Severity of Obstructive Sleep Apnea in Patients With and Without Cardiovascular-Related Diseases

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BACKGROUND: Previous studies have often investigated the association of obstructive sleep apnea (OSA) with cardiovascular morbidity and mortality, but the possibility of reverse causation has not been clearly defined. OBJECTIVE: To examine if the presence of any of the cardiovascular-related diseases, including hypertension, diabetes mellitus, coronary artery disease, and/or cerebrovascular disease, correlates with more severe OSA. METHODS: This was a retrospective study where all patients age ≥ 18 years referred to our sleep laboratory for suspected OSA were included. The data from the full-night baseline and split-night polysomnographic reports were reviewed. Data were then evaluated by logistic regression analysis to compare between 2 groups, the severity of OSA (respiratory disturbance index [RDI] < 15 vs RDI ≥ 15, and RDI < 5 vs RDI ≥ 5), other polysomnographic variables and daytime sleepiness score (Epworth Sleepiness Scale [ESS] score < 10 and ≥ 10). RESULTS: 190 patients were analyzed. The patients with any of the cardiovascular-related diseases were noted to have more severe sleep apnea (RDI ≥ 15), with an adjusted odds ratio of 3.24. Sleep efficiency ≥ 90% and mean oxygen saturation ≥ 95% were observed less commonly in the patients with any of the cardiovascular-related diseases (adjusted odds ratios of 0.45 and 0.36, respectively). There was no statistically significant difference in ESS score. CONCLUSIONS: Patients with any of the cardiovascular-related diseases are at a higher risk of having moderate to severe OSA without significant increase in daytime sleepiness. Therefore, we suggest that patients with any of the cardiovascular-related diseases should be screened for OSA, even if they are asymptomatic. *Key words: obstructive sleep apnea; cardiovascular-related diseases.* [Respir Care 2012;57(9):1476–1482. © 2012 Daedalus Enterprises]

Introduction

Obstructive sleep apnea (OSA) is a relatively common disease, with an incidence of approximately 4% in men and 2% in women when diagnosed by using an apnea-hypopnea index (AHI) of ≥ 5 events/hour in conjunction with self-reported hypersomnolence. However, when only the AHI criterion was applied to a general population of

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middle-age adults, up to 24% of men and 9% of women met the criterion for OSA.[1] There have been extensive studies regarding the association between OSA and many cardiovascular-related diseases. The mechanisms by which OSA increases the risk of cardiovascular diseases include intermittent hypoxia, sleep fragmentation, sleep deprivation (which causes sympathetic activation), dysregulation of the hypothalamus-pituitary axis, increase of reactive oxygen species , and activation of inflammatory pathways including tumor necrosis factor alpha, interleukin-6, nuclear factor kappa B, leptin, prothrombotic factors (fibrinogen and plasminogen activator inhibitor-1), and C-reactive protein.[2,3] Despite strong evidence regarding a correlation between OSA and cardiovascular morbidity and mortality, systemic inflammation, and impaired glucose metabolism, the possibility of reverse causation is not clearly defined. Our aim was to examine if the presence of any cardiovascular-related disease, including hypertension, diabetes mellitus, coronary artery disease, and/or cerebrovascular disease, correlates with more severe OSA, compared to absence of all the cardiovascular-related diseases. The secondary aim was to evaluate if the Epworth Sleepiness Scale (ESS) score is different between these 2 groups.

QUICK LOOK

Current knowledge

Obstructive sleep apnea is commonly associated with substantial cardiovascular morbidity and mortality. Intermittent hypoxia, sleep deprivation, and activation of inflammatory pathways all play a role in this relationship.

What this paper contributes to our knowledge

Patients with any of the cardiovascular-related diseases are at a higher risk of having moderate to severe obstructive sleep apnea, without significant increase in daytime sleepiness, despite adjusting for age, sex, and body mass index. Screening for obstructive sleep apnea in patients with cardiovascular-related diseases, but who are asymptomatic, may be warranted.

Methods

This was a retrospective study where all patients age ≥ 18 years referred to the sleep laboratory at the Excellence Center for Sleep Disorders, King Chulalongkorn Memorial Hospital/Thai Red Cross Society for suspected OSA from January 1 to June 30, 2010, were included. All polysomnography was conducted in our sleep laboratory, using standard electroencephalography monitoring, including frontal leads (F1, F2), central leads (C3, C4), occipital leads (O1, O2), and reference leads at the mastoids (M1, M2); electromyography; and electrooculography methodology. S_{pO_2} was measured with a finger probe. Air flow was measured by 2 methods: nasal pressure transducer and oral-nasal thermocouple. Sleep stages were scored in 30-second epochs, according to American Academy of Sleep Medicine standard criteria.[4] Apnea was defined using oral-nasal thermocouple excursion, and hypopnea was defined using nasal pressure transducer excursion. Apnea, hypopnea and respiratory-effort related arousals were scored according to the American Academy of Sleep Medicine standard criteria.[4]

The number of apneas, hypopneas, and respiratory-effort related arousals per hour of non-rapid-eye-movement (non-REM), rapid-eye-movement (REM), and total sleep time (TST) are reported as the non-REM respiratory disturbance index (NREM RDI), REM RDI, and total RDI, respectively. All respiratory indexes were classified as obstructive apnea index (OI), central apnea index (CI), hypopnea index (HI), and mixed apnea index (MI).[4] Parameters of oxygenation included in the study were absolute nadir oxygen saturation during TST and mean oxygen saturation during TST. Arousals per hour of TST are reported as the arousal index (AI). Sleep efficiency was defined as TST as a percentage of the total recording time. Time spent in NREM1, NREM2, NREM3, and REM was calculated as percentage of the TST. Periodic leg movements per hour of TST were measured and reported as the periodic leg movements index. Only the full-night baseline and split-night polysomnographic reports were reviewed. For split-night, only the baseline portion was used for analysis.

In order to evaluate for the presence of cardiovascular-related diseases, the information was obtained from pre-test questionnaires that all the patients were required to complete prior to undergoing polysomnographic study. The pre-test questionnaires were self-administered "yes" or "no" questions. The patients were asked if they have hypertension, diabetes, coronary artery disease, or cerebrovascular disease. If the patients had any of the cardiovascular-related diseases (hypertension, diabetes, coronary artery disease, or cerebrovascular disease) or are being treated for such conditions, they were classified in the group with cardiovascular-related disease. If they reported absence of all the above cardiovascular-related diseases, they were classified in the group without cardiovascular-related diseases.

The patients were asked to report other medical conditions, including renal disease, hyperthyroidism, hypothyroidism, anemia, asthma, cancer, iron deficiency, and depression. The ESS, which was recently validated to the Thai language,[5] was also obtained from pre-test questionnaires. Social history, including history of smoking and alcohol use, was obtained. For smoking history, each pa-

tient was required to choose whether he or she had never smoked, previously smoked, or was an active smoker. For alcohol use history, the patient was required to choose whether he or she had never drunk, previously drank, or was an active alcohol drinker.

Other clinical information that was obtained from each patient included age (years), sex, body mass index (BMI), and neck size. Neck size was generally measured approximately at the cricothyroid membrane, prior to the start of the polysomnography. Polysomnographic data used for analysis included total RDI, NREM RDI, REM RDI, OI, CI, HI, MI, AI, sleep efficiency, nadir oxygen saturation, mean oxygen saturation, %NREM1/TST, %NREM2/TST, %NREM3/TST, %REM/TST, and periodic limb movement index. The continuous data were evaluated by *t* test to compare the difference of the baseline information between 2 groups. The nominal data were evaluated by chi-square. Logistic regression analysis was used to compare between the 2 groups the adjusted odds ratio (OR) for developing RDI $\geq$ 15, total OI $\geq$ 5, total HI $\geq$ 5, total MI $\geq$ 5, total CI $\geq$ 5, RDI REM $\geq$ 15, RDI NREM $\geq$ 15, mean oxygen saturation $\geq$ 95%, nadir oxygen saturation $\geq$ 85%, sleep efficiency $\geq$ 90%, periodic limb movement index $>$ 15, and ESS $\geq$ 10. Statistics software (SPSS 17.0, SPSS, Chicago, Illinois) was used for statistical analyses. Our study was approved by the institutional review board, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Results

A total of 230 studies were reviewed in our laboratory from January2 to June 30, 2010. We excluded 8 CPAP studies and 9 studies with the patient's age $<$ 18 years old. We excluded 23 more studies due to incomplete questionnaires resulting in missing information on 4 comorbidities (hypertension, diabetes, coronary artery disease, and cerebrovascular disease). A total of 190 patients were analyzed. There were 88 patients in the group with reported cardiovascular-related diseases, and 102 patients in the group without reported cardiovascular-related diseases. Table 1 demonstrates baseline characteristics, including clinical characteristics (age, sex, BMI, neck circumference, and ESS), underlying disease, and polysomnographic findings.

The results demonstrate that the group with cardiovascular-related diseases was noted to be older, more obese, and had a larger neck size. However, for ESS there was no statistically significant difference between 2 groups. There was also no statistically significant difference found on underlying disease; however, renal disease appeared to be higher in the group with cardiovascular-related diseases, though it did not reach a statistically significant difference (P = .05). There was no statistically significant difference in smoking history or alcohol use history. Polysomnographic data of the 2 groups did not show any statistically significant difference in any parameters except for higher NREM1%/TST and lower sleep efficiency in the group with cardiovascular-related diseases.

After adjusting for age, sex, BMI, neck circumference, and the presence of renal disease, the patients with any of the cardiovascular-related diseases had more severe sleep apnea (RDI $\geq$ 15) with an adjusted OR of 3.24. The increase in RDI was primarily from increase in total obstructive apneic index (OI $\geq$ 5) (adjusted OR of 3.71), and primarily during REM sleep (RDI REM $\geq$ 15) (adjusted OR of 2.77). Good sleep efficiency ($\geq$ 90%) and good mean oxygen saturation ($\geq$ 95%) were noted to be less frequently observed in the group with cardiovascular-related diseases (adjusted OR of 0.45 and adjusted OR of 0.36, respectively) (Tables 2 and 3).

Discussion

Prior studies have shown that higher AHI increases the OR of hypertension. In AHI of 0–4.9, 5–14.9, and $\geq$ 15, the ORs of hypertension in the following 4 years were 1.42, 2.03, and 2.89, respectively.[6] OSA was also found to be linked to coronary artery disease, specifically nocturnal ischemia. The proposed mechanisms were increased sympathetic activity, arousal-related tachycardia, and increased left ventricular afterload.[7] Other cardiovascular-related diseases were also linked to OSA, including cerebrovascular disease and diabetes mellitus. A prior study has shown that AHI of $\geq$ 20 increases the OR of cerebrovascular disease occurrence to 4.33.[8]

Many studies supported the association between OSA and insulin resistance. Only a few longitudinal studies were conducted, The Wisconsin sleep cohort was one of them, which enrolled a total of 1,387 subjects and demonstrated an increased prevalence of diabetes mellitus in patients with OSA after adjustment for other variables. However, after a 4 year-follow up, such association was diminished.[9] The largest cross-sectional study, in which overnight polysomnography and oral glucose tolerance test were performed in 595 men, demonstrated a prevalence of diabetes mellitus in 1 in 3 patients diagnosed with OSA. The study also found a correlation between the severity of OSA and the severity of insulin resistance, as well as the level of glucose intolerance after corrected for BMI and age.[10]

Despite strong evidence demonstrating that OSA increases the risk of major cardiovascular-related diseases, OSA is still under-recognized and under-diagnosed worldwide. Many patients frequently present with important cardiovascular-related diseases; however, physicians frequently do not address the importance of uncovering the potential coexisting OSA. Only a few studies have con-

Table 1. Baseline Characteristics Comparing the Group With to the Group Without Cardiovascular-Related Diseases

	Group With Cardiovascular-Related Diseases	Group Without Cardiovascular-Related Diseases	*P*
Age, y	57.3 ± 11.2	47.2 ± 13.0	< .001
Male, %	74.5	71.6	.74
Body mass index, kg/m^2	28.9 ± 6.0	26.4 ± 7.0	.01
Neck circumference, cm	39.6 ± 4.3	37.8 ± 4.6	.01
Epworth Sleepiness Scale score	10.3 ± 4.5	9.5 ± 4.9	.24
Underlying Disease, %			
Renal disease	6.8	1.0	.05
Hyperthyroid	2.3	1.0	.60
Hypothyroid	1.1	1.0	> .99
Anemia	3.4	1.0	.34
Iron deficiency	0.0	1.1	.46
Asthma	6.9	4.9	.76
Depression	7.0	3.9	.52
Cancer	3.5	1.0	.34
Polysomnographic Findings			
Respiratory Disturbance Index			
TST	34.9 ± 26.7	27.9 ± 26.2	.07
REM time	33.8 ± 24.5	29.2 ± 22.5	.20
NREM time	34.2 ± 27.8	27.2 ± 27.2	.08
Mean asleep S_{pO_2}	93.5 ± 4.1	94.3 ± 3.7	.17
Nadir S_{pO_2}	79.8 ± 8.0	80.2 ± 11.1	.80
Total arousal index	34.0 ± 29.7	32.4 ± 27.0	.71
Percent of TST in			
NREM1	17.6 ± 13.1	12.7 ± 13.4	.01
NREM2	55.2 ± 13.8	58.1 ± 15.2	.17
NREM3	12.4 ± 10.2	13.6 ± 11.0	.47
REM	14.0 ± 8.2	15.7 ± 8.3	.18
Sleep efficiency, %	85.4 ± 12.4	90.8 ± 8.3	< .001
Total central apnea index	0.7 ± 1.6	0.6 ± 1.6	.56
Total obstructive apnea index	16.1 ± 18.4	14.0 ± 23.2	.50
Total mixed apnea index	0.8 ± 2.4	0.4 ± 1.3	.14
Total hypopnea index	16.7 ± 15.8	12.9 ± 11.3	.06
Periodic leg movements index	13.3 ± 23.6	10.4 ± 16.8	.34

± Values are mean ± SD.
REM = rapid-eye-movement sleep
NREM = non-rapid-eye-movement sleep

firmed this potential reverse causation. Logan et al demonstrated that in a resistant hypertension group, the incidence of OSA using the criterion of AHI ≥ 10 was noted to be as high as 83%.[11] Also another prior study has shown that metabolic syndrome and obesity may increase the risk of OSA.[12] The findings of our study have added to currently limited data. The presence of only one of the cardiovascular-related diseases increases adjusted OR of having at least moderate degree of OSA (RDI ≥ 15) to 3.24 times, compared to the group without it. However, we did not find a statistically significant increase in overall OSA (RDI ≥ 5) in the group with cardiovascular-related diseases.

Our results may be important as an indication that the group with cardiovascular-related diseases has increased risk of more severe OSA, but not the milder form. We purposefully addressed the OR of having a moderate to severe degree of OSA, since an increase in morbidity and mortality associated with a milder degree of OSA is currently still controversial. The increase in RDI in our study was confirmed to be secondary to OSA, not central apnea, with the given increase in RDI noted to be primarily from an increase in OI. When comparison was made with the group without cardiovascular-related diseases, the group with cardiovascular-related diseases was also noted to have a lower incidence of good mean oxygen saturation (≥ 95%). This finding is very important, since a prior study has shown that oxygen desaturations—even more so than AHI—are associated with an increased risk of pulmonary arterial hypertension in OSA.[13]

Table 2. Univariate Analysis Comparing Clinical Outcome of the Group With Cardiovascular-Related Diseases to the Group Without Cardiovascular-Related Diseases*

Variable	TST RDI ≥ 15	TST RDI ≥ 5	Total CI ≥ 5	Total OI ≥ 5	Total MI ≥ 5	Total HI ≥ 5	REM RDI ≥ 15	NREM RDI ≥ 15	Mean Asleep S_{pO_2} ≥ 95%	Nadir Asleep S_{pO_2} ≥ 85%	SE ≥ 90%	ESS ≥ 10	PLMI > 15
Age > 60 y	0.75 (0.36–1.63)	1.56 (0.41–8.83)	1.94 (0.55–6.15)	0.92 (0.44–1.94)	2.73 (0.88–8.04)	1.12 (0.45–3.08)	0.73 (0.24–2.45)	1.44 (0.53–4.57)	0.79 (0.38–1.64)	1.47 (0.70–3.06)	0.35 (0.16–0.74)	0.70 (0.29–1.68)	1.54 (0.67–3.40)
Male	5 (2.38–10.00)	6.66 (2.17–25.00)	1.22 (0.35–5.26)	4.76 (2.27–10.00)	6.25 (0.42–6.25)	1.92 (0.82–4.35)	0.83 (0.23–2.56)	4.55 (1.89–11.11)	0.45 (0.21–0.93)	0.5 (0.25–1.01)	1.10 (0.54–2.22)	1.28 (0.59–2.78)	0.98 (0.45–2.27)
Body mass index ≥ 25 kg/m^2	1.89 (0.96–3.70)	1.46 (0.47–4.37)	1.95 (0.57–8.54)	1.01 (0.52–1.94)	3.35 (0.90–18.5)	1.33 (0.58–2.97)	0.51 (0.14–1.57)	1.6 (0.69–3.67)	0.32 (0.16–0.64)	0.47 (0.24–0.91)	0.87 (0.45–1.68)	0.79 (0.39–1.57)	1.41 (0.66–3.13)
Neck size ≥ 40.6 cm	2.38 (0.93–7.14)	4.35 (0.62–100)	1.92 (0.4–7.14)	3.13 (1.27–8.33)	2.78 (0.75–9.09)	1.54 (0.52–5.56)	0.44 (0.14–1.59)	1.41 (0.48–5.00)	0.11 (0.04–0.31)	0.48 (0.18–1.18)	0.52 (0.23–1.19)	0.93 (0.38–2.38)	1.59 (0.63–3.85)
Renal disease	1.30 (0.21–14.03)	ND	8.95 (1.17–57.50)	ND	7.73 (1.02–49.24)	1.44 (0.17–68.02)	0.70 (0.08–34.05)	1.04 (0.10–6.65)	1.01 (0.17–7.09)	2.02 (0.33–14.13)	0.48 (0.07–2.97)	1.52 (0.21–17.23)	0.48 (0.01–4.09)
Cardiovascular-related diseases	2.25 (1.15–4.44)	2.54 (0.80–9.46)	1.67 (0.54–5.41)	2.35 (1.24–4.50)	2.66 (0.89–8.91)	2.05 (0.91–4.84)	1.0 (0.34–2.93)	2.85 (1.18–7.39)	0.32 (0.16–0.64)	0.61 (0.32–1.15)	0.44 (0.23–0.84)	0.75 (0.38–1.45)	1.29 (0.64–2.64)

* Values are odds ratio (95% CI).
TST RDI = respiratory disturbance index during total sleep time
CI = central apnea index
OI = obstructive apnea index
MI = mixed apnea index
HI = hypopnea index
REM RDI = respiratory disturbance index during rapid-eye-movement sleep
NREM RDI = respiratory disturbance index during non-rapid-eye-movement sleep
SE = sleep efficiency
ESS = Epworth Sleepiness Scale score
PLMI = periodic leg movements index
ND = No data. Variable was not tested because it was not observed in the group.

Table 3. Multivariate Analysis Comparing Clinical Outcome of the Group With Cardiovascular-Related Diseases to the Group Without Cardiovascular-Related Diseases*

Variable	TST RDI ≥ 15	TST RDI ≥ 5	Total CI ≥ 5	Total OI ≥ 5	Total MI ≥ 5	Total HI ≥ 5	REM RDI ≥ 15	NREM RDI ≥ 15	Mean Asleep S_{pO_2} ≥ 95%	Nadir Asleep S_{pO_2} ≥ 85%	SE ≥ 90%	ESS ≥ 10	PLMI > 15
Age > 60 y	0.62 (0.25–1.52)	1.91 (0.37–9.78)	2.33 (0.63–8.56)	0.61 (0.24–1.52)	2.94 (0.90–9.63)	1.21 (0.43–3.39)	0.39 (0.15–1.07)	0.71 (0.24–2.07)	1.03 (0.43–2.45)	1.21 (0.53–2.76)	0.50 (0.23–1.09)	0.52 (0.21–1.27)	1.23 (0.51–2.96)
Male	4.17 (1.96–9.09)	6.25 (2.08–20.00)	1.47 (0.36–5.88)	6.25 (2.78–14.29)	1.96 (0.50–7.69)	1.96 (0.86–4.35)	1.30 (0.54–3.13)	6.25 (1.72–25.00)	0.45 (0.41–2.33)	0.46 (0.22–0.94)	1.33 (0.66–2.78)	1.27 (0.58–2.78)	0.88 (0.40–1.96)
Body mass index ≥ 25 kg/m^2	1.22 (0.56–2.67)	1.03 (0.32–3.36)	2.76 (0.58–13.20)	0.54 (0.24–1.23)	5.71 (0.97–33.62)	1.16 (0.48–2.78)	1.68 (0.68–4.15)	1.54 (0.56–4.24)	0.51 (0.23–1.11)	0.54 (0.26–1.12)	1.33 (0.62–2.83)	0.68 (0.33–1.40)	1.17 (0.51–2.69)
Neck size ≥ 40.6 cm	2.27 (0.80–2.64)	4.0 (0.46–33.33)	1.52 (0.38–5.88)	4.55 (1.62–12.5)	1.85 (0.56–6.25)	1.35 (0.44–4.17)	2.08 (0.81–5.26)	6.67 (2.5–16.67)	0.14 (0.05–0.41)	0.68 (0.27–1.72)	0.45 (0.19–1.08)	1.04 (0.43–2.56)	1.43 (0.58–3.57)
Renal disease	1.05 (0.14–8.0)	ND	9.02 (1.26–64.56)	ND	7.60 (1.03–56.33)	1.09 (0.11–10.60)	1.37 (0.20–9.27)	ND	1.62 (0.26–10.33)	1.68 (0.29–9.93)	0.93 (0.17–5.11)	3.31 (0.35–31.03)	0.86 (0.40–1.88)
Cardiovascular-related diseases	3.24 (1.45–7.22)	1.99 (0.57–6.93)	0.74 (0.20–2.74)	3.71 (1.63–8.44)	1.44 (0.42–4.97)	1.79 (0.74–4.29)	2.77 (1.22–6.29)	1.61 (0.65–3.94)	0.36 (0.17–0.78)	0.51 (0.25–1.06)	0.45 (0.22–0.91)	0.98 (0.47–2.06)	0.86 (0.40–1.88)

* Values are adjusted odds ratio (95% CI).
TST RDI = respiratory disturbance index during total sleep time
CI = central apnea index
OI = obstructive apnea index
MI = mixed apnea index
HI = hypopnea index
REM RDI = respiratory disturbance index during non-rapid-eye-movement sleep
SE = sleep efficiency
ESS = Epworth Sleepiness Scale score
PLMI = periodic leg movements index
ND = No data. Variable was not tested because it was not observed in the group.

We also demonstrated a significant reduction in sleep efficiency in the group with cardiovascular-related diseases. This finding can be interpreted that the sleep quality of the patients with cardiovascular-related diseases may be worse, compared to the group without it. Interestingly, we have found no difference in ESS; however, this finding is not unexpected. A prior study has shown that ESS is not correlated with the degree of OSA.[14] This finding may support the need of screening for OSA in these high risk groups, even though they may not be symptomatic or lack excessive daytime sleepiness. Even though our study was conducted in Thailand, prior study has shown that OSA characteristics in the Thai population are similar to the western countries, so the findings from our study should be applicable in the general population.[15]

We have adjusted the OR for the most important factors; age, sex, BMI, and neck circumference, as well as the presence of renal disease, which was noted to be more frequently observed in the group with cardiovascular-related diseases. Even though the presence of renal disease did not reach the statistically significant P value ($P = .05$), in order to control for the most possible factors, we used it as one of the adjusting factors for univariate and multivariate analyses. Nevertheless, we are still aware of many confounding factors that could not be adjusted, given the nature of this retrospective study. Also, given the fact that the presence of underlying diseases was obtained from self-administered questionnaires, there was a possibility that the patients were not aware of their underlying diseases. However, this problem would have weakened the difference between the 2 groups, which means that the difference may have even been higher in reality.

Conclusions

Patients with any of the cardiovascular-related diseases are at a higher risk of having moderate to severe OSA, without significant increase in daytime sleepiness, despite adjusting for age, sex, and BMI. Therefore, we suggest that patients with any of the cardiovascular-related diseases should be screened for OSA, even if they may not be symptomatic.

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