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Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients

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Abstract The purpose of this study was to determine the relationship between obstructive sleep apnea (OSA) and cardiovascular disorders in a large Japanese population, and to assess the efficacy of continuous positive airway pressure (CPAP) in the treatment of OSA-associated arrhythmias. The study population comprised 1394 Japanese subjects (1086 men and 308 women) who were divided into four groups on the basis of polysomnography (PSG) analysis as follows: the no sleep apnea (N-SA) group (n = 44, apnea–hypopnea index [AHI] < 5), the mild OSA (Mi-OSA) group (n = 197, 5 < AHI < 15), the moderate OSA (Mo) group (n = 368, 15 < AHI < 30), and severe OSA (S-OSA) group (n = 785, AHI < 30). The following baseline characteristics were significantly associated with OSA: age (P < 0.001), gender (P < 0.001), body mass index (P < 0.001), hypertension (P < 0.001), diabetes (P = 0.009), and hyperlipidemia (P = 0.013). In the OSA group, PSG revealed the predominance of paroxysmal atrial fibrillation (PAF) (P = 0.051), premature atrial complex short run (P < 0.005), premature ventricular complex (PVC, P = 0.004), sinus bradycardia (P = 0.036), and sinus pause (arrest >2 s, P < 0.001) during the PSG recording. A total of 316 patients from the group underwent CPAP titration and were then re-evaluated. Continuous positive airway pressure therapy significantly reduced the occurrences of PAF (P < 0.001), PVC (P = 0.016), sinus bradycardia (P = 0.001), and sinus pause (P = 0.004). The results of this study demonstrate a significant relationship between OSA and several cardiac disorders, and also demonstrate the efficacy of CPAP in preventing OSA-associated arrhythmias in a large population of Japanese patients.

Key words Apnea · Arrhythmia · Cardiovascular disease · Sleep

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Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of decreased or total cessation of respiratory airflow during sleep, and occurs in approximately 5%–15% of the population.[1,2] Obstructive sleep apnea was widely accepted to be associated with high rates of morbidity and mortality, predominantly due to cardiovascular disorders and traffic accidents. In particular, recent evidence indicates that OSA is associated with hypertension, ischemic heart disease, heart failure, cerebral ischemia, and cardiac arrhythmias.[2–5] Consequently, in view of its high prevalence and its emerging association with cardiovascular morbidity, OSA is considered to be a major public health problem.

Continuous positive airway pressure (CPAP) has been demonstrated to be one of the effective therapies for OSA, and it is gaining recognition as one of the therapeutic methods for OSA-associated cardiac failure and high blood pressure[6–8] and also in the prevention of ischemic heart diseases.[9] In addition, some notable reports have suggested that CPAP is a suitable therapy for the prevention of the occurrence of arrhythmias in OSA patients.[10,11] Thus, the therapeutic role of CPAP in the management of cardiovascular diseases that coexist with OSA is promising. However, since these studies were performed in Western countries such as the United States, Australia, and countries in Europe,[1,12,13] the association of OSA with cardiac disorders and the efficacy of CPAP therapy in Asian patients remains undetermined. In fact, several studies indicate that the correlation between obesity and the severity of breathing disorders is weaker in Asian subjects than in Caucasian ones,[14,15] suggesting that racial factors may affect the prevalence. In addition, a majority of the clinical studies involving a large

number of patients have evaluated OSA by using a nocturnal pulse oximetry as a substitute for polysomnography (PSG) – a diagnostic tool that is regarded as the "gold standard" for assessing OSA. Although recent investigations have recognized the usefulness of oximetry, it has also been demonstrated to be insufficient with respect to its specificity and sensitivity to be used as an alternative to PSG.[16,17] In the present study, we performed PSG to evaluate OSA in a large population of Japanese patients and determined the relationship between OSA and cardiovascular disorders; further, we assessed the effect of CPAP therapy on OSA-associated arrhythmias.

Patients and methods

Study subjects

The study population was recruited from patients referred to the outpatient department of Matsumoto Kyoritsu Hospital. All of the patients ($n = 1456$) were suspected of having sleep apnea syndrome based on clinical history and symptoms, and consecutively underwent PSG study between July 2003 and February 2008. This study was approved by the Institutional Review Board of the Matsumoto Kyoritsu Hospital. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.[18] Hypertension was defined as the elevation of blood pressure levels (≥130/85 mmHg) or treatment with antihypertensive agents at the time of inclusion in the study. Diabetes mellitus was defined as the elevation of a fasting blood glucose level (≥126 mg/dl) or treatment with pharmacological agents.[19] Hyperlipidemia was defined as elevation in the serum levels of cholesterol (≥220 mg/dl) and triglycerides (≥150 mg/dl), and a decrease in high-density lipoprotein (HDL) cholesterol (<40 mg/dl).

Sleep study, PSG scoring, and CPAP titration

All of the patients underwent PSG between 19:00 and 07:00 h, and were scored by PSG technologists at our sleep center laboratory. The PSG was performed using a SleepWatcher polysomnograph (Compumedics, Abbotsford, Australia). To detect airflow, both a nasal pressure transducer and airflow sensor thermocouple were used. Apnea was defined as the absence of airflow for over 10 s and hypopnea, as a discernible 50% decrease in the amplitude of a valid measure of breathing for at least 10 s. The apnea–hypopnea index (AHI) was calculated as the number of episodes of apnea and hypopnea per hour during sleep. Figure 1 represents the study design. Patients were divided into categories according to the frequency of apneas and hypopneas per hour of sleep (i.e., AHI): the no sleep apnea (N-SA) group ($n = 44$, AHI < 5), the mild OSA (Mi-OSA) group ($n = 197$, 5 < AHI < 15), the moderate OSA (Mo) group ($n = 368$, 15 < AHI < 30), and severe OSA (S-OSA) group ($n = 785$, AHI < 30); and central sleep apnea (CSA, AHI ≥ 5/h of sleep, of which >50% were central, $n = 62$). The absence of airflow in the upper airway with and without ribcage and/or abdominal movement was defined as obstructive and central apnea, respectively. Continuous positive airway pressure therapy was performed according to the indication to treat severe OSA patients (AHI > 20) with CPAP therapy in the guidelines of the Japanese Respiratory Society. The patients with predominantly central sleep apnea were excluded from further analysis. We investigated the relationship among four groups in terms of age, sex, BMI, and cardiovascular disorders. We also reviewed the arrhythmias occurring during sleep from the electrocardiograph output of the PSG. The OSA patients ($n = 316$) who accepted CPAP treatment underwent a full sleep study for CPAP automatic titration (average 3.9 weeks after PSG), and were re-evaluated to assess the efficacy of CPAP therapy and the occurrence of OSA-associated arrhythmias. Other OSA patients ($n = 573$) were refused the treatment with CPAP therapy.

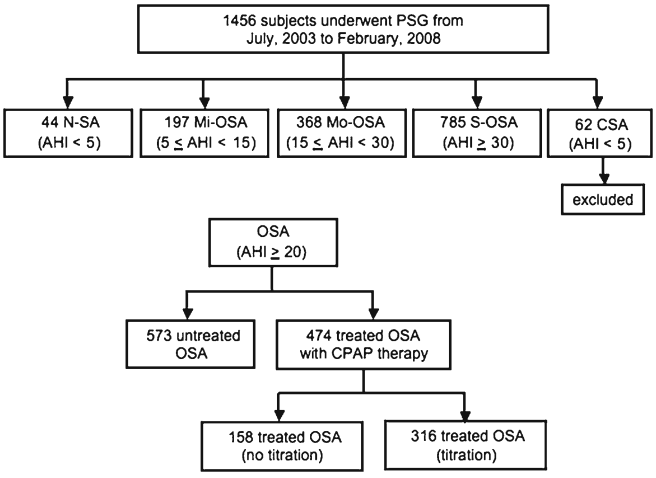

Fig. 1. Study profile. *AHI*, apnea–hypopnea index; *CPAP*, continuous positive airway pressure; *OSA*, obstructive sleep apnea; *N-SA*, no sleep apnea; *Mi-OSA*, mild OSA; *Mo-OSA*, moderate OSA; *S-OSA*, severe OSA; *CSA*, central sleep apnea; *PSG*, polysomnography

Arrhythmia analysis

Paroxysmal atrial fibrillation (PAF) was defined as irregular R-R intervals and an F wave lasting 30 s. Chronic atrial fibrillation (AF) was defined as AF persisting for 1 year in which cardioversion has not been attempted or has failed. Premature atrial complex (PAC) short-run was regarded as >3 beats of PAC. Premature ventricular complex (PVC) classified IVa, b, and V of the Lown classification was analyzed. Nonsustained ventricular tachycardia (NSVT) was defined as six or more consecutive ventricular complexes and lasting for less than 30 s. Bradycardia was defined as a rhythm of less than 40 beats/min. Sinus pause was defined as sinus arrest that lasted for at least 2 s. The patients with pacemaker and/or implantable cardioverter–defibrillator were analyzed under pacing-on condition. All ECG data were reviewed by two observers blinded to respiratory events.

Statistical analysis

The data are presented as the mean ± SD. We used the trend *P* test for comparing continuous variables and the chi-square (χ^2) test for categorical variables. Simple logistic regression was modeled when determining the independent association of the variables between the groups; the results are presented as odds ratios with a 95% confidence interval (CI). Stepwise multiple logistic regression analysis was performed to include statistically significant valuables from the univariate analysis. For all tests, $P < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics

Table 1 describes the baseline characteristics of the study population. The associations between OSA and age ($P < 0.001$), gender ($P < 0.001$), and BMI ($P < 0.001$) were demonstrated to be statistically significant. Table 2 shows the characteristics of the patients' lifestyle-related diseases and cardiovascular disorders. The number of patients with hypertension ($P < 0.001$) and diabetes mellitus ($P < 0.001$) was significantly associated with OSA. However, there was no significant association between OSA and hyperlipidemia and history of old myocardial infarction, heart failure, chronic AF, vasospastic angina, stroke, pacemaker implantation, or implantable cardioverter–defibrillator implantation.

Relationship between OSA and cardiac arrhythmias during PSG

To precisely investigate the relationship between OSA and the presence of arrhythmias, we analyzed the patient number of arrhythmias during the PSG recording. As shown in Table 3, the occurrence of PAF ($P = 0.051$), PAC short-run ($P = 0.005$), PVC ($P = 0.004$), sinus bradycardia ($P = 0.036$), and sinus pause (sinus arrest >2 s; $P < 0.001$) were higher in the OSA. As expected, lowest SpO_2 levels and the percentage of <90% SpO_2 were also significantly increased in the OSA ($P < 0.0001$).

Table 1. Baseline characteristics

	N-SA ($n = 44$)	Mi-OSA ($n = 197$)	Mo-OSA ($n = 368$)	S-OSA ($n = 785$)	*P* for trend
Age (years)	41.0 ± 18.8	50.0 ± 18.4	57.9 ± 14.3	58.8 ± 14.5	<0.001
Male (%)	22 (50.0%)	132 (67.0%)	266 (72.3%)	666 (84.8%)	<0.001
Body weight (kg)	59.1 ± 12.5	62.2 ± 11.5	64.6 ± 13.2	71.5 ± 14.8	<0.001
BMI (kg/m^2)	22.2 ± 3.6	23.1 ± 3.2	24.2 ± 3.8	26.4 ± 4.4	<0.001

Values are *n* (%) or mean ± SD
N-SA, no sleep apnea; OSA, obstructive sleep apnea; Mi-OSA, mild OSA; Mo-OSA, moderate OSA; S-OSA, severe OSA; BMI, body mass index

Table 2. Baseline characteristics of cardiovascular disorders

	N-SA ($n = 44$)	Mi-OSA ($n = 197$)	Mo-OSA ($n = 368$)	S-OSA ($n = 785$)	*P* for trend
Hypertension	6 (13.6%)	37 (18.8%)	111 (30.2%)	326 (41.5%)	<0.001
Diabetes mellitus	1 (2.3%)	13 (6.6%)	34 (9.2%)	100 (12.7%)	<0.001
Hyperlipidemia	7 (15.9%)	20 (10.2%)	56 (15.2%)	132 (16.8%)	0.067
OMI	4 (9.1%)	17 (8.6%)	47 (12.8%)	84 (10.7%)	0.646
Heart failure	4 (9.1%)	16 (8.1%)	41 (11.1%)	57 (7.3%)	0.284
PAF	1 (2.3%)	15 (7.6%)	19 (5.2%)	52 (6.6%)	0.616
Chronic AF	1 (2.3%)	7 (3.6%)	19 (5.2%)	30 (3.8%)	0.929
VSA	1 (2.3%)	5 (2.5%)	11 (3.0%)	34 (4.3%)	0.138
Stroke	2 (4.5%)	5 (2.5%)	15 (4.1%)	33 (4.2%)	0.483
PM implantation	0 (0.0%)	5 (2.5%)	17 (4.6%)	33 (4.2%)	0.174
ICD implantation	2 (4.5%)	5 (2.5%)	11 (3.0%)	10 (1.3%)	0.129
Medication					
Digitalis	3 (6.8%)	13 (6.6%)	18 (4.9%)	29 (3.7%)	0.0526
ACEi	2 (4.5%)	18 (9.1%)	59 (16.0%)	72 (9.2%)	0.6687
ARB	6 (13.6%)	30 (15.2%)	49 (13.3%)	141 (18.0%)	0.1005
Ia	1 (2.3%)	2 (1.0%)	8 (2.1%)	4 (0.5%)	0.0955
Ib	1 (2.3%)	1 (0.5%)	3 (0.8%)	7 (0.9%)	0.9162
Ic	1 (2.3%)	4 (2.0%)	5 (1.4%)	20 (2.5%)	0.4755
II	5 (11.4%)	22 (11.2%)	44 (12.0%)	102 (13.0%)	0.4409
III	0 (0.0%)	4 (2.0%)	13 (3.5%)	24 (3.1%)	0.3165
Ca antagonists	4 (9.1%)	22 (11.2%)	68 (18.5%)	195 (24.8%)	<0.0001

Values are *n* (%)
OMI, old myocardial infarction; PAF, paroxysmal atrial fibrillation; chronic AF, chronic atrial fibrillation; VSA, vasospastic angina; PM, pacemaker; ICD, implantable cardioverter–defibrillator; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 3. Relationship between OSA and patient number of cardiac arrhythmias during polysomnography

	N-SA (n = 44)	Mi-OSA (n = 197)	Mo-OSA (n = 368)	S-OSA (n = 785)	P for trend
PAF	0	2 (1.0%)	12 (3.3%)	27 (3.4%)	0.051
PAC short run	0	5 (2.5%)	29 (7.9%)	61 (7.8%)	0.005
PVC Lown IVa or b, V	0	1 (0.5%)	11 (3.0%)	33 (4.2%)	0.004
Nonsustained VT	0	2 (1.0%)	3 (1.5%)	10 (1.3%)	0.417
Sinus bradycardia	1 (2.3%)	5 (2.5%)	16 (4.3%)	45 (5.7%)	0.036
Pause	1 (2.3%)	2 (1.0%)	6 (1.6%)	48 (6.1%)	<0.001
2nd degree AV block	0	2 (1.0%)	1 (0.3%)	10 (1.3%)	0.267
3rd degree AV block	0	0	0	1 (0.1%)	0.444
Lowest SpO_2 (%)	91.2 ± 3.8	88.5 ± 3.4	84.6 ± 5.6	76.8 ± 8.8	<0.0001
<90% SpO_2 (%)	0.009 ± 0.036	0.5 ± 3.0	1.9 ± 6.0	14.4 ± 19.1	<0.0001

Values are n (%)
PAC, premature atrial complex; PVC, premature ventricular complex; VT, ventricular tachycardia; AV block, atrioventricular block

Table 4a. Univariate relation to the risk of PAF incidence

	Odds ratio (95% CI)	P value
OSA	6.67 (1.60–27.76)	0.009
Age (>65 years old)	1.16 (0.62–2.18)	0.645
Male	1.39 (0.61–3.16)	0.434
BMI (>25)	1.11 (0.60–2.07)	0.743
Hypertension	1.85 (0.99–3.45)	0.053
Diabetes mellitus	1.46 (0.60–3.54)	0.399
Dyslipidemia	1.57 (0.74–3.33)	0.243
OMI	1.14 (0.44–2.95)	0.787
Heart failure	0.85 (0.26–2.80)	0.789
Chronic AF	0.58 (0.08–4.29)	0.592
PAF	7.05 (3.46–14.37)	<0.001
VSA	2.15 (0.64–7.20)	0.215
Stroke	1.26 (0.30–5.35)	0.755
PM implantation	1.98 (0.59–6.61)	0.269
ICD implantation	2.62 (0.60–11.42)	0.200

Odds ratio and 95% confidence intervals (CI) were based on univariate logistic regression analysis

Table 4b. Multivariate relation to the risk of PAF incidence

	Odds ratio (95% CI)	P value
OSA	6.44 (1.53–27.08)	0.011
Hypertension	1.45 (0.77–2.74)	0.253
PAF	6.79 (3.28–14.07)	<0.001
VSA	1.55 (0.43–5.50)	0.501

Logistic regression analysis controlling for listed variables

Univariate analysis identified associations between PAF incidence and OSA (P < 0.009), hypertension (P = 0.053), and prevalent PAF (P < 0.001) occurring during sleep (Table 4a). In the multiple logistic regression models, OSA was significantly and independently associated with the incidence of PAF (adjusted odds ratio, 6.44; 95% CI, 1.53–27.08; P = 0.011). As expected, prevalent PAF was also associated with the incidence of PAF (adjusted odds ratio, 6.79; 95% CI, 3.28–14.07; P < 0.001; Table 4b).

Effect of CPAP therapy on arrhythmias

Table 5 shows the effect of CPAP therapy on the occurrence of arrhythmias during sleep in patients with OSA. The CPAP therapy significantly improved AHI (P < 0.001), arousal index (P < 0.001), lowest SpO_2 (P < 0.001), percentage of <90% SpO_2 (P < 0.001), and significantly prevented the occurrence of PAF (P < 0.001), PVC (P = 0.016), sinus bradycardia (P = 0.001), and sinus pause (P = 0.004).

Discussion

This study confirmed that the association of established lifestyle-related diseases, such as obesity, hypertension, and diabetes, to OSA is highly relevant in Japanese patients. We also demonstrated a significant relationship between OSA and arrhythmias. Furthermore, we demonstrated the therapeutic efficacy of CPAP therapy for the prevention of OSA-associated arrhythmias in those subjects. Since, to date, little information is available regarding cardiac disorders in Asian patients with OSA, these data strongly support the hypothesis that OSA is an independent risk factor for cardiovascular disorders and that treatment with CPAP therapy is effective for OSA-associated arrhythmias.

In the United States, at least four large population studies (Wisconsin Sleep Cohort, Sleep Heart Health Study, Pennsylvania Sleep Cohort, and Cleveland Family Study) have provided the data to assess the natural history of sleep-disordered breathing (SDB) and SDB-associated cardiovascular disorders;[1,20–24] however, little information is available for its natural history and cardiovascular disorders in Asian subjects. Since there are a number of differences between Asia and United States with respect to lifestyles and the prevalence of obesity, it was necessary to elucidate the natural history of OSA and OSA-associated cardiovascular disorders in Asian subjects by means of a large-scale study.

Cardiac arrhythmias have been documented in up to 48% of patients suffering from OSA,[25–27] and have been proposed to be one of the factors contributing to their increased mortality. Previous studies have demonstrated evidence of a causal association between OSA and a number of cardiac arrhythmias such as bradycardia, atrioventricular block, AF, PVC, and ventricular tachycardia;[10,27,28] however, other studies have been unable to prove this association for some of these arrhythmias.[29–31] Thus, the relationship between OSA and certain types of arrhythmias remains

Table 5. Effects of continuous positive airway pressure (CPAP) therapy on patient number of cardiac arrhythmias and sleep parameters during polysomnography

	Before CPAP (n = 316)	After CPAP (n = 316)	P value
PAF	16	1	<0.001
PAC short run	12	7	0.226
PVC Lown IVa or b, V	16	5	0.016
Nonsustained VT	5	1	0.103
Sinus bradycardia	13	1	0.001
Pause	13	2	0.004
2nd degree AV block	4	1	0.180
3rd degree AV block	1	0	0.318
AHI	50.3 ± 22.3	10.8 ± 12.0	<0.001
Apnea	27.5 ± 20.5	2.9 ± 4.5	<0.001
Hypopnea	16.1 ± 10.7	6.7 ± 5.6	
Arousal index	43.7 ± 19.1	25.7 ± 13.9	<0.001
Lowest SpO_2 (%)	77.3 ± 9.6	88.6 ± 5.4	<0.001
<90% SpO_2 (%)	13.3 ± 18.8	1.5 ± 8.1	<0.001
REM sleep (%)	14.3 ± 8.3	16.6 ± 7.3	0.023

Values are n, %, or mean ± SD
AHI, apnea–hypopnea index

controversial. In the present study, we clearly demonstrated a high occurrence of PAF, PAC short-run, PVC, bradycardia, and sinus pause in OSA patients. Moreover, we identified that OSA was an independent risk factor for the occurrence of PAF. Consistent with our findings, Gami et al.[28] found that approximately half of the patients with chronic AF are likely to have OSA; further, they suggested that AF is a strong independent risk factor for OSA. This group also reported that patients with OSA have a higher recurrence of AF after cardioversion than patients without OSA,[32] suggesting the pathogenic role of OSA in the occurrence of AF. More recently, the same group performed a retrospective large cohort study and found that magnitude of nocturnal oxygen desaturation was an independent risk factor for incident AF in subjects younger than 65 years of age.[33] The large-scale Sleep Heart Health Study also recently demonstrated that a fourfold increase in the prevalence of chronic AF in the patients with severe OSA (AHI > 30).[27] Conversely, Porthan et al.[31] showed that the prevalence of AF was not higher in patients with OSA as compared to those without OSA. In terms of other cardiac arrhythmias, the Sleep Heart Health Study reported that PVC and NSVT, but not sinus pause, were more common in patients with OSA.[27] On the other hand, Roche et al.[30] reported that the number of episodes of bradycardia and sinus pauses increased corresponding to the severity of OSA. An association of bradyarrhythmias with OSA has been frequently demonstrated.[10,25,27,30,34] Zwillich et al.[35] reported that hypoxemia and the cessation of respiration are essential in the development of cyclic variation of heart rate and bradycardia. In fact, an oxygen supply has been shown to reduce bradycardia.[35] The mechanism of such bradycardia is generally explained by a reflex increase in the vagal tone triggered by a combination of apnea and hypoxemia.[26,36] Furthermore, in patients with OSA an increased activity of the sympathetic tone in response to apnea and hypoxemia has also been reported.[37] Therefore, we postulate that fluctuations in the autonomic tone may contribute to the occurrence of AF and other arrhythmias. Further investigations are required to elucidate the mechanisms underlying cardiac arrhythmias due to OSA.

Treatment with CPAP has been shown to abolish the majority of bradyarrhythmias and ectopic beats in patients with OSA;[10,11,30] however, the efficacy of this therapy in AF remains undefined. In this study, CPAP therapy significantly eliminated not only sinus bradycardia and sinus pause but also PAF in OSA patients. Interestingly, it is reported that atrial paring reduced the severity of OSA based on AHI,[38] suggesting a role of cardiac rhythm in the pathophysiology of OSA. Taken together, the data obtained from our study and others indicate the therapeutic efficacy of CPAP treatment in OSA-associated arrhythmias; this suggests that the sleep studies should be considered in bradyarrhythmia patients with suspected OSA before implanting a pacemaker, because CPAP therapy could improve OSA-associated bradyarrhythmias.[39]

Study limitations

Several limitations of the present study should be noted. First, only a single bipolar lead was used for ECG analysis, which prevented us from evaluating an abnormal axis and ST-T wave abnormalities. Second, this study evaluated ECG data from the sleep period alone. Since it has been reported that circulation rhythm influences the occurrence of PAF,[40] we could not assess the association between daytime (or wake) and nocturnal (or sleep) rhythm disturbance. Third, the mean AHI was significantly improved by CPAP therapy; however, the AHI after CPAP therapy was slightly high because auto-titration devices for the first titration were used in this study.

Conclusions

The results of this study demonstrated a significant association between OSA and cardiovascular disorders such as

hypertension and arrhythmias, and revealed the efficacy of CPAP therapy in preventing OSA-associated arrhythmias in a large population of Japanese patients.

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