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*Clinical Report*

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# Effect of continuous positive airway pressure on proteinuria in obstructive sleep apnea

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**Abstract**
Obstructive sleep apnea (OSA) is common in patients with renal disease, and an association between OSA and proteinuria has been proposed. However, the effect on proteinuria of OSA treatment with continuous positive airway pressure (CPAP) is unknown. We experienced a case of severe OSA, where proteinuria was clearly improved after CPAP initiation without any changes of medication or body weight. The remarkable reduction of repetitive apnea and hypopnea by CPAP might ameliorate proteinuria by lessening renal hypoxia and sympathetic nerve activation. This case suggests that CPAP is a promising option for OSA with proteinuria.

**Keywords:** continuous positive airway pressure; obstructive sleep apnea; proteinuria; renal hypoxia

## Background

Sleep-disordered breathing (SDB), characterized by repetitive apnea and hypopnea during sleep, is common in patients with chronic kidney disease (CKD) [1, 2]. We recently reported that SDB in dialysis patients (CKD stage 5D) predicts cardiovascular events and mortality [3]. An association between obstructive sleep apnea (OSA), the most common form of SDB, and proteinuria has been proposed [4–6]. However, it is unclear whether continuous positive airway pressure (CPAP), a standard treatment for OSA, ameliorates proteinuria. We report a case of severe OSA, where proteinuria was clearly decreased after CPAP without any changes of medication or body weight. This report proposes CPAP as a promising treatment for OSA with proteinuria.

## Case report

A 60-year-old man was referred to Japanese Red Cross Koga Hospital with the main complaint of proteinuria and hypertension in September 2008. At another clinic, proteinuria had been identified in 2003, and hypertension and hyperlipidemia had been diagnosed in 2007. A medication regimen of amlodipine (2.5 mg/day) and pitavastatin (2 mg/day) began in January 2008. The patient had no history of diabetes or other glomerular diseases. Physical findings at the first visit to our hospital were the following: height 157.6 cm, body weight 68.0 kg, body mass index (BMI) 27.4, blood pressure (BP) 148/91 mmHg, pulse rate 73 beats/min, body temperature 36.4°C and the tonsils were not enlarged. Blood examination showed blood urea nitrogen 3.89 mmol/L (10.9 mg/dL), serum creatinine 88.4 μmol/L (1.00 mg/dL), uric acid 39.2 μmol/L (6.6 mg/dL), serum albumin 43 g/L (4.3 g/dL), total cholesterol 4.87 mmol/L (188 mg/dL), immunoglobulin (Ig) G 13.49 g/L (1349 mg/dL), IgA 4.35 g/L (435 mg/dL) and IgM 0.83 g/L (83 mg/dL). Autoimmune serological findings and tumor markers such as CEA and CA19-9 were within normal ranges. Urine examination revealed proteinuria (protein and creatinine ratio) 0.67 g/g Cr and urinary red blood cells at 3 per high power field. Urinary protein was determined by Protein Assay Rapid Kit (Wako; Pure Chemical Industries Ltd, Tokyo, Japan). Renal biopsy was not performed because the patient refused it. We added candesartan (2 mg/day), an angiotensin II receptor antagonist, to decrease BP and proteinuria [7]. As a result, the BP decreased while in our hospital to within the normal range (120–130/80–85), but proteinuria increased gradually. In September 2010, he complained of repetitive apnea during sleep which his wife had noticed and pointed out to him. Therefore, we decided to screen for sleep apnea by first performing pulse oximetry (PULSOX-Me300; Teijin Pharma Ltd, Tokyo, Japan) and Epworth Sleepiness Scale (ESS), a questionnaire about daytime sleepiness [8]. In these tests, 3% oxygen desaturation index by pulse oximetry was 56.88 (normal range $< 5$) and ESS score was 10 (normal range $\leq 10$). As these results indicated severe sleep apnea, polysomnography (PSG) was performed for a detailed examination (Sleep Watcher E; Teijin Pharma, Ltd and Compumedics Ltd, Victoria, Australia). We then diagnosed severe OSA based on the following data: total apnea–hypopnea index (AHI) 78.3 events per h, obstructive AHI 77.6 events per h, average oxygen saturation ($SaO_2$) 94.0%, minimum $SaO_2$ 65.0% and cumulative time percentage of total sleep time when $SaO_2$ was $<$90% ($SaO_2$ $<$90%) 20.7% (Figure 2 and Table 1).

After obtaining informed consent, CPAP treatment using a nasal mask (AutoSet C; Teijin Pharma Ltd and ResMed, Sydney, Australia) was initiated. The setting of the device

was auto-titration mode (pressure 4.0–20.0 cm $H_2O$), and we instructed the patient to use it overnight. This device could store compliance and efficacy data, which were downloaded using software at follow-up visits every month. At 3 months after CPAP initiation, CPAP usage days and daily hours were 96.4% and 5.3 h, respectively (Table 1). Then, PSG was performed to evaluate the effect of CPAP on OSA. The data exhibited clear improvement of OSA: total AHI, 6.1 events per h; average $SaO_2$, 96.0%; minimum $SaO_2$, 93.0% and $SaO_2$ <90%, 0% (Table 1). Importantly, total elimination of saturated oxygen levels <90% indicated the disappearance of severe hypoxia during sleep. Along with the reduction of apnea and hypopnea events, proteinuria also clearly decreased (Table 1 and Figure 1), although no other medication was changed. In addition, home BP in the morning, which was measured within 1 h after waking as described previously [9, 10], decreased mildly (Figure 1 and Table 1). Then, we stopped amlodipine at 5 months after CPAP initiation (Figure 1). Heart rate (HR) and pulse rate rise index-6, the number of pulse rate increases ≥6 per h determined by pulse oximetry, decreased clearly after CPAP treatment (Table 1). On the other hand, an apparent change of BMI was not found during the period (Figure 1). At 6 months after CPAP initiation, the low level of proteinuria (≤0.3 g/g Cr) had continued (Figure 1). In addition, average proteinuria for 6 months after CPAP was markedly lower (0.3 g/g Cr) than before CPAP treatment (1.2 g/g Cr).

**Table 1.** Characteristics of the patient before and after CPAP initiation[a]

| Characteristics | Before CPAP | After CPAP (3 months) |
|---|---|---|
| Proteinuria (g/g Cr) | 1.5 | 0.3 |
| PSG data | | |
| Total AHI (events per h) | 78.3 | 6.1 |
| Total AI (events per h) | 76.0 | 1.4 |
| Obstructive AHI (events per h) | 77.6 | 5.8 |
| Average $SaO_2$ (%) | 94.0 | 96.0 |
| Minimum $SaO_2$ (%) | 65.0 | 93.0 |
| $SaO_2$ <90% (%) | 20.7 | 0 |
| Arousal Index (arousals per h) | 80.2 | 21.6 |
| CPAP used (% of days) | n/a | 96.4 |
| CPAP used (h/day) | n/a | 5.3 |
| ESS | 10 | 0 |
| BMI ($kg/m^2$) | 28.0 | 27.7 |
| Systolic BP (mmHg)[b] | 122.8 ± 1.2 | 119.9 ± 1.6 |
| Diastolic BP (mmHg)[b] | 82.5 ± 1.4 | 77.2 ± 1.3 |
| HR (beats/min)[b] | 83.3 ± 2.2 | 71.8 ± 2.3 |
| Pulse rate rise index-6 (events per h)[c] | 55.0 | 8.3 |

[a]CPAP, continuous positive airway pressure; PSG, polysomnography; AHI, apnea-hypopnea index; AI, apnea index; $SaO_2$, oxygen saturation; $SaO_2$, ≤ 90% (%); cumulative time percentage of total sleep time when $SaO_2$ was less than 90%; n/a, not applicable; ESS, Epworth Sleepiness scale; BMI, body mass index; BP, blood pressure; HR, heart rate.
[b]Average of fourteen consecutive days of home measurements taken in the morning. Values expressed as mean ± SE.
[c]Pulse rate rise index-6, the number of pulse rate increases ≥6 per h determined by pulse oximetry.

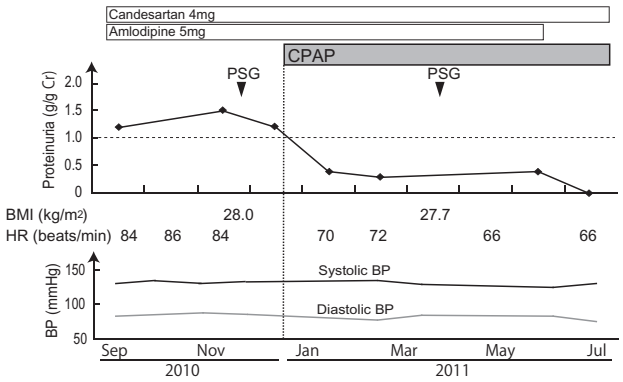


**Fig. 1.** Changes of proteinuria, BMI, HR and BP before and after CPAP initiation. Proteinuria clearly decreased after CPAP initiation without any changes of medication. PSG was performed before and after CPAP initiation. HR and BP were measured at home in the morning.

## Discussion

We report a severe OSA patient, whose proteinuria clearly decreased after CPAP treatment without any changes of medication or body weight. Previous studies have reported that OSA is associated with increased proteinuria [4–6], but other reports have denied this [11–13]. Therefore, the association between OSA and proteinuria has been controversial. The remarkable amelioration of proteinuria after CPAP initiation in our case suggests a probable relationship between OSA and proteinuria.

Convincing mechanisms of the beneficial effects of CPAP on proteinuria are (i) the amelioration of renal hypoxia, (ii) the improvement of sympathetic nerve activation (SNA) and (iii) the decrease of nocturnal BP.

The amelioration of renal hypoxia by CPAP might play a critical role in the decrease of proteinuria. It is reported that renal hypoxia increases proteinuria [14, 15], and the amelioration of hypoxia could decrease proteinuria [14]. Detailed mechanisms of hypoxia-induced proteinuria have been proposed in direct and indirect pathways. One of the mechanisms is direct glomerular damage due to hypoxia. In an experimental study, hypoxic condition increased podocyte apoptosis, which led to alteration of the glomerular filtration barrier [16]. In this report, the authors suggest that steady podocyte loss may be a novel pathophysiological

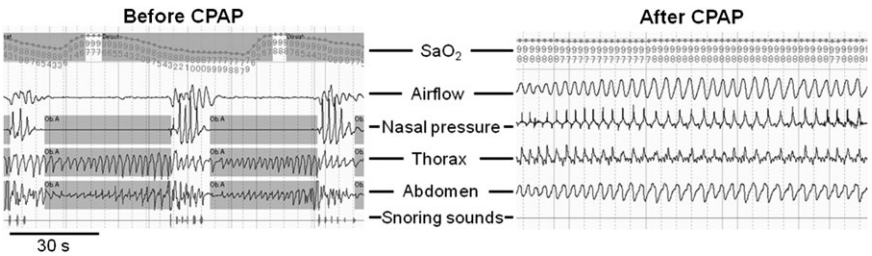


**Fig. 2.** Representative records of PSG before and after CPAP initiation. PSG before CPAP initiation exhibits repetitive obstructive apnea, which was diagnosed by airflow absence with paradoxical thoracic and abdominal movements. Along with sustained apnea, oxygen saturation ($SaO_2$) gradually decreased to <80%. In contrast, PSG after CPAP initiation shows a normal breathing pattern.

finding of OSA-related glomerular disease [16]. Similarly, glomerular endothelial cells, which have an important role in the preservation of the glomerular capillary network, are induced to apoptotic death in hypoxic conditions [17]. Therefore, renal hypoxia directly causes glomerular damage. On the other hand, hypoxia-induced medullar injury is another glomerular damage pathway. The renal medulla is poorly oxygenated under normal conditions because blood flow to the renal medulla is lower than that of the cortex [18]. Therefore, a hypoxic condition can readily affect the renal medulla and lead to tubular injury through profibrotic pathways such as transforming growth factor-$\beta$ and collagen [18]. Furthermore, along with the progression of hypoxia, the injured area could spread to the superficial cortex, which includes glomeruli [18]. From these studies, we conclude that hypoxia-induced direct and indirect glomerular damage could play an important role in proteinuria. In our case, the remarkable improvement of hypoxia by CPAP, which is evident in PSG data ($SaO_2 < 90\%$, $20.7\% \rightarrow 0\%$; Table 1), might decrease proteinuria through the amelioration of glomerular damage.

The improvement of SNA by CPAP might also decrease proteinuria. Nocturnal apnea and hypopnea due to OSA causes systemic SNA [19], and CPAP treatment attenuates OSA-induced SNA [19]. In addition, several experimental studies have shown that intermittent hypoxia could induce renal SNA [20, 21], which is associated with increased proteinuria [22]. In our case, HR and pulse rate rise index, possible markers for SNA [23], decreased clearly after CPAP treatment (Table 1). Accordingly, the attenuation of SNA by CPAP might be an important mechanism for the reduction of proteinuria.

Furthermore, the decrease of nocturnal BP might have a beneficial effect on proteinuria. OSA plays an important role in nocturnal hypertension [24], which could cause increased proteinuria [25]. In our case, home BP in the morning showed mild reductions after CPAP initiation (Table 1). Although we did not examine nocturnal BP using 24-h ambulatory BP, the change of nocturnal BP might influence the reduction of proteinuria.

Additionally, good compliance of CPAP in this case (average usage 5.3 h/day, Table 1) might strengthen the favorable effects on proteinuria. Actually, it is reported that CPAP treatment with good compliance (average usage $\geq 4$ h/day) ameliorated the renal resistance index, a predictor of renal dysfunction, although short-time CPAP treatment (average usage $< 4$ h/day) had no effect on this parameter [26].

There are several limitations in this report. First, the lack of renal biopsy is a major limitation because the pathological findings for diagnosing renal etiology are unknown. In OSA patients with or without obesity, several glomerular changes such as glomerulomegaly, focal segmental glomerulosclerosis and mesangial proliferative changes have been noted [27, 28]. However, whether OSA itself initiates or increases the progression of these abnormalities is entirely unknown. Further studies are needed to evaluate the association between OSA-related glomerular damage and proteinuria. Second, our case alone is not sufficient to prove the effect of CPAP on proteinuria. Several cross-sectional studies showed that significant proteinuria is uncommon in patients with OSA [11, 13]. On the other hand, a recent prospective interventional study of 121 OSA patients demonstrated that albuminuria, which reflects generalized endothelial dysfunction, decreased after CPAP treatment [29]. In the same manner, an accumulation of cases is needed to confirm the effect of CPAP on proteinuria. Third, measurement of 24-h ambulatory BP is necessary to examine detailed data about nocturnal BP.

We experienced a severe OSA case, where proteinuria was clearly ameliorated after CPAP treatment without any changes of medication or body weight. The remarkable reduction of repetitive apnea and hypopnea by CPAP might ameliorate proteinuria through the improvement of severe renal hypoxia and SNA. This case suggests a potential beneficial effect of CPAP on proteinuria with OSA.

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