the morning of the first study day. This subject was studied in an identical fashion post-CPAP therapy, including ingestion of candesartan, to allow for comparison of pre–post CPAP results. This subject was included in the primary analyses, but excluded in a sensitivity analysis.

Subject Characteristics

Subject characteristics are presented in Table 1. Twenty newly diagnosed OSA subjects with nocturnal hypoxemia were recruited (15 men and 5 women [1 premenopausal, 4 postmenopausal]; age = 50 [29–68] years). All had BP < 140/90 mm Hg, and none were taking medications that act on the RAS at the time of kidney function assessment. Seven subjects were on antihypertensive medications, which included calcium-channel blocker (n = 3), angiotensin-converting enzyme (ACE) inhibitor (n = 2), angiotensin receptor blocker (n = 2), β-blocker (n = 1). One subject was on dual therapy (calcium-channel blocker and ACE inhibitor). ACE inhibitors, angiotensin receptor blockers, and β-blockers were switched to the calcium-channel blocker amlodipine to control BP 2 weeks prior to each assessment of the RAS and kidney function, as this class of medication has been shown to have minimal interference with the RAS (33). All subjects were nondiabetic nonsmokers with normal kidney function and in high-salt balance.

CPAP Therapy

All subjects were adherent with CPAP therapy, which corrected their OSA and nocturnal hypoxemia (Tables 1 and E2). Duration to acclimatize to CPAP was 142 [68–261] days. During the 4-week period prior to reassessment of their renal function, CPAP was used on 92 ± 2% of nights (81 ± 4% with usage >4 h/night), with an average nightly usage of 6.4 ± 0.3 h/night, indicating very good CPAP adherence. Sixteen subjects completed the study on auto-CPAP, and four subjects were converted to fixed CPAP to optimize therapy. Final CPAP prescriptions are reported in the online supplement. All subjects met acceptable criteria for correction of OSA (RDI <10/h), and nocturnal hypoxemia was corrected in all but three subjects (duration Sa_{O_2} < 90% for <12% monitoring time). In those three subjects, the post-CPAP mean Sa_{O_2} was >90%. A sensitivity analysis excluding these three subjects showed similar results.

Pre- versus Post-CPAP Therapy

Baseline characteristics. Changes in baseline characteristics are reported in Table 1. Fasting blood glucose, Vitamin D, and urine sodium and potassium excretion did not change post-CPAP therapy. Body mass index (BMI) was higher post-CPAP therapy.

CPAP treatment improved baseline renal hemodynamics (Figure 1), manifested by reductions in GFR, FF, and RVR, and led to a borderline increase in RPF. Reductions in urinary total protein excretion and BP indices were also observed. There were no changes in circulating levels of PRA or AngII post-CPAP. However, there was a significant reduction in serum aldosterone levels post-CPAP therapy (Figure 2).

Responses to angiotensin II. Responses to AngII pre- and post-CPAP therapy are reported in Table 2. As anticipated, all subjects demonstrated significant changes in RPF, FF, RVR, all BP indices, PRA, and aldosterone (all P-values < 0.001) in

Table 1. Baseline Characteristics (N = 20)

Parameter	Pre-CPAP	Post-CPAP	*P* Value
Age, yr	50 ± 2	–	–
Gender, n (%) male	15 (75)	–	–
Race, n (%) white	14 (60)	–	–
BMI, kg/m^2	33 ± 1	34 ± 1	0.033
Urinary Na^+, mmol/d	375 ± 24	353 ± 27	0.083
Urinary K^+, mmol/d	86 ± 3	87 ± 5	1.0
Fasting glucose, mmol/L	4.8 ± 0.1	4.9 ± 0.1	0.6
25′OH Vitamin D, nmol/L	65 ± 5	70 ± 5	0.2
Heart rate, beats/min	67 ± 2	64 ± 2	0.2
RDI, h^{-1}	41.7 ± 4.2	3.8 ± 0.6	<0.001
Sa_{O_2} < 90, % monitoring time	35.8 ± 5.1	5.6 ± 2.0	<0.001
Mean Sa_{O_2}, %	90.0 ± 0.5	92.5 ± 0.3	<0.001
Minimum Sa_{O_2}, %	72.3 ± 1.2	85.8 ± 0.8	<0.001
GFR, ml/min*	124 ± 8	110 ± 6	0.014
RPF, ml/min*†	692 ± 36	749 ± 40	0.059
FF, %*†	18.9 ± 1.6	15.3 ± 1.0	0.004
RVR, mm Hg/ml/min*†	0.14 ± 0.01	0.12 ± 0.01	0.003
UTPE, mg/d‡	61 (39–341)	56 (22–204)	0.003
SBP, mm Hg*	127 ± 3	121 ± 2	0.026
DBP, mm Hg*	78 ± 2	73 ± 2	0.002
MAP, mm Hg*	94 ± 2	89 ± 2	0.002
PRA, ng/L/s‡	0.24 (0.06–6.03)	0.22 (0.01–4.33)	0.6
AngII, ng/L‡	18 (12–48)	16 (12–73)	1.0
Aldosterone, pmol/L	149 ± 18	109 ± 10	0.003

Definition of abbreviations: AngII = angiotensin II; BMI = body mass index; CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; GFR = glomerular filtration rate; FF = filtration fraction; MAP = mean arterial pressure; PRA = plasma renin activity; RDI = respiratory disturbance index; RPF = renal plasma flow; RVR = renal vascular resistance; Sa_{O_2} = oxyhemoglobin saturation; SBP = systolic blood pressure; UTPE = urinary total protein excretion.
*Mean of two readings.
†*N* = 19.
‡Median (range).

response to AngII challenge compared with baseline values in both the pre- and post-CPAP states. However, although pre-CPAP subjects showed a significant decline in GFR in response to 3 ng/kg/min AngII ($P = 0.02$), GFR was maintained in response to the same AngII dose post-CPAP ($P = 0.8$, $P = 0.03$ vs. pre-CPAP state) (Figure 3A). No differences in the GFR response to 6 ng/kg/min AngII were observed pre- and post-CPAP. Conversely, although there was no difference in the RPF response to the low dose of AngII pre- versus post-CPAP ($P = 0.2$), there was a significantly greater decrease in RPF in response to the higher dose of AngII post-CPAP ($P = 0.02$) (Figure 3B). There were no changes in the FF or RVR responses post-CPAP therapy.

Study subjects initially demonstrated increased DBP sensitivity, manifested as a greater DBP increase in response to AngII, at 15 minutes post-CPAP therapy compared with pre-CPAP ($P = 0.02$). The MAP response followed a similar pattern. No other differences in the BP responses to AngII were observed. There were no differences in PRA or aldosterone sensitivity to AngII pre- versus post-CPAP therapy.

Sensitivity analyses. Exclusion of the subject who took candesartan did not alter our results. Similarly, exclusion of the seven subjects with controlled hypertension did not alter our primary findings. Neither exclusion of the five female subjects nor removal of the three subjects with persistent hypoxemia while using CPAP significantly altered our findings.

Discussion

We examined RAS activity in humans with OSA before and after CPAP therapy. To our knowledge, this is first study in which the effect of CPAP treatment on the renal hemodynamic, circulating RAS, and BP responses to an AngII challenge, a well-accepted indirect measure of RAS activity (23, 25, 30, 31), has been examined. Our primary findings are that treatment of OSA with CPAP resulted in (*1*) reduced filtration fraction, (*2*) decreased baseline aldosterone levels, and (*3*) reduced renal RAS activity as reflected by the greater decrease in RPF in response to AngII post-CPAP therapy. These findings suggest not only that treatment of OSA with CPAP reduce filtration fraction, a marker of renal and cardiovascular risk (34–37), but that the mechanism by which this occurs is through down-regulation of renal RAS activity. These findings support a role for the RAS in mediating OSA-induced hypertension and kidney disease in humans. CPAP down-regulates RAS activity, which may be a contributory mechanism by which CPAP therapy decreases BP and maintains normotension in OSA patients (38).

We and others have shown that OSA is associated with altered RAS activity (16–19, 22, 26, 39–41). Several studies have examined the effect of CPAP therapy on components of the RAS. Follenius and colleagues reported that 1 night of CPAP therapy increased PRA and aldosterone levels (40), whereas Saarelainen and colleagues reported a decrease in plasma aldosterone but no change in renin after 3 months of CPAP treatment in 11 male hypertensive subjects without other comorbidities (39). In a randomized trial of 101 male OSA subjects randomized to therapeutic or sham CPAP therapy, there were no differences in renin levels post-CPAP therapy but equivalent increases in aldosterone levels after 1 month (41). Moller and colleagues administered CPAP to 13 OSA patients for 14 months and found no statistically significant reductions in renin or AngII (18). However, CPAP therapy reduced BP, and the reduction in BP was correlated with a decrease in both plasma renin and AngII concentrations (18). Svatikova and colleagues compared aldosterone and renin levels in 21 OSA patients without coexisting cardiovascular disease to those of similarly obese healthy control subjects (21). The authors found that neither OSA nor CPAP treatment acutely affected overnight plasma aldosterone or renin levels (21). Similarly to Saarelainen and colleagues, we found a reduction in plasma aldosterone but no change in PRA or AngII. The discrepancies in findings likely reflect differences in baseline hypertension, use of antihypertensive medications, duration and adherence to CPAP therapy, presence of comorbidities, and severity of OSA and/or

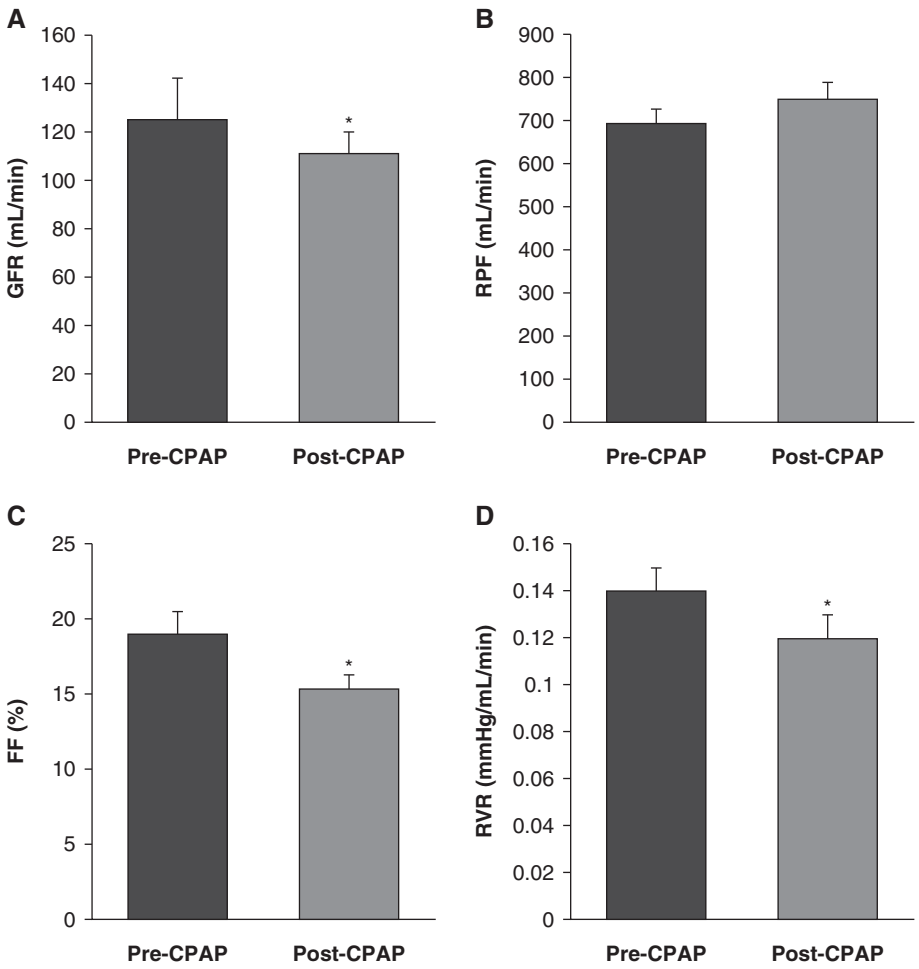

Figure 1. Baseline renal hemodynamics pre- and post-CPAP therapy. *$P < 0.05$ versus pre-CPAP. CPAP = continuous positive airway pressure; FF = filtration fraction; GFR = glomerular filtration rate; RPF = renal plasma flow; RVR = renal vascular resistance.

hypoxemia. These studies are limited because they included only male subjects and did not quantify or examine the hypoxemia profile of their subjects, and, most important, a majority did not control for salt intake, kidney function, or other factors known to affect the RAS. Hence, the mechanistic relationship between OSA and the RAS in patients without comorbidities remains unclear. Our study addresses several of the limitations of these previous studies. We included women and subjects with significant nocturnal hypoxemia and controlled for factors known to affect the RAS.

To our knowledge, researchers in only one previous study have examined the effect of CPAP on kidney function. Kinebuchi and colleagues reported that OSA patients have increased FF and reduced RPF compared to controls (22). Most importantly, and consistent with our findings, treatment of OSA with CPAP therapy for 1 week resulted in a significant reduction in FF, which was mediated by an increase in RPF (22). Although the mechanism for the decrease in FF was not evaluated, a sensitivity analysis showed that it was limited to patients who were not receiving RAS blockade (22), thereby implicating a role for the RAS. We confirm and extend the findings of Kinebuchi and colleagues by demonstrating that the decrease in filtration fraction associated with CPAP is mediated through a RAS-dependent mechanism, as indicated by the increased RPF sensitivity to AngII. The discordance observed between the GFR and RPF responses has been reported in previous studies (31, 42, 43). It likely reflects differences between the various renal vascular beds. AngII is a powerful endogenous vasoconstrictor with selective action on the renal blood supply (9). Consequently, even small changes in concentration lead to renal vasoconstriction and a decrease in RPF (44), though the impact of AngII on GFR is far less predictable. Furthermore, the enhanced renovascular response to AngII in the post-CPAP period compared with the pre-CPAP period was not reflected in the BP, plasma renin activity, or AngII responses to AngII challenge, which were not different between the study days, thus suggesting only a difference in RAS activation at the level of the kidney.

Although RAS blockade has been shown to be more effective than CPAP in reducing BP in hypertensive OSA subjects, it remains unclear which treatment has the most value in the kidney function of OSA patients without hypertension or in OSA patients with CKD (45). However, RAS blockade does not mitigate the daytime symptoms of OSA, whereas CPAP therapy effectively improves cognitive function, daytime sleepiness, and quality of life (46). In patients for whom CPAP treatment is not feasible, consideration should be given to prescribing a medication that blocks RAS activity (16, 45). Combined CPAP and RAS blockade therapy may be more effective (45) and is an important area of future study.

There is growing recognition of the consequences of increased aldosterone secretion and its contributions to hypertension (16, 17, 47–50). Treatment with aldosterone antagonists reduces morbidity, mortality, and hospitalizations in patients with hypertension and systolic heart failure (47–49). Administration of the aldosterone antagonist spironolactone for 8 weeks has been reported to attenuate OSA severity by ~50% in subjects with treatment-resistant hypertension (16). The results of our present study suggest that CPAP therapy is effective in lowering

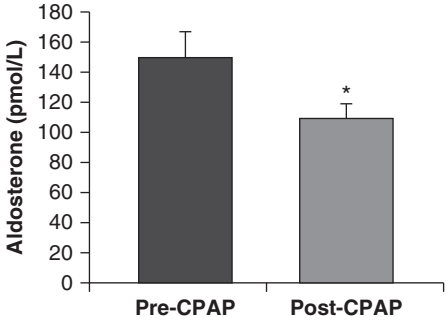

Figure 2. Baseline plasma aldosterone pre- and post-CPAP therapy. *$P < 0.01$ versus pre-CPAP. CPAP = continuous positive airway pressure.

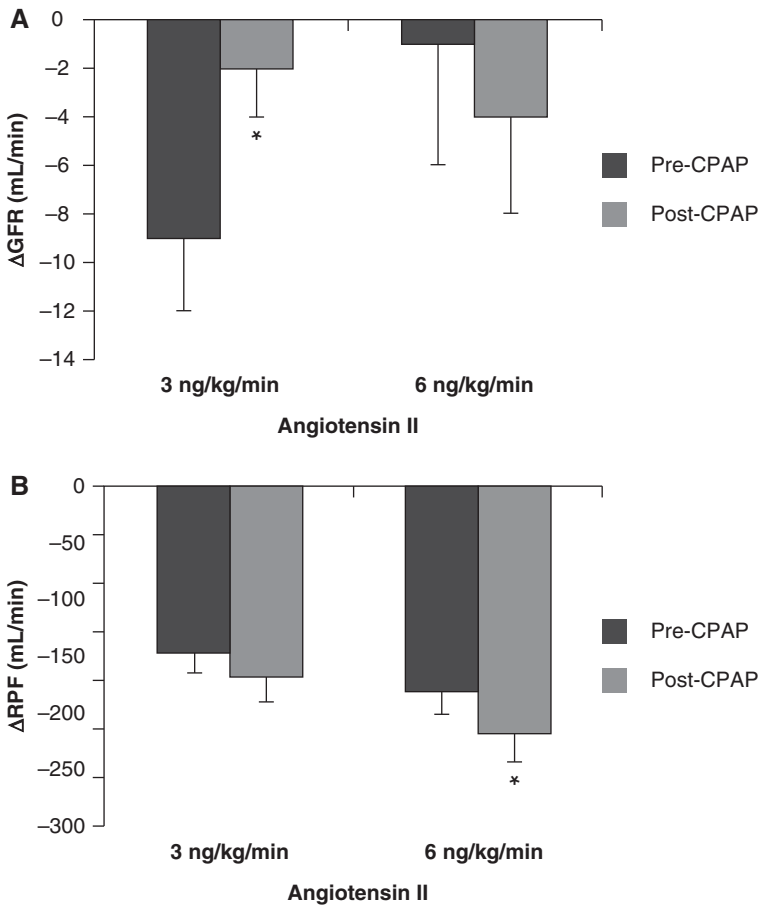

Figure 3. Renal hemodynamic responses to angiotensin II infusion pre- and post-CPAP therapy. *$P < 0.05$ versus pre-CPAP. CPAP = continuous positive airway pressure; GFR = glomerular filtration rate; RPF = renal plasma flow.

circulating aldosterone levels. Aldosterone excess has been hypothesized to contribute to OSA through increased sodium and water retention, thus promoting tissue edema localized to the neck in the supine position and leading to airway obstruction and worsening of OSA (50).

Our study has several strengths. We utilized a well-accepted measure of RAS activity (23, 25, 30, 31) and controlled for factors known to affect the RAS, such as salt intake, exogenous hormone use, and menstrual status. All subjects had newly diagnosed and untreated moderate to severe OSA with marked nocturnal hypoxemia, suggesting that any of the effects of OSA and CPAP therapy on the RAS should have been evident in our study population. We included only subjects with BP <140/90 mm Hg who had no other coexisting diseases and were not taking medications known to alter RAS activity. The pre–post CPAP study design allowed us to comment on causality and to assess the effect of CPAP on RAS activity independent of age, sex, obesity, and other residual confounders, including salt balance, as all subjects were in a high-salt state, a state of maximal RAS suppression (25). The mild increase in BMI observed post-CPAP in OSA patients has been reported previously (51–53), and, although this may have been due to fluid retention, it is unlikely to have affected the RAS, owing to similarities in salt balance. Increased BMI has been associated with increased RAS activity in humans (54); thus, it is possible that the decrease in RAS activity associated with CPAP in our study may actually have been an underestimate. Further, we included women as well as subjects with controlled hypertension, thereby increasing the generalizability and clinical implications of our results.

We did not examine the specificity of the responses to AngII. However, in animal studies, researchers who have examined the vasoconstrictor effect of AngII and the non-AngII vasoconstrictor norepinephrine have demonstrated that the renal vasculature's responsiveness to AngII is specific (55). Further, in healthy humans, norepinephrine and AngII have been demonstrated to have different effects on control of the renal blood supply (56). Hence, we do not believe that we would have observed similar changes with the utilization of a non-AngII vasoconstrictor agent.

Notwithstanding these strengths, our study has limitations. First, our study sample was limited to OSA subjects without comorbidities, thus limiting the generalizability of our study results. However, by studying a healthier population of OSA subjects, we were able to examine the impact of CPAP therapy on renal hemodynamics, BP, and circulating RAS components without confounding factors. Further, by design, we included only subjects with both moderate to severe OSA and significant nocturnal hypoxemia. Consequently, it remains unclear whether it was the correction of apnea or intermittent hypoxemia that was responsible for our findings. Certainly, the results of our sensitivity analyses excluding the subjects with partially corrected hypoxemia suggest that treatment of intermittent hypoxemia provides additional benefit with regard to RAS activity. Second, our sample size was relatively small, and our study did not include control groups of non-OSA subjects, hypertensive OSA subjects, or poorly compliant OSA subjects, which may limit the generalizability of the results. However, we attempted to minimize the effect of sample size, intraindividual variability and comorbid disease by utilizing a homogeneous study group and careful prestudy design. Although we included no control group, conditions during the assessment of RAS and kidney function were standardized to minimize any potential effect of confounders. Specifically, subjects were studied in the morning to account for circadian variations in the RAS (57), in a high-salt state to ensure maximal suppression of the RAS (58), during the same stage of the menstrual cycle to eliminate estrogen-mediated RAS differences (59), and all subjects were free of medications known to alter RAS activity and exogenous sex hormones. As such, it is unlikely that the observed changes in RAS activity and renal function were due to

Table 2. Responses to Angiotensin II Infusion (N = 20)

Parameter	Pre-CPAP	Post-CPAP	*P*-Value
ΔGFR, ml/min*			
3 ng/kg/min	−9 ± 3†	−2 ± 2	0.033
6 ng/kg/min	−1 ± 5	−4 ± 1†	1.0
ΔRPF, ml/min*‡			
3 ng/kg/min	−148 ± 17†	−169 ± 20†	0.2
6 ng/kg/min	−182 ± 22†	−219 ± 25†	0.024
ΔFF, %*‡			
3 ng/kg/min	3.1 ± 0.8†	3.9 ± 0.5†	0.4
6 ng/kg/min	6.0 ± 1.2†	5.7 ± 0.5†	0.6
ΔRVR, mm Hg/ml/min*‡			
3 ng/kg/min	−0.07 ± 0.03†	−0.13 ± 0.03†	0.4
6 ng/kg/min	−0.10 ± 0.02†	−0.10 ± 0.01†	0.8
ΔSBP, mm Hg*			
3 ng/kg/min × 15 min	15 ± 2†	18 ± 3†	0.2
3 ng/kg/min × 30 min	17 ± 3†	18 ± 3†	0.9
6 ng/kg/min × 15 min	25 ± 3†	27 ± 3†	0.3
6 ng/kg/min × 30 min	23 ± 3†	26 ± 4†	0.2
ΔDBP, mm Hg*			
3 ng/kg/min × 15 min	8 ± 1†	11 ± 1†	0.016
3 ng/kg/min × 30 min	10 ± 2†	11 ± 1†	0.2
6 ng/kg/min × 15 min	13 ± 2†	15 ± 1†	0.2
6 ng/kg/min × 30 min	12 ± 2†	14 ± 1†	0.5
ΔMAP, mm Hg*			
3 ng/kg/min × 15 min	10 ± 1†	14 ± 2†	0.032
3 ng/kg/min × 30 min	12 ± 2†	14 ± 2†	0.2
6 ng/kg/min × 15 min	17 ± 1†	19 ± 2†	0.3
6 ng/kg/min × 30 min	16 ± 2†	18 ± 2†	0.4
ΔPRA, ng/L/s			
3 ng/kg/min	−0.08 ± 0.01†	−0.09 ± 0.02†	0.7
6 ng/kg/min	−0.18 ± 0.05†	−0.15 ± 0.04†	0.6
ΔAldosterone, pmol/L			
3 ng/kg/min	139 ± 15†	150 ± 19†	0.6
6 ng/kg/min	214 ± 23†	239 ± 28†	0.2

List of abbreviations: CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; GFR = glomerular filtration rate; FF = filtration fraction; MAP = mean arterial pressure; PRA = plasma renin activity; RPF = renal plasma flow; RVR = renal vascular resistance; SBP = systolic blood pressure.
*Mean of two readings.
†$P < 0.05$ versus baseline.
‡$N = 19$.

factors other than treatment with CPAP. Third, the duration that patients used CPAP prior to reassessment of the RAS varied because of differences in the ability of individual patients to become acclimated to it, which is well-recognized in patients with OSA (60, 61). However, by ensuring that all subjects were on effective CPAP therapy for the same amount of time (4 wk) before their RAS and kidney function were reassessed, we were able to standardize this intervention and determine the effect of OSA treatment on RAS activity. Fourth, we used an indirect measure of RAS activity because it is not feasible to measure vascular RAS activity directly in humans, and thus it is possible that the observations of this study may simply reflect a generalized impairment in endothelial function. Notwithstanding this limitation, the response to AngII challenge is a well-accepted and validated measure of RAS activity (23, 25, 30, 31, 62). It has been shown that the RPF response to AngII challenge is highly correlated with the RPF response to ACE inhibition in human subjects (63–65). Although indirect, this approach to testing the hypothesis that the RPF response to AngII challenge truly represents activation of the intrarenal RAS is one of the few methods available in humans. Furthermore, the enhanced renovascular response to AngII in the post-CPAP period compared to the pre-CPAP period was not reflected in the BP, plasma renin activity, and AngII levels, which were not different between the study days, thus suggesting a difference in RAS activation only at the level of the kidney. Fifth, we used portable monitoring instead of polysomnography both to diagnose OSA and to evaluate patients' response to CPAP treatment. However, the use of portable monitoring was appropriate for the population we studied according to current guidelines (8). Further, the findings are objective and unequivocal. Sixth, the duration of CPAP therapy may have been insufficient to demonstrate its full benefits with regard to RAS activity. However, the treatment period we chose has been shown to improve other cardiovascular outcomes in previous studies (66, 67).

In this community-based OSA population, CPAP therapy was associated with an improvement in renal hemodynamics and a down-regulation of renal RAS activity, suggesting a potential therapeutic benefit of this therapy for kidney function. Although it remains unclear whether the effects of CPAP on the kidney persist after treatment is discontinued, or if timing of initiation or duration of use plays a role, the association between CPAP therapy and improvement in renal and RAS parameters in our study merits further attention. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the FMC Sleep Centre for patient recruitment and sleep diagnostic testing.

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