



Effects of continuous positive airway pressure on anxiety, depression, and major cardiac and cerebro-vascular events in obstructive sleep apnea patients with and without coronary artery disease

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is associated with bad cardiovascular outcomes and a high prevalence of anxiety and depression. This study investigated the effects of continuous positive airway pressure (CPAP) on the severity of anxiety and depression in OSA patients with or without coronary artery disease (CAD) and on the rate of cardio- and cerebro-vascular events in those with OSA and CAD. **Materials and Methods:** This prospective study included patients with moderate-to-severe OSA, with or without a recent diagnosis of CAD; all were started on CPAP therapy. Patients completed the Chinese versions of the Beck Anxiety Inventory (BAI) and Beck Depression Inventory-II (BDI-II) at baseline and after 6-month follow-up. The occurrence of major adverse cardiac and cerebrovascular events (MACCE) was assessed every 3 months up to 1 year. **Results:** BAI scores decreased from 8.5 ± 8.4 at baseline to 5.4 ± 6.9 at 6 months in CPAP-compliant OSA patients without CAD ($P < 0.05$). BAI scores also decreased from 20.7 ± 14.9 to 16.1 ± 14.5 in CPAP-compliant OSA patients with CAD. BDI-II scores decreased in CPAP-compliant OSA patients without CAD (from 11.1 ± 10.7 at baseline to 6.6 ± 9.5 at 6 months) and in CPAP-compliant OSA patients with CAD (from 20.4 ± 14.3 to 15.9 ± 7.3). In addition, there was a large effect size (ES) of BAI and BDI in 6-month CPAP treatment of OSA patients with CAD and a large ES in those with OSA under CPAP treatment. In OSA patients with CAD, the occurrence of MACCE was significantly lower in CPAP-compliant patients than that in CPAP noncompliant patients (11% in CPAP compliant and 50% in noncompliant; $P < 0.05$). **Conclusions:** CPAP improved anxiety and depression in OSA patients regardless of CAD. In OSA patients with CAD, CPAP-compliant patients had a lower 1-year rate of MACCE than CPAP-noncompliant patients.

KEYWORDS: Anxiety, Continuous positive airway pressure, Coronary artery disease, Depression, Obstructive sleep apnea

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INTRODUCTION

Obstructive sleep apnea (OSA) is a type of sleep-disordered breathing that involves recurrent upper airway collapse leading to repetitive episodes of hypoxemia and arousal during sleep [1]. Cross-sectional and longitudinal studies have shown an association between OSA and hypertension [2,3], cardiovascular disease [4-6], and cerebrovascular events [7].

In patients with coronary artery disease (CAD), the prevalence of at least moderate OSA is approximately 50% [8-10], and OSA has been shown to be a significant predictor of incident CAD in males ≤ 70 years old after adjustment for other risk factors [4]. Therefore, OSA is an important comorbidity in patients with CAD.

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA. Treatment with CPAP has been shown to have positive effects on cardiovascular outcomes, including in studies conducted in patients with CAD [11-14]. However, the beneficial effects of treating OSA with CPAP in patients with CAD have not been confirmed in the recent studies [15-18].

OSA has also been linked with depression and anxiety, although the correlation between objective measures of OSA severity and subjective symptoms such as anxiety and depression is not

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consistent [19-21]. There is also a reported link between depression and several aspects of heart disease [22]. In addition, CAD outcomes appear to be worse in the presence of anxiety and/or depression [22-24]. Treatment of OSA with CPAP has been shown to improve anxiety and depression symptoms [25,26]. However, less is known about the effects of CPAP treatment on anxiety and depression in patients with both OSA and CAD.

This study investigated the effects of CPAP therapy on anxiety and depression in patients with OSA alone or OSA plus CAD. The effects of CPAP on major adverse cardiac and cerebrovascular events (MACCE) over 1 year of follow-up in patients with OSA and CAD were also assessed.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institution (IRB 102-62). Informed written consent was obtained from all patients prior to their enrollment in this study.

Participants

This prospective study was conducted from 2010 to 2014 at Hualien Tzu-Chi General Hospital, Taiwan. Consecutive patients with moderate-to-severe OSA (apnea-hypopnea index ≥ 15 /h) based on an overnight polysomnographic study (Embla A10, Embla, Broomfield, CO) at the sleep center, with or without a recent diagnosis of CAD (within the previous year), were eligible for the study. Patients < 20 years old and those receiving treatment for anxiety and depression were excluded.

Continuous positive airway pressure therapy and compliance

All patients were started on CPAP treatment (S8; ResMed, San Diego, CA, USA) and underwent titration of therapy. CPAP compliance was defined as CPAP device usage for ≥ 4 h/night and use on $\geq 70\%$ of days over 6 months of therapy and CPAP noncompliance was defined as CPAP device usage for < 4 h/night and use on $< 70\%$ of days over 6 months of therapy or refusal to use CPAP therapy. Data on CPAP usage were downloaded from the memory card in the CPAP machine with the agreement of all patients.

Data collection and follow-up

Baseline data collection included patient age, sex, body mass index, and daytime sleepiness (using the Epworth Sleep Scale [ESS] [27]). The presence of anxiety and depression was determined using Chinese versions of the Beck Anxiety Inventory (BAI) and Beck Depression Inventory-II (BDI-II), respectively, which have been shown to have moderate-to-strong validity and reliability [28,29]. Patients completed the BAI and BDI-II questionnaires at baseline and again at the 6-month follow-up.

All patients with OSA and CAD were assessed for the occurrence of MACCE; cardiac death, myocardial infarction, unplanned revascularization, and stroke. Follow-up was conducted via telephone every 3 months up to 1 year. MACCE was verified by the patient's doctor and/or hospital medical records.

Statistical analysis

Analysis was performed using SPSS version 14.0 statistical package for Windows (SPSS, Chicago, IL, USA).

Repeated-measures analysis of variance was used to compare scores on the ESS, BAI, and BDI-II at baseline and follow-up within each patient group. Statistical significance was set at $P < 0.05$. Kaplan-Meier analyses and Cox proportional hazards models were performed in the intention-to-treat population to estimate the impact of CPAP on the rate of MACCE.

RESULTS

Patient characteristics

A total of 79 patients were enrolled, of whom 43 patients had OSA only and 36 patients had both OSA and CAD. There were no statistically significant differences between the two patient groups with respect to patient data, polysomnographic findings, or anxiety and depression at baseline [Table 1].

Continuous positive airway pressure compliance

After 6 months' follow-up, only 9 of the 36 patients with OSA and CAD were CPAP compliant; the remaining 27 of the 36 patients with OSA and CAD were CPAP noncompliant. For patients with OSA only 27 of 43 were CPAP compliant and 16 of 43 were CPAP noncompliant.

Anxiety and depression

Based on the BAI scores, there was a significant reduction in anxiety in CPAP-compliant OSA patients without CAD after 6 months of follow-up ($P < 0.05$), but not in CPAP-compliant OSA patients with CAD after 6 months of follow-up [Table 2]. Changes in the BAI from baseline to 6 months had a significantly larger effect size (ES) in CPAP-compliant OSA patients with CAD than in CPAP-compliant OSA patients without CAD (ES: 1.14) [Table 3]. The treatment difference and ES did not show differences in CPAP-compliant OSA patients without CAD (ES: 0.08) [Table 3].

Depression (assessed using the BDI-II score) also improved significantly from baseline to 6 months during CPAP treatment in CPAP-compliant OSA patients without CAD ($P < 0.05$), but not in CPAP-compliant OSA patients with CAD [Table 2]. As seen with anxiety, changes in the BDI-II score from baseline to 6 months had larger ESs in CPAP-compliant OSA patients with CAD than in CPAP-noncompliant OSA patients without CAD (ES: 1.22) and CPAP-compliant OSA patients without CAD (ES: 0.97) [Table 3].

Major adverse cardiac and cerebrovascular events

In OSA patients with CAD, good CPAP compliance was associated with a significant reduction in the incidence of MACCE after 1 year of follow-up (11% in CPAP-compliant and 50% in CPAP-noncompliant patients, $P < 0.05$) [Figure 1].

DISCUSSION

The results of this study showed that good compliance with CPAP decreased anxiety and depression in OSA patients without CAD. While improvements were not statistically significant in patients with OSA and CAD, the treatment difference in the ES showed significant reductions in the BAI and BDI-II scores after 6-month follow-up in CPAP-compliant patients. In addition, in patients with OSA and CAD, good CPAP compliance was found to significantly reduce the 1-year rate of MACCE compared with poor CPAP compliance or no CPAP use.

Table 1: Patient data at baseline

	OSA with CAD (n=36)	OSA without CAD (n=43)	P
Male, n (%)	32 (88.9)	35 (81.4)	0.531
Age (years)	61.9±11.2	48.1±13.3	0.07
BMI (kg/m ²)	29.7±7.3	30.7±6.3	0.90
ESS score	10.8±6.6	9.3±4.3	0.30
Neck circumference (cm)	39.2±5.7	39.9±3.1	0.22
Sleep efficiency (%)	79.2±14.2	85.1±10.1	0.13
AHI (/h)	49.8±31.3	52.7±24.7	0.41
ODI (/h)	39.6±31.4	37.4±29.8	0.81
BAI score	11.8±10.3	8.1±9.0	0.83
BDI-II score	11.6±9.8	9.9±9.9	0.77

Data are shown as mean±SD, or number of patients (%). OSA: Obstructive sleep apnea, CAD: Coronary artery disease, AHI: Apnea-hypopnea index, BAI: Beck Anxiety Inventory, BDI-II: Beck Depression Inventory version 2, BMI: Body mass index, ESS: Epworth Sleepiness Scale, ODI: Oxygen desaturation index, SD: Standard deviation

Table 2: Beck Anxiety Inventory and Beck Depression Inventory-II scores before and after the 6-month follow-up

	OSA with CAD		OSA without CAD	
	CPAP (+) (n=9)	CPAP (-) (n=27)	CPAP (+) (n=27)	CPAP (-) (n=16)
BAI score				
Baseline	20.7±14.9	9.7±7.8	8.5±8.4	7.3±10.1
6-month follow-up	16.1±14.5	10.8±9.3	5.4±6.9*	5.8±7.1
BDI-II score				
Baseline	20.4±14.3	9.5±7.2	11.1±10.7	7.8±8.4
6-month follow-up	15.9±7.3	10.8±8.5	6.6±9.5*	6.8±9.5

*P<0.05 versus baseline. Values are presented as mean±SD.

CAD: Coronary artery disease, CPAP: Continuous positive airway pressure, CPAP (+): CPAP-compliant over 6 months' follow-up, CPAP (-): CPAP-noncompliant over 6 months' follow-up, OSA: Obstructive sleep apnea, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, SD: Standard deviation

Table 3: Comparison of treatment differences and effect sizes of 6-month treatment with continuous positive airway pressure in obstructive sleep apnea patients with or without coronary artery disease between continuous positive airway pressure-compliant and continuous positive airway pressure-noncompliant groups

Groups	A-B	C-D
BAI score		
Mean±SD	9.9±3.7*	-0.5±2.5
ES	1.14	0.08
BDI score		
Mean±SD	13.7±3.8*	8.0±2.8†
ES	1.22	0.97

*A-B significantly comparing with C-D, P<0.05, †A-B significantly comparing with C-D, P<0.05. Group A: OSA with CAD, CPAP compliant over 6 months, Group B: OSA with CAD, CPAP noncompliant over 6 months, Group C: OSA without CAD, CPAP compliant over 6 months, Group D: OSA without CAD, CPAP noncompliant over 6 months, ES: Effect size, CPAP: Continuous positive airway pressure, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, SD: Standard deviation, OSA: Obstructive sleep apnea, CAD: Coronary artery disease

OSA is associated with sympathetic vasoconstriction along with simultaneous changes in intrathoracic and cardiac transmural

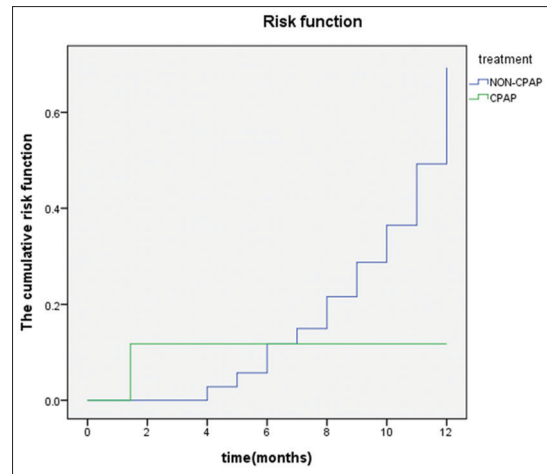


Figure 1: Kaplan–Meier analysis of major adverse cardiac and cerebrovascular events over 1 year of follow-up in obstructive sleep apnea patients with coronary artery disease among CPAP-compliant and CPAP-noncompliant patients. CPAP, continuous positive airway pressure

pressures, which could contribute to the development of cardiac ischemia [17]. CPAP treatment of OSA is associated with reductions in desaturations, oxidative stress, sympathetic activity, inflammation, and possible myocardial ischemia during sleep [18]. Although a number of studies have reported beneficial effects of CPAP in patients with CAD [12-14], available evidence is far from consistent. Most recently, two large randomized controlled trials found no significant reduction in the rate of adverse cardiovascular outcomes during CPAP treatment in nonsleepy OSA patients with CAD (RICCADSA study) [17], or in those with coronary or cerebrovascular disease plus moderate-to-severe OSA and minimal sleepiness (SAVE trial) [18]. A nonrandomized longitudinal cohort study also found that CPAP treatment after an acute coronary syndrome event did not reduce the risk of a composite cardiovascular end point over a median follow-up of 75 months [16]. On-treatment analysis in the RICCADSA study suggested that higher levels of CPAP usage could significantly reduce cardiovascular risk, and patients who were adherent to CPAP therapy had a significantly lower risk of stroke compared with the non-CPAP group [17]. In our study, rates of MACCE in CPAP-compliant OSA patients with CAD were significantly reduced versus rates in CPAP-noncompliant OSA patients with CAD after 1 year of follow-up, but not after 6 months, suggesting that a longer follow-up might be required to detect any beneficial effects of CPAP on hard cardiovascular end points.

Anxiety and depression can affect patients with both OSA and CAD. It has been suggested that there is a link between OSA and psychological symptoms [19], and that psychosocial factors can influence the development of CAD and the occurrence of adverse cardiac events [22-24]. Previous neuroimaging data showed that nocturnal intermittent hypoxemia with OSA resulted in hippocampus atrophy and white matter changes that could possibly lead to cognitive and mood dysfunction [30]. However, the mechanism of CAD in anxiety and depression is still unknown. A recent systematic review and meta-analysis suggested that treatment of OSA with CPAP has a moderately positive effect on anxiety and depression [25]. Furthermore, the

SAVE study in patients with OSA and CAD documented significant reductions in anxiety and depression in patients treated with CPAP compared with usual care [18]. In our study, CAD seemed to add to the severity of anxiety and depression in those with pure OSA. On the other hand, CPAP can decrease significant ES of CPAP in anxiety and depression in those with OSA/CAD, rather than only depression showed more ES of CPAP used in pure compliant OSA. The beneficial effects of CPAP on mood were greater in both OSA and OSA/CAD patients with good CPAP compliance compared with poor compliance or no CPAP. However, low compliance and unwillingness to use CPAP were seen in more of our OSA patients with CAD than without CAD (25% vs. 63%). When CPAP compliance was poor, we found greater reductions in anxiety over 6 months' follow-up in patients with OSA than those with OSA and CAD [Table 2, BAI decreased 1.5 from baseline to the 6-month follow-up in OSA and increased 1.1 in OSA with CAD for noncompliance group]. The potential of CPAP to reduce anxiety and depression could be clinically significant given that high levels of anxiety and depression have been linked with an increased mortality risk in CAD patients [31]. To our knowledge, this is the first study to compare the effects of CAD on mood in OSA patients with long-term CPAP treatment.

Several limitations need to be taken into account when interpreting our study findings. First, the use of CPAP was based on clinical indications for each patient and there was no randomization to therapy or use of a sham CPAP control group, meaning that potential sources of bias were not controlled for. Second, patient numbers in each patient group were small, especially the number of OSA/CAD patients who had good compliance with CPAP therapy. This limited our ability to detect statistically significant between-group differences. On the other hand, compliance with CPAP was poorer in OSA/CAD patients than those with OSA alone that would also affect the benefits of CPAP. Furthermore, we did not have any information on whether the improvements in anxiety and depression seen during CPAP therapy had any impact on objective clinical outcomes in our patients. Larger randomized trials are needed to further assess the effects of CPAP on mood in patients with OSA and CAD and to determine the effects of any changes on long-term clinical outcomes.

CONCLUSIONS

We showed that good CPAP compliance reduced anxiety and depression in patients with OSA regardless of CAD. In addition, good CPAP compliance significantly decreased the 1-year rate of MACCE in OSA patients with CAD.

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Conflicts of interest

There are no conflicts of interest.

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