Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome

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ABSTRACT

Patients with OSAS (obstructive sleep apnoea syndrome) demonstrate renal signs such as proteinuria, glomerular hypertrophy and focal glomerular sclerosis. We performed a clinical study to investigate the glomerular function in OSAS patients and the short-term effect of CPAP (continuous positive airway pressure) on it. OSAS patients underwent a sodium thiosulphate and p-aminohippurate double clearance test, polysomnography and ambulatory blood pressure monitoring before and a week after the induction of CPAP. Twenty-seven consecutive patients (24 males) with moderate-to-severe OSAS admitted to our hospital for the induction of CPAP, and 32 healthy donors for renal transplantation as controls participated in the study. Before treatment, the glomerular filtration rate, estimated by the sodium thiosulphate clearance test, was within normal range, and the renal plasma flow was significantly lower than normal in the OSAS patients, thus the FF (filtration fraction) value was much higher than normal. FF before CPAP was not significantly correlated with age, body mass index or blood pressure; however, indices of increased hypoxaemia correlated with increased FF values. Polysomnographic variables after CPAP showed significant improvements in all patients, and only the nocturnal blood pressures were slightly lower than before CPAP. In 21 patients who underwent the clearance test after CPAP, FF significantly decreased from 0.26 ± 0.04 to 0.23 ± 0.03 (P < 0.001). OSAS patients were generally in a glomerular-hyperfiltrating condition that appeared to cause the renal findings associated with OSAS. CPAP might prevent nephropathy by ameliorating the glomerular hyperfiltration in OSAS patients.

Key words: filtration fraction, kidney function, renal plasma flow, sleep-disordered breathing, treatment outcome.

Abbreviations: AASM, American Academy of Sleep Medicine; ACE-i, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; AHI, apnoea/hypopnoea index; ANP, atrial natriuretic peptide; BMI, body mass index; CPAP, continuous positive airway pressure; CThio, sodium thiosulphate clearance; FF, filtration fraction; GFR, glomerular filtration rate; OSAS, obstructive sleep apnoea syndrome; PAH, p-aminohippurate; CPAH, PAH clearance; RPF, renal plasma flow; SpO2, oxygen saturation; CT90 %, cumulative percentage of sleep time with SpO2 below 90 %.

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INTRODUCTION

Patients with OSAS (obstructive sleep apnoea syndrome) sometimes demonstrate proteinuria, which occasionally develops to the nephrotic stage and is associated with renal dysfunction [1–8]. Glomerular hypertrophy and/or focal segmental glomerulosclerosis are characteristic histological findings in biopsy studies of these patients [1–3,9]. Generally, proteinuria, glomerular hypertrophy and focal segmental glomerulosclerosis are considered to be the consequences of glomerular overload [10], which can be assessed by elevated FF (filtration fraction) levels in clinical practice. Although there have been a few reports on renal function in patients with OSAS [11–13], whether OSAS is associated with glomerular hyperfiltration remains unknown.

Thus we performed a clinical study to investigate the renal function in patients with OSAS, paying special attention to FF levels. We investigated further the short-term effect of CPAP (continuous positive airway pressure) on the change in glomerular function.

METHODS

Subjects
The study was planned according to the Ethics Guidelines of the Helsinki Declaration, and was approved by the Institutional Research Ethics Board at Niigata University Medical Hospital. Twenty-seven patients (24 males and 3 females) with moderate-to-severe OSAS diagnosed on the basis of polysomnography, who had been admitted to our hospital for the induction of CPAP treatment, were consecutively enrolled in the study from May 2000 to May 2002. Patients with a history of renal failure, cardiac failure or diabetes were excluded from the study. The clinical characteristics of the 27 patients are summarized in Table 1.

All except one patient had normal vital capacity and three had mild airway obstruction. Fifteen patients had a history of hypertension and were treated with antihypertensive drugs. Antihypertensive medication included calcium blockers (n = 13), ACE-i (angiotensin-converting-enzyme inhibitors; n = 4), ARB (angiotensin receptor blockers; n = 4), α1 blockers (n = 3), β-blockers (n = 1) and diuretics (n = 1). The medication was unchanged during the study. All the participants were duly informed about the study protocol and written consent was obtained before the study.

Healthy donors (n = 32) for living related kidney transplantation, who underwent a standard sodium thiosulphate and PAH (p-aminobenzoic acid) double clearance test before the operation, were enrolled as controls for normal renal function. Renal biopsy studies performed at the operation for renal removal revealed that none of them had significant glomerular lesions.

<table>
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<th>Table 1 Characteristics of OSAS patients and controls</th>
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<td>Values are mean ± S.D. **P &lt; 0.001 compared with OSAS patients. FEV1, %, forced expiratory volume in 1 s as a percentage of the forced vital capacity; %VC, percentage vital capacity.</td>
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<td>OSAS patients</td>
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<td>Age (year)</td>
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Polysomnography
Polysomnography (Somnostar; SensorMedics, Yorba Linda, CA, U.S.A.) included the following measurements: EEG, electromyogram, electro-oculogram, ECG, airflow by oronasal thermistor, chest and abdominal wall movements, SpO₂ (oxygen saturation) by pulse oximeter, snoring sounds by tracheal microphone and body position. The findings were defined according to the recommendations advocated by the AASM (American Academy of Sleep Medicine) task force in 1999 [14]. Briefly, apnoea was defined as the complete absence of oronasal airflow for at least 10 s. Hypopnoea was defined as a > 50 % decrease in oronasal airflow accompanied by a 3 % fall in SpO₂ from baseline or an EEG arousal from sleep. Sleep-disordered breathing was assessed by AHI (apnoea/hypopnoea index), lowest SpO₂ and CT90 % (cumulative percentage of sleep time with SpO₂ below 90 %). A second polysomnography was performed a week after CPAP induction to determine the effect of CPAP on the sleep-disordered breathing.

CPAP
After the baseline assessment of the patients, CPAP therapy was introduced if (i) AHI was > 30 events/h, regardless of symptoms, or (ii) AHI was 5–30 events/h accompanied by symptoms of excessive daytime sleepiness, impaired cognition, mood disorder or insomnia, as suggested by the consensus statement of the American College of Chest Physicians [15]. Either of two CPAP devices [Tranquility–Auto (Respironics, Murraysville, PA, U.S.A.) and Goodnight 418P (Tyco Healthcare, Villers-les-Nancy, France)] were used in auto–CPAP mode. The read out of the compliance (average h/day) was obtained from the integrated processor using commercial software (Encore; Respironics; or Silverlining 2; Tyco Health Care).
Diurnal renal function test

On the day before the initiation of CPAP, all patients underwent a standard sodium thiosulphate and PAH double clearance test [16]. In brief, it was performed during the daytime (between 14:00 and 15:00 hours) with a constant infusion of sodium thiosulphate and PAH, and two blood samples were taken in 20 min and catheterized urinary collection between the samplings. GFR (glomerular filtration rate) was estimated by CThio (sodium thiosulphate clearance), which was calculated as follows: CThio (ml/min) = urinary sodium thiosulphate level x urinary volume (ml)/mean serum sodium thiosulphate level during the clearance study/clearance time (min) x 1.73/body surface area. RPF (renal plasma flow) was estimated by CPAH (PAH clearance), which was calculated as follows: CPAH (ml/min) = urinary PAH level x urinary volume (ml)/mean serum PAH level during the clearance study/clearance time (min) x 1.73/body surface area. FF was calculated as the ratio of CThio/CPAH. A second double clearance test was performed the day after the second polysomnography.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (Takeda TM-2421, A&D, Tokyo, Japan) for 24 h was performed in 27 patients; 10 of these were only monitored before and the other 17, who had hypertension (> 140/90 mmHg) and/or hypertensive medication, were monitored both before and a week after CPAP. Blood pressure was measured every 30 min during the day (06:00–22:00 hours) and every hour during the night (22:00–06:00 hours). Diurnal (09:00–21:00 hours) and nocturnal (24:00–06:00 hours) blood pressures were compared before and after CPAP. Mean values of systolic, diastolic and mean blood pressures were calculated for each period.

Statistical analysis

Data are expressed as means ± S.D. Correlations between FF and various parameters before the induction of CPAP were determined by simple linear regression analysis. Multiple regression analysis was used for the further examination of the association of independent factors with OSAS, such as BMI (body mass index), age, sex, blood pressure and AHI and desaturation indices. The data before and after CPAP were compared using the Wilcoxon signed-rank test. A P value < 0.05 was considered significant. The analysis was performed using GB-STAT version 8.0 software (Dynamic Microsystems, Silver Spring, MD, U.S.A.).

RESULTS

Moderate-to-severe OSAS was diagnosed in all 27 patients who underwent polysomnography, according to the AASM recommendation, and nocturnal nasal CPAP therapy was introduced. The body weight of the patients did not change 1 week after the induction of CPAP therapy.

CThio levels in the 27 OSAS patients before CPAP induction were comparable with those in the 32 controls (122.6 ± 40.9 compared with 136.6 ± 31.7 ml/min; P value is not significant). However, FF levels were significantly higher in patients with OSAS (Table 1).

Figure 1 shows the correlation between FF and respiratory parameters before the induction of CPAP. There was no significant correlation between FF and AHI (r = 0.35, P = 0.07). However, FF was significantly correlated with the lowest $SpO_2$ (r = -0.62, P < 0.001) and CT90% (r = 0.44, P = 0.02). FF was not correlated with age, BMI or blood pressure. Multiple regression analysis showed that the lowest $SpO_2$ was the only
The results of ambulatory blood pressure monitoring before and after CPAP in 17 patients showed slight reductions in nocturnal diastolic blood pressure (76 ± 9 mmHg; *P < 0.05) and nocturnal mean blood pressures (91 ± 10 compared with 87 ± 8 mmHg; *P < 0.05).

Urinary protein in the patients changed from 0.18 ± 0.34 g/day before to 0.07 ± 0.04 g/day after CPAP. Clinically significant proteinuria (> 0.5 g/day) was seen in only two patients before the treatment. One patient who had proteinuria of 1.74 g/day refused to continue CPAP. The other had a reduction in urinary protein from 0.55 g/day before to 0.10 g/day after CPAP with a slight reduction in FF from 0.22 to 0.21.

**DISCUSSION**

According to the ‘hyperfiltration theory’, glomerular pressure overload and hyperfiltration are common mechanisms of progressive renal dysfunction [17]. Thus it is important to assess and attempt to reduce the glomerular filtration load in the clinical treatment of progressive renal diseases. FF is generally accepted as an estimate of glomerular filtration load [18–20], because it is the only parameter concerned with glomerular load that can be measured at the bedside.

In the present study, we successfully demonstrated that glomeruli in patients with OSAS are generally in a hyperfiltrating condition, and nocturnal nasal CPAP is effective in ameliorating glomerular hyperfiltration, as shown by changes in FF. The direct consequences of glomerular hyperfiltration are glomerular enlargement and glomerular sclerosis, which are both characteristics of focal segmental glomerulosclerosis. Nephrotic syndrome and renal dysfunction due to the advancement of

![Graphs showing changes in GFR, RPF, and FF before and after CPAP](image-url)
Sleep apnoea and glomerular hyperfiltration

Figure 3  Comparison of renal function before and after nocturnal nasal CPAP in groups without and with ACE-i and/or ARB

Values are means ± S.D. Of the 21 patients tested for renal function before and after CPAP, six patients received ACE-i and/or ARB and 15 patients did not. (A) GFR did not significantly change after CPAP in either group. (B) RPF was significantly increased after CPAP in the group without ACE-i/ARB; however, there was no significant change in the group with ACE-i/ARB. (C) FF was significantly decreased after CPAP in the group without ACE-i/ARB; however, there was no significant change in the group with ACE-i/ARB. *P < 0.05 and **P < 0.001 compared with patients without ACE-i/ARB before CPAP.

focal segmental glomerulosclerosis sometimes appear in patients with OSAS [1]. Thus CPAP therapy has the potential to prevent renal dysfunction by ameliorating glomerular hyperfiltration in patients with OSAS.

Hypertension, aging, obesity and diabetes mellitus are also known to affect FF levels [20,21]. As shown in Table 1, there is a difference in BMI between OSAS patients and controls, and obesity might make FF higher in OSAS patients. However, FF and RPF improved after CPAP despite no change in BMI. This meant that OSAS might cause higher FF. This study cannot completely deny low statistical power, due to the variability of AH1 or the small number of the subjects, to elucidate the relationship between AH1 and FF. However, our data show that the lowest SpO2 was a better indicator than AH1, because it was correlated significantly with FF and the r value was higher than that for the correlation between AH1 and FF. Furthermore, multiple regression analysis revealed that only the lowest SpO2 was a significant determinant for high FF and other factors, including age, sex, BMI and AH1, did not have any significant correlation with FF in the present study. The effect of nocturnal hypoxia on FF seemed to be so strong that it could mask the effect of other factors.

On the other hand, it is widely recognized that the use of ACE-i or ARB decreases FF by dilating glomerular efferent arterioles. This action demonstrates a renoprotective effect in various glomerular diseases [22–24]. In fact, FF was not elevated before CPAP, and was unchanged after CPAP in the OSAS patients who had received ACE-i and/or ARB in the present study (Figure 3). Thus ACE-i/ARB and CPAP did not show an additive effect on FF reduction, which could be due to both therapies affecting a common target, the efferent arterioles. The dilated efferent arterioles, but not constricted afferent arterioles, seem to be the main intrarenal microhaemodynamic change after CPAP.

Two possible mediators could be considered to raise FF levels in OSAS. First, a high sympathetic activity is associated with glomerular hyperfiltration. OSAS is related to high sympathetic activity, which is reduced after CPAP in both sleep and awake states [25–27]. Activation of the renal sympathetic nerve decreases renal blood flow and increases FF [28,29]. Animal experiments have shown that hypoxia increases renal sympathetic nerve activity and renal postglomerular vascular resistance [30]. The reduction in daytime sympathetic activity after CPAP is compatible with the amelioration of glomerular hyperfiltration during the daytime. Thus high sympathetic activity is likely to be a factor in promoting glomerular hyperfiltration in patients with OSAS. Secondly, hormonal factors such as ANP (atrial natriuretic peptide) are also candidates for the mediator promoting glomerular hyperfiltration in this condition. ANP mainly decreases the afferent arteriolar resistance with a modest increase in efferent arteriolar resistance [31], resulting in a high intraglomerular pressure. Moreover, the increased levels of ANP in patients with OSAS are reported to be decreased by CPAP [32,33]. Further studies must be undertaken to confirm which factors mediate glomerular hyperfiltration from hypoxia in patients with OSAS.

Interestingly, many obese patients present glomerular abnormalities similar to those of patients with OSAS, referred to as obesity-related glomerulopathy. However, the link between obesity and glomerulopathy remains unclear [34–36]. We assume that OSAS is one of the links...
between them because most of these obese patients have a high risk of OSAS. Further study is needed to elucidate the relationship between obesity-related glomerulopathy and OSAS.

In conclusion, renal function in patients with OSAS was generally in the hyperfiltrating condition, and nocturnal nasal CPAP could ameliorate the glomerular hyperfiltration in patients with OSAS within a week. Thus glomerular hyperfiltration in patients with OSAS is likely to be a consequence of apnoea-related hypoxaemia during sleep.

REFERENCES


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