

Sleepiness in Obstructive Sleep Apnea: A Harbinger of Impaired Cardiac Function?

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Study Objectives: Daytime sleepiness is a common clinical presentation in both obstructive sleep apnea (OSA) and cardiovascular diseases. The purpose of this study was to assess the relationship between degree of subjective daytime sleepiness and cardiac performance in patients with obstructive sleep apnea.

Design: Observational study

Setting: General Clinical Research Center

Patients: The study sample was comprised of 86 patients (68 men and 18 women) with an average age of 47 years. All were suspected of having obstructive sleep apnea and underwent confirmatory diagnostic polysomnography (respiratory disturbance index ≥ 15).

Measurements and Results: Stroke volume and cardiac output were measured using impedance cardiography and corrected for body surface area to yield stroke index and cardiac index. Daytime sleepiness was

quantified using the Epworth Sleepiness Scale. A higher Epworth Sleepiness Scale score, suggesting more daytime sleepiness, was significantly related to lower stroke index and cardiac index. In multiple regression analyses, the relationships of Epworth Sleepiness Scale score with both stroke index and cardiac index were significant ($p < .05$), even after controlling for age, sex, ethnicity, respiratory disturbance index, and mean sleep oxygen saturation.

Conclusions: These results suggest that daytime sleepiness is independently associated with decreases in cardiac function as assessed by impedance cardiography in patients with obstructive sleep apnea.

Keywords: Sleepiness, hemodynamics, obstructive sleep apnea

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA) IS ASSOCIATED WITH SEVERE MORBIDITY AND APPRECIABLE MORTALITY, PARTICULARLY FROM CARDIOVASCULAR diseases,¹ hypertension,^{2,3} cardiac arrhythmias,⁴ stroke,⁵ and heart failure.⁶ OSA is associated with activation of a number of neural, humoral, thrombotic, metabolic, and inflammatory disease mechanisms, all of which have also been implicated in the pathophysiology of cardiac and vascular disease.^{7,8}

Daytime sleepiness is a common symptom in patients with OSA and is an important criterion for establishing the severity and clinical implication of OSA. Patients with OSA are sleepier than control subjects when assessed by multiple sleep latency testing or by sleep-symptom questionnaires, and their sleepiness correlates with OSA severity, as determined by the respiratory disturbance index (RDI).^{9,10}

Daytime sleepiness is also a common clinical presentation of patients with cardiovascular diseases.¹¹ Several studies have ex-

amined daytime sleepiness with regard to cardiovascular disease in various settings. In the large National Health and Nutrition Survey, the risk of stroke was found to be significantly increased in subjects with daytime sleepiness relative to that of subjects who were not sleepy.¹² High Epworth Sleepiness Scale (ESS) scores have been found in elderly women who reported having hypertension,¹³ and the ESS has been used to identify individuals at risk for hypertension.¹⁴ A recently reported study of community-dwelling older men showed that daytime sleepiness was associated with a significant increase in ischemic heart disease events.¹⁵ These studies suggest that daytime sleepiness may be a harbinger of underlying cardiovascular pathophysiology.

To our knowledge, there has been no study that examined the relationship between daytime sleepiness and cardiac hemodynamic performance in OSA. Perhaps one of the reasons that cardiac hemodynamics have not been routinely studied in patients with OSA is the mistaken belief that assessments of cardiac function require invasive techniques. Impedance cardiography has been reliably used as a noninvasive alternative to pulmonary artery catheterization for assessment of cardiac performance,¹⁶ even in obese subjects.¹⁷ Using impedance cardiogram, Nelesen et al¹⁸ reported disrupted cardiac adrenergic regulation in patients with OSA. Furthermore, impedance cardiography has revealed that these disruptions are reversed by continuous positive airway pressure such that stroke volume and cardiac output increase and systemic vascular resistance decreases.¹⁹ Advances in technology have facilitated the refinement of this older technique to the point that these noninvasive techniques correlate at a level of 0.95 or higher with more traditional methods of measuring hemodynamics, such as dye dilution.²⁰

The purpose of this study was to assess the relationship between subjective daytime sleepiness and cardiac performance measured by impedance cardiogram in patients with OSA. We hypothesized that patients with OSA with more daytime sleepiness would have more impaired cardiac performance, even after controlling for possible confounding variables.

Disclosure Statement

This was not an industry supported study. Dr. Ancoli-Israel is a consultant and/or advisory board member for Acadia, Cephalon, King Pharmaceuticals, Merck, Neurocrine Biosciences, Inc., Neurogen, Inc., Pfizer, Sanofi-Aventis, Sepracor, Somaxon, and Takeda Pharmaceuticals North America, Inc.; and is a member of the speakers' bureau for Cephalon, King Pharmaceuticals, Neurocrine Biosciences, Inc., Pfizer, Sanofi-Aventis, Sepracor, and Takeda Pharmaceuticals North America, Inc. Dr. Dimsdale has received research support from Sepracor. Drs. Choi, Nelesen, Loredó, Mills, and Ziegler have indicated no financial conflicts of interest.

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METHODS

Patients

We recruited patients with suspected OSA for this study via public advertisement and referral from sleep-disorder clinics. All patients gave written informed consent to participate in the protocol, which was approved by the University of California at San Diego Human Subjects Committee. Screening studies included complete blood count, chemistry panel, electrocardiogram, spirometry, medical history, and physical examination.

Patients with major medical disorders other than hypertension and OSA were excluded. Thus, the study did not include patients with a history or current evidence of heart disease, chronic obstructive pulmonary disease, liver or renal disease, diabetes, severe asthma, cerebrovascular disease, or cancer. In addition, women were excluded if they had a diagnosis of premenstrual syndrome, took oral contraceptives, or were pregnant.

Patients receiving antihypertensive medications underwent frequent blood pressure measurements while medicines were slowly tapered and then withheld for 3 weeks prior to testing. Patients whose blood pressure exceeded 170/105 were returned to antihypertensive treatment and were excluded from further testing. All patients underwent home monitoring (Night-Watch System; Respirationics; Murrysville, PA) to screen for sleep apnea. Patients with an RDI of 20 or higher on home testing were eligible to continue in the study.

Study Protocol

Patients were admitted to the University of California, San Diego General Clinical Research Center for overnight polysomnography, which recorded central and occipital electroencephalography derivations, bilateral electrooculogram, submental and bilateral tibialis anterior electromyogram, nasal/oral airflow (using a thermistor and pressure transducer), and thoracic and abdominal respiratory movements using Resptrace respiratory inductance plethysmography. Oxygen saturation was monitored using a pulse oximeter (Biox 3740, Datex-Ohmeda, Louisville, Colo) and was analyzed using specialized computer software (Profox Associates, Inc., Escondido, CA)

Electroencephalographic recordings during sleep were scored according to the criteria of Rechtschaffen and Kales.²¹ Apneas were defined as decrements in airflow of at 90% or more from baseline for at least 10 seconds. Hypopneas were defined as decrements in airflow of at least 50% but less than 90% from baseline for at least 10 seconds. Most subjects had solely obstructive type events; only a few subjects showed evidence of central apneas. Participants who showed predominantly central apneas (> 50% of total apneas) were excluded. The number of apneas and hypopneas per hour were calculated to obtain the RDI. Significant OSA was defined as an RDI of at least 15.

The noninvasive stroke volume and cardiac output were obtained by impedance cardiography (Minnesota Impedance Cardiograph 304B; Surcom; Minneapolis, MN). The testing was done in the afternoon following the overnight polysomnography between the hours of 2:00 PM and 4:00 PM. Impedance cardiographic tape was applied in a tetrapolar configuration.

The electrocardiogram (ECG) lead configuration was selected to enhance the Q and T waves for the purpose of facilitating off-line signal event detection. The 3 ECG electrodes were placed

on either side of the rib cage and on the sternum, inferior to the suprasternal notch. Either a Lead I or II configuration was selected on the basis of the magnitude of the Q wave. Of the 4 impedance cardiography leads, Lead II was affixed first in a location just superior to the suprasternal notch of the thorax, at the base of the neck. Lead I was placed precisely 3 cm superior to Lead II on the upper neck. Lead III was placed around the thorax overlying the xiphoid process at the inferior end of the sternum. Lead IV was placed on the lower portion of the thorax precisely 10 cm inferior to Lead III. These 4 ICG leads were placed around the body while the subject was standing erect, such that the impedance electrodes were parallel to the floor. This was done to ensure uniform current spread over the body. After application of the impedance cardiography electrodes, the ECG (model 78352C; Hewlett-Packard; Andover, MA) electrodes were applied in a modified standard lead I or lead II configuration to maximize the R wave.

Subjects sat quietly for 30 minutes for habituation to the instrumentation and testing environment before the testing began. Following the 30 minutes, 3-minute data were collected, and these data were used for the analysis. Signals were ensemble averaged off line over a 3-minute interval using a computer program that summed the digitized beat-by-beat waveforms, time synchronized to the ECG R-wave, and divided by the number of cardiac cycles. The ensemble average was then graphically displayed, and the waveform events were scored by computer signal processing techniques, the precision of which has been described previously.^{22,23} Each ensemble average, including the placement of cursors over the computer-detected events, was then viewed by the operator.

The stroke volume was calculated using the Kubicek formula,²⁴ $SV = \rho \times (L/Z)' \times LVET \times dZ/dt_{max}$, in which SV is the stroke volume and ρ is the blood resistivity in Ohms cm-1 and was calculated using the formula, $\rho = 53.2e(0.022)HCT$, where HCT is the hematocrit as measured from complete blood count and Z is the mean thoracic impedance. The electrode distance (L) in cm between ICG Leads II and III was measured while the subject was seated in the chair prior to the observation period and LVET is the left ventricular ejection time. Cardiac output (or Q), measured in liters per minute was calculated by multiplying the heart rate by the SV.^{24,25}

Because obesity is commonly associated with OSA, it is advantageous to control for obesity as a potential confound. One can do this by measuring cardiac output and stroke volume while controlling for BMI. Alternatively, in cardiovascular studies, it is more common to calculate stroke index and cardiac index as a way of correcting for body surface area (stroke index = stroke volume/body surface area; cardiac index = cardiac output/body surface area). We provide, in this paper, a calculation of stroke index and cardiac index as a convenient metric for examining hemodynamics after controlling for differences in body habitus. Participants completed the ESS²⁶ during their stay in University of California, San Diego General Clinical Research Center. The ESS is a well-validated 8-item self-completion questionnaire that asks the subject to rate his or her likelihood of falling asleep in a variety of commonly encountered situations. Possible scores range from 0 (the least sleepy) to 24 (the most sleepy).

Statistical Analysis

Natural logarithm transformation was used to achieve normal

distributions of stroke index and cardiac index. Descriptive statistics were used to examine the effect of such transformations on skewness and kurtosis. Pearson correlation analysis was used to determine the association between the cardiac variables (log stroke index and log cardiac index) and other variables. Multiple hierarchical linear regression analysis was used with cardiac variables (log stroke index and log cardiac index) as the dependent variables. At step 1, we forced the entry of demographic variables (age, sex, and ethnicity). At step 2, we entered RDI and mean oxygen saturation during sleep. At step 3, we entered the ESS score. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 12.0 for Windows (SPSS Inc, Chicago, IL), and statistical significance was determined at the α level of .05; all tests were 2 tailed.

RESULTS

Table 1 provides the sample characteristics. Briefly, all 86 patients recruited into the study had OSA with an RDI of at least 15. On average, the patients were mildly obese (body mass index 31.1 ± 5.1 kg/m²), had mild excessive daytime sleepiness (ESS score 11.5 ± 5.3), and had severe OSA (RDI 56.1 ± 29).

Table 2 summarizes the Pearson correlation coefficients between cardiac variables (log stroke index and log cardiac index) and other variables. The log stroke index was significantly correlated with RDI, mean oxygen saturation during sleep, and ESS score, and the log cardiac index was significantly correlated with RDI and ESS score ($p < .05$).

We then analyzed these data with hierarchical multiple linear regression analysis with cardiac variables (log stroke index and log cardiac index) as the dependent variables (Table 3 and Table 4). Age, sex, and ethnicity accounted for 6.4% of the variance in the log stroke index and 4.6% of the variance in log cardiac index ($p > .05$). When RDI and mean oxygen saturation during sleep were entered into the equation, they accounted for an additional 8.0% of the variance in the log stroke index and 4.6% in the log

Table 1—Characteristics of the 86 Subjects

Characteristics	Results
Age, y	47.0 \pm 9.2
BMI, kg/m ²	31.1 \pm 5.1
BSA, m ²	2.1 \pm 0.2
RDI, events/h	56.1 \pm 29.0
SpO ₂ , %	92.4 \pm 4.3
SBP, mm Hg	129.8 \pm 15.3
DBP, mm Hg	80.1 \pm 9.7
Heart rate, beats/min	77.8 \pm 13.1
SV, mL	63.5 \pm 22.7
SI, mL/m ²	30.3 \pm 10.8
CO, L/min	4.9 \pm 1.8
CI, L·min ⁻¹ ·m ⁻²	2.3 \pm 0.8
ESS score	11.5 \pm 5.3

Data are presented as mean \pm SD.

BMI refers to body mass index; BSA, body surface area; RDI, respiratory disturbance index; SpO₂, mean sleep oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; SV, stroke volume; SI, stroke index; CO, cardiac output; CI, cardiac index; ESS, Epworth Sleepiness Scale.

Table 2—Univariate Pearson correlations Between Log Stroke Index and Log Cardiac Index and Other Variables

Variables	Log stroke index r (p)	Log cardiac index r (p)
Age, y	0.201 (0.063)	0.141 (0.194)
RDI, events/h	-0.318 (0.003) ^a	-0.222 (0.040) ^a
SpO ₂ , %	0.259 (0.017) ^a	0.203 (0.064)
Slow wave sleep, min	-0.125 (0.254)	-0.086 (0.432)
Sleep efficiency, %	0.172 (0.116)	0.080 (0.469)
Wakefulness after sleep onset, min	0.043 (0.698)	0.101 (0.355)
SBP, mm Hg	-0.066 (0.547)	-0.029 (0.795)
DBP, mm Hg	-0.034 (0.759)	-0.019 (0.862)
ESS score	-0.334 (0.003) ^a	-0.338 (0.003) ^a

Abbreviations: See Table 1

^a $p < .05$

Table 3—Final Model of the Hierarchical Multiple Regression Analysis Predicting Log Stroke Index

Variables	B	SEB	β	R ²	Δ R ²	p
Step 1				0.064		.193
Age	0.003	0.005	0.082			.489
Sex	-0.104	0.105	-0.113			.328
Ethnicity	-0.004	0.039	-0.011			.918
Step 2				0.144	0.080	.052
RDI	-0.003	0.002	-0.225			.098
SpO ₂	0.008	0.013	0.076			.571
Step 3				0.233	0.089	.005 ^a
ESS score	-0.023	0.008	-0.308			.007 ^a

Abbreviations: See Table 1 and RDI, respiratory disturbance index.

^a $p < .05$

cardiac index ($p > .05$). ESS score significantly accounted for an additional 8.9% of the log stroke index variance ($p = .005$) and 9.6% of the log cardiac index variance ($p = .024$) after controlling for age, sex, ethnicity, mean oxygen saturation during sleep, and RDI. The ESS score was an independent predictor of log stroke index ($p = .007$) and log cardiac index ($p = .006$).

DISCUSSION

Our data suggest that daytime sleepiness as measured by the ESS is related to daytime cardiac function in patients with severe untreated OSA. The ESS score was negatively associated with stroke and cardiac indexes after controlling for age, sex, ethnicity, mean oxygen saturation during sleep, and RDI (Tables 2-4), suggesting that the more sleepy the patient, the lower the stroke and cardiac indexes. In this sense, the “sleepiness” in patients with OSA may not just reflect sleep deprivation, but may also be a harbinger of impaired cardiac hemodynamics.

Previous studies have examined acute nighttime hemodynamic changes associated with obstruction in OSA and have shown reductions in stroke volume and cardiac output as an apneic event progresses from early to late apnea, with further reduction at ap-

Table 4—Final Model of the Hierarchical Multiple Regression Analysis Predicting Log Cardiac Index

Variables	B	SEB	β	R ²	Δ R ²	p
Step 1				0.046		.341
Age	0.001	0.005	0.031			.800
Sex	-0.066	0.103	-0.075			.524
Ethnicity	-0.023	0.038	-0.068			.551
Step 2				0.092	0.046	.236
RDI	-0.002	0.002	-0.144			.299
SpO ₂	0.007	0.013	0.071			.608
Step 3				0.188	0.096	.024 ^a
ESS score	-0.022	0.008	-0.321			.006 ^a

Abbreviations: See Table 1 and RDI, respiratory disturbance index.

^ap < .05

nea termination.^{27,28} Our data add to this literature documenting daytime cardiac hemodynamic changes associated with daytime sleepiness in patients with OSA. The link between daytime sleepiness and impaired cardiac hemodynamics in OSA is an important finding in that it might suggest a way of identifying patients with OSA who are at increased risk for having impaired cardiac function.

Although commonly viewed as a benign occurrence, daytime sleepiness has been associated with an increased risk of cardiovascular morbidity and mortality.^{12,14,15,29,30} Interestingly, Barbe et al³¹ and Robinson et al³² reported that continuous positive airway pressure treatment had a beneficial impact on blood pressure only in sleepy patients with OSA and not in nonsleepy patients. These various studies suggest that daytime sleepiness might in some way be a significant factor in the pathogenesis of cardiovascular diseases in OSA.

The mechanism for the cardiovascular disease of OSA is uncertain but is likely to be at least partially related to increased sympathetic tone.³³⁻³⁵ One of the suggested reasons for increased sympathetic tone in OSA is frequent arousals from disordered breathing,³⁶ and frequent arousals in OSA also contribute to the occurrence of daytime sleepiness. Therefore, increased sympathetic tone associated with sleep fragmentation could provide a link between daytime sleepiness and impaired cardiac function in OSA. This is a natural area for future investigation.

Daytime sleepiness is also one of the clinical presentations of patients with cardiovascular diseases, particularly, congestive heart failure.¹¹ Although there has been no study investigating directly the relationship between daytime sleepiness and congestive heart failure, it has been argued that sleep apnea may be a consequence of congestive heart failure, with evidence that indexes of central sleep apnea and possibly OSA improve with measures to improve cardiac function.^{37,38} Conversely, there is evidence that sleep apnea may contribute to the progression of congestive heart failure by a number of mechanisms, including recurrent myocardial hypoxemia, increased oxygen demand, and sympathetic activation.^{39,40} Because daytime sleepiness is also a result of these mechanisms, cardiac dysfunction and daytime sleepiness would be thought to be progressing together.

In our sample population of patients with OSA, we specifically

excluded any patient with heart disease or congestive heart failure. Therefore, the associations found in our study between sleepiness and lower stroke index and cardiac index (Tables 2-4) could be looked at as a marker of impaired cardiac function even in the absence of clinically significant heart disease or symptoms. A recent echocardiographic study showed diminished left ventricular ejection fraction in patients with sleep apnea.⁴ We did not perform cardiac echocardiography to determine the presence of structural heart abnormalities. Further research is needed to correlate to see if daytime sleepiness is associated with structural heart changes that could potentially result in depressed cardiac function.

Even though patients with OSA are usually obese, we did not include body mass index in our model (Table 3 and 4) because we already controlled for body surface area when calculating stroke index and cardiac index. As a check, we reran secondary analyses including body mass index in our analyses, and we found similar findings, ie, higher ESS score was still significantly associated with lower stroke index and cardiac index.

One of the limitations of our study is the relatively modest sample size. Another potential limitation of this study could be the inclusion of hypertensive patients. Hypertension is common in sleep apnea.^{2,3} However, we also performed secondary analyses on the subset of normotensive patients (n = 57), and found similar findings, ie, higher ESS score was independently significantly associated with lower stroke index and cardiac index.

Because patients with OSA are usually obese, there are concerns that the excess adipose tissue of obese patients may complicate noninvasive assessment of hemodynamic monitoring. Recently, Brown et al¹⁷ compared cardiac index measurements obtained from both impedance cardiography and pulmonary artery catheterization in critically injured obese patients. They concluded that the impedance cardiographic data might be used reliably as a noninvasive alternative to pulmonary artery catheterization for assessment of cardiac performance in obese patients.

Sleepiness was measured using the ESS in our study. It is unclear if these observations would hold using other methods for measuring sleepiness, such as the Multiple Sleep Latency Test or the Stanford Sleepiness Scale. However, the ESS is a widely used, validated questionnaire. The ESS has been shown to reliably measure persistent daytime sleepiness in adults,²⁶ and the ESS score has been shown to be inversely correlated with sleep latency on the Multiple Sleep Latency Test (r = -0.42).⁴²

Although we did not address whether these associations between daytime sleepiness and lower cardiac function were reversible following treatment with continuous positive airway pressure, Nelesen et al¹⁹ found that continuous positive airway pressure corrected the altered cardiac contractility in patients with sleep apnea.

In conclusion, our data suggest that daytime sleepiness is an independent predictor of lower cardiac function as assessed by impedance cardiography in patients with severe untreated OSA. It remains to be determined if this is a chance observation or if it hints at extensive undiagnosed hemodynamic limitations in patients with OSA.

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