Depression and Obstructive Sleep Apnea in Patients With Coronary Heart Disease

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Objective: Depression is a risk factor for cardiac events in patients with coronary heart disease (CHD). Obstructive sleep apnea/hypopnea syndrome (OSAHS) is frequently comorbid with depression and is also a risk factor for cardiac events. Undetected OSAHS could help explain the increased risk associated with depression. **Methods:** Medically stable patients with CHD and major (MD, $n = 53$), minor (md, $n = 36$), or no depression (ND, $n = 43$) were evaluated for 2 nights in a sleep medicine laboratory. **Results:** The prevalence of OSAHS did not differ across groups (MD 66%, md 69%, ND 77%; $p > .05$). Patients with MD had a significantly greater frequency of apneic episodes, a significantly longer duration of apneas and hyponeas, and more oxygen desaturations per hour than those with md, but there were no differences between MD and ND in frequency of apneic episodes or oxygen desaturations. However, males with MD tended to have more obstructive episodes per hour than did ND males, whereas females with MD had fewer episodes than did ND females. Apnea duration was longer in patients with MD compared with patients with no ND. There was no difference in the mean duration of apnea per hour between the md and ND groups. **Conclusions:** Although OSAHS is not more common in depressed patients with CHD, MD is associated with longer obstructive sleep apneic episodes in both men and women and with a higher frequency of episodes in men. **Key words:** depression, sleep-disordered breathing, coronary heart disease.

CHD = coronary heart disease; **MD** = major depression; **md** = minor depression; **ND** = nondepressed; **OSAHS** = obstructive sleep apnea/hypopnea syndrome; **AHI** = apnea/hypopnea index; **LVEF** = left ventricular ejection fraction; **BDI** = Beck Depression Inventory; **BMI** = body mass index; **DISH** = Depression Interview and Structured Hamilton.

INTRODUCTION

Depression is a risk factor for cardiac morbidity and mortality in patients with coronary heart disease (CHD), but little is known about the underlying mechanisms that account for this. Major depression affects approximately 15% to 20% of patients with CHD, and minor depression is present in another 20% (1). Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a chronic sleep-related breathing disorder characterized by a complete (apnea) or partial (hypopnea) blockage of the upper airway. In patients with CHD, OSAHS is a potent trigger of nocturnal myocardial ischemia, heart rhythms characteristic of cardiac sympathetic predominance, and a heightened risk of myocardial infarction (2–6).

Between 30% and 50% of patients with CHD have been reported to have at least mild OSAHS (7–9). However, despite its prevalence and extensive medical morbidity, OSAHS is markedly underdiagnosed. It has been estimated that 93% of moderate to severe cases of OSAHS in women and 82% in men escape clinical diagnosis (10).

Depressive symptoms are very common in patients with OSAHS (11–14). OSAHS is also common in patients with major depression. The prevalence of OSAHS (apnea/hypopnea index ≥ 5) in middle-aged men with major depression is estimated to be approximately 15% (15). Thus, depression and OSAHS are highly comorbid, underdiagnosed, and risk factors for cardiac events. Undetected obstructive sleep apnea could help to explain the increased risk for cardiac events associated with depression. We therefore hypothesized that 1) the prevalence of OSAHS is higher among patients with major depression (MD) than in nondepressed (ND) patients with established CHD; and 2) in the subset of patients who have OSAHS, apneas and hypopneas are more frequent, longer, and associated with more oxygen desaturation among patients with MD than in those who are not depressed. We further hypothesized that OSAHS is more prevalent and that episodes of obstructive sleep apnea and hypopnea are more frequent, longer, and associated with more oxygen desaturation among patients with CHD with MD than in those with minor depression (md).

METHODS

Subjects

Patients with CHD, as defined by a history of myocardial infarction or angiographically documented coronary artery disease, were recruited from cardiology services, cardiac rehabilitation units, public announcements, general internal medicine practices, pharmacies, and cardiology practices affiliated with the Washington University School of Medicine. Medically eligible patients were screened for depression with the Beck Depression Inventory (BDI) (16). The research was described to potential participants as a study of heart disease, depression, and sleep disorders. Interested patients signed an informed consent document that had been approved by the Washington University Medical Center Human Subjects Committee.

Patients were excluded from the study if they:

1. Had moderate to severe cognitive impairment, a severe psychiatric disorder other than unipolar depression or anxiety, active suicidal ideation, consumed >2 ounces of alcohol per day, or had current substance abuse not including tobacco use;
2. Had coronary artery bypass graft surgery in the last 10 weeks or an acute myocardial infarction within the past 6 months, were pacemaker-dependent, or in atrial fibrillation;
3. Had either a clinical diagnosis of active congestive heart failure or a left ventricular ejection fraction (LVEF) <35%;
4. Had evidence of diabetic neuropathy, severe asthma, or chronic obstructive pulmonary disease;
5. Were physically unable to tolerate the study protocol;

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6. Were currently taking an antidepressant, a benzodiazepine, or clonidine; or
7. Were currently under treatment for, or had been diagnosed with, OSAHS or any other sleep disorder.

Depression Assessment

Patients who were not excluded by the previously mentioned criteria were administered the Depression Interview and Structured Hamilton (DISH) (17). The DISH was used to diagnose major and minor depression according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria (18) and to measure the severity of depression on an embedded 17-item version of the Hamilton Rating Scale for Depression (HRSD). The interviews were conducted by experienced research nurses who were trained in the administration of the DISH and in deriving depression diagnoses.

All of the eligible depressed patients were enrolled, but only approximately half of the nondepressed patients were enrolled to accrue approximately equal numbers of patients with major depression, minor depression, and no depressive disorder. This was accomplished by waiting to enroll the next available nondepressed patient until after two depressed patients had been enrolled.

All participants were scheduled for two consecutive nights at the Sleep Medicine Center at Washington University School of Medicine. The primary analyses were based on the data from the second night of the sleep study, except for patients for whom a second night's study was unavailable as a result of OSAHS that was severe enough to require intervention during the first study night. The data from the first night were used in these cases.

The participants were not asked to discontinue any prescribed medications during their sleep study. This decision was based on two considerations. First, there were ethical concerns about discontinuing cardiac medications even temporarily in patients with CHD. Second, discontinuing medications would have diminished the ecological validity of the findings, because patients with depression and disordered sleep are at increased risk for cardiac morbidity and mortality even when taking cardioprotective medications.

Polysomnography

The Sleep Medicine Center is staffed by neurologists, pulmonologists, nurses, and technicians. The staff were blinded to the depression status of the patients. Polysomnographic data were obtained from Respironics Alice 3 and Alice 4 digital systems.

Participants arrived at the sleep laboratory approximately 2 hours before their normal bedtime. Eighteen cranial electroencephalogram electrodes were applied using standard techniques. Oral and nasal airflow was measured by a thermocouple device. Oxygen saturation was measured by pulse oximetry. Respiratory events were determined by trained technicians using the criteria described subsequently.

The following variables were calculated from the polysomnographic recordings:

1. Frequency of apneas and hypopneas: the number of apneic and hypopneic events per hour of sleep; events are defined as a cessation (apnea) or reduction (hypopnea) in airflow greater than 10 seconds that results in either an arousal or in a 3% or greater oxygen desaturation;
2. Desaturation index: the number of times per hour that oxygen saturation fell 3% or more below baseline levels;
3. Maximum O_2 desaturation: the lowest oxygen level recorded during sleep; and
4. Duration of apneic and hypopneic episodes: the duration of the cessations or reductions in airflow that result either in an arousal or in a 3% or greater oxygen desaturation.

Statistical Methods

OSAHS was defined a priori as ≥5 apneic or hypopneic episodes per hour of sleep (19). The hypothesis that the prevalence of OSAHS differs among the groups with major depression, minor depression, or no depressive disorder was tested both in univariate analyses and with logistic regression models adjusting for age, sex, and body mass index (BMI). Logistic regression adjusts the raw prevalence, p = probability of mean frequency of apnea/hypopneas ≥5/hour by modeling $\text{logit}(p) = \log(p/1 - p)$, which transforms the raw prevalence in the interval [0, 1] onto the continuous scale of real numbers from negative to positive infinity. The logit is then modeled as $\text{logit}(p) = \alpha + \beta' x$, in which x is a vector of covariates, each of which may account for some portion of the variance in the logit(p). In this sense, the estimate of the effect of one of the covariates (e.g., β_1) is considered to be adjusted for the effects of the other covariates (e.g., $\beta_2 - \beta_k$) (20).

The primary analyses were conducted for the entire sleep period. Obstructive sleep apneas and hypopneas were stratified by rapid eye movement (REM) versus nonrapid eye movement (NREM) in secondary analyses. Fisher exact test was used to test statistical differences in tables that were small enough to allow for exact calculations; otherwise, the Pearson chi-squared test was used. Analysis of covariance models were used to compare the severity and duration of apneic and hypopneic episodes across groups. The models were adjusted for factors known to affect sleep or the presence or severity of sleep apnea, including age, sex, BMI, history of hypertension, pulmonary disease, smoking, current diabetes, current use of beta blockers, calcium channel blockers, and either angiotensin-II receptor blockers or angiotensin-converting enzyme inhibitors.

All pairwise comparisons among the three depression diagnostic groups were of interest; therefore, the resulting p values were adjusted by Tukey's method within each model. The duration in seconds of each apneic and hypopneic episode was calculated by the sleep laboratory. Among the 124 patients with usable episode-level data, there were 12,947 episodes (range: 1–489 per patient; median: 71; interquartile range: 29–146). An additional component of variance was added to the linear regression model to account for the correlation of repeated measurements within patients. In addition to the covariates listed here, models of event duration were adjusted by sleep state (REM versus NREM) and the interaction between depression diagnosis and sleep stage.

Before conducting these analyses, histograms of the severity measures were examined for outliers. Several outliers were identified, and they were verified to have resulted from something other than data entry error. Jackknife residuals (a measure of distance) and Cook's standard deviation (a measure of the influence of outliers) were examined and used to determine which, if any, of the outliers had to be excluded from the primary analyses (21). SAS for Windows software (SAS/STAT) version 9.0 (SAS Institute, Inc., Raleigh, NC) was used for all statistical analyses.

RESULTS

Of a total of 1167 cardiac patients screened from October 2001 to March 2004, 503 were eligible for enrollment. The most common medical reasons for exclusion were congestive heart failure and chronic obstructive pulmonary disease. Of the 503 medically eligible patients, 134 agreed to participate in the study. Black patients were less likely to participate than were white patients ($p = .004$). There were no other significant differences between participants and nonparticipants.

Of the 134 participants, 53 met the DSM-IV criteria for a current episode of MD, 37 met the DSM-IV criteria for md, and 44 were not depressed. Table 1 compares the demographic and medical characteristics of these groups. Patients with MD were younger and more likely to be diabetic than the other patients. Sleep data for two patients were missing as a result of technical problems. They were excluded from the analyses, leaving 53 patients with MD, 36 with md, and 43 nondepressed patients. Sleep data from the second night were used in all of the analyses except for three ND and four MD patients.

TABLE 1. Medical and Demographic Characteristics by Depression Status

Variable	Major Depression (n = 53)	Minor Depression (n = 36)	No Depression (n = 43)	p^b
Age	53.8 (9.0)	61.4 (10.5)	61.0 (8.6)	<.01
Sex (percent female)	47.2	36.1	32.6	.33
Beck Depression Inventory score	23.6 (9.0)	16.6 (4.1)	2.3 (2.1)	<.01
Hamilton Depression Rating Scale	19.9 (5.0)	13.9 (3.9)	1.6 (2.0)	<.01
Body mass index (kg/m^2)	30.1 (6.8)	30.0 (5.9)	28.7 (4.1)	.23
Left ventricular ejection fraction <40%[a]	8.9	11.5	2.7	.36
Diabetes	34	16.7	14	.05
History of hypertension	66.0	63.9	62.8	.97
Smoking history	75.5	58.3	62.8	.19
History hypercholesterolemia	77.4	77.8	86	.51
Other medical illnesses	35.8	25.7	53.5	.04
History thyroid disease	15.1	13.9	16.3	.99
History of myocardial infarction	58.5	52.8	55.8	.86
History of angina	64.2	52.8	67.4	.40
History of stroke/transient ischemic attack	9.4	5.6	16.3	.33
History of congestive heart failure	13.2	19.4	16.3	.72
History of coronary artery bypass grafting	26.4	30.6	39.5	.40
History of percutaneous transluminal coronary angioplasty	45.3	58.3	58.1	.35

Note: Continuous variables are reported as means (standard deviations); categorical variables are listed as columnwise percentage.
[a] Left ventricular ejection fraction available for 108 patients.
[b] p values correspond to the Fisher exact test for categorical variables and the analysis of variance global F test for continuous variables.

Prevalence of Obstructive Sleep Apnea/Hypopnea Syndrome

The prevalence of clinically significant OSAHS, defined as five or more episodes of obstructive apnea/hypopnea events per hour (apnea/hypopnea index [AHI]), did not differ across the three groups. Seventy-seven percent of the ND patients, 69% of the patients with md, and 66% of the patients with MD had clinically significant OSAHS (md versus ND: odds ratio [OR] = 0.59, p = .25, 95% confidence interval [CI]: 0.24–1.46; MD versus ND: OR = 0.69, p = .47, 95% CI: 0.25–1.88). The prevalence rates adjusted for age, sex, and BMI were 74% (ND), 68% (md), and 73% (MD). The adjusted rates also showed no statistically significant differences between ND patients and those with md (OR = 0.76, p = .62, 95% CI: 0.25–2.28) or between ND patients and those with MD (OR = 0.94, p = .90, 95% CI: 0.33–2.69). The Wald test comparing the coefficients for md versus MD diagnosis was not statistically significant (p = .56).

Frequency and Duration of Obstructive Apneas and Hypopneas

Table 2 displays comparisons of the mean number and duration of obstructive events per hour, the mean number of oxygen desaturations ≥3% per hour, the maximum oxygen desaturation recorded during sleep, and the mean number of minutes spent below 90% oxygen saturation. Between one and four outliers per variable were excluded from the major analyses.

Although the difference in the mean frequency of respiratory events between the ND patients and those with MD was in the expected direction, the difference was not statistically significant. On the other hand, patients with MD had more frequent episodes of obstructive sleep apnea than did patients with md after adjusting for the covariates (see "Statistical Methods;" p = .003). There were no other significant differences in apneic or hypopneic events between MD versus ND.

Also as predicted, patients with MD had longer episodes of obstructive sleep apnea than did patients with md (p = .02) or ND (p = .03) after adjusting for the covariates. However, episode durations did not differ between the md and ND groups. The duration of hypopneic events was longer among patients with MD than md (p = .004).

Patients with MD also had more oxygen desaturations >3% per hour and tended to have lower maximum oxygen desaturation during the night than did md patients. There was no difference across groups in time spent below 90% oxygen saturation during sleep.

Effect of Gender on Frequency of Respiratory Events

The total number of apneic episodes per hour trended in opposite directions for males compared with females with MD versus those with ND. The number of apneic events per hour among males in the ND, md, and MD groups was 6.2, 3.2, and 8.9, respectively, versus 4.6, 1.6, and 1.7 among females. An exploratory model of the total number of apneic events per hour with covariates for depression diagnosis, sex, age, BMI, and all possible interaction terms found the interaction between depression diagnosis and sex to be marginally significant (p = .08, adjusted means for males: 5.4, 3.1, and 8.7; females: 2.9, 1.3, and 2.1 for ND, md, and MD, respectively). These findings suggest MD is associated with more frequent episodes of apnea among males but not among females.

TABLE 2. Frequency and Severity of Sleep Apnea and Hypopnea Across Groups

Variable[a]	Major Depressed	Minor Depression	No Depression	Group Comparisons	P[b]
Mean obstructive apneas (hr)[c]	6.1 (0.8)	1.5 (1.0)	4.4 (0.9)	Non vs. Min	0.06
				Maj vs. Min	0.003
				Non vs. Maj	0.43
Obstructive hypopneas (hr)	8.6 (1.2)	7.3 (1.4)	10.9 (1.3)	Non vs. Min	0.12
				Maj vs. Min	0.40
				Non vs. Maj	0.77
Apnea duration (secs)[c]	23.3 (1.1)	20.0 (1.3)	20.5 (1.3)	Non vs. Min	0.90
				Maj vs. Min	0.02
				Non vs. Maj	0.03
Hypopnea duration (secs)	21.6 (0.6)	19.4 (0.7)	20.9 (0.7)	Non vs. Min	0.09
				Maj vs. Min	0.004
				Non vs. Maj	0.44
O_2 desaturations >3% (hr)	17.8 (1.9)	9.7 (2.2)	14.6 (2.1)	Non vs. Min	0.22
				Maj vs. Min	0.02
				Non vs. Maj	0.51
Lowest O_2 saturation (%) during sleep	84% (0.9)	87% (1.1)	84% (1.0)	Non vs. Min	0.11
				Maj vs. Min	0.07
				Non vs. Maj	0.96
O_2 < 90% (min)	23.3 (4.8)	10.2 (5.8)	19.8 (5.5)	Non vs. Min	0.43
				Maj vs. Min	0.21
				Non vs. Maj	0.89

[a] Variables are reported as means (standard error) or percent adjusted by age, sex, BMI and other confounders (see Statistical Methods).
[b] *p* values from Tukey pair wise comparison test.
[c] Includes obstructive and obstructive/central (mixed) events.

DISCUSSION

The prevalence of OSAHS did not differ among patients with MD, md, or ND even after adjustment for potential confounders. The unadjusted prevalence rates ranged from 66% to 77%. These rates are higher than the unadjusted estimates of 30% to 50% that have been reported in previous studies of patients with CHD (7–9).

As hypothesized, the frequency of obstructive apneic episodes was higher in patients with MD than in those with md. Although there was no difference between patients with MD and nondepressed patients in the sample as a whole, males with MD tended to have more obstructive episodes than did those with md or ND, whereas women with MD tended to have fewer episodes than the women without depression. Also as hypothesized, the apneic and hypopneic episodes were longer in patients with MD than in those with md or ND. However, the duration did not differ between those with md versus ND.

Patients with MD had more episodes of oxygen desaturation (≥3%) than did patients with md, but there was no difference in the number of desaturations between patients with md and ND or between those with MD versus ND. The peak oxygen desaturation during sleep tended to be more severe in both MD and ND patients than in patients with md, but it did not differ between MD and ND patients. There were no between-group differences in the mean time below 90% oxygen saturation.

The longer duration of apneic episodes in patients with MD suggests that the feedback mechanism that triggers the arousal that opens the airway and terminates these episodes may be blunted in patients with MD. This blunting could be a result of depression-related abnormalities in central or autonomic nervous system functioning (1). Because obstructive events are associated with larger increases in systolic blood pressure, myocardial ischemia, and an increased risk of cardiac arrhythmias, longer apneic episodes might have cumulative adverse effects, especially in patients with cardiac disease.

There were between one and four outliers in each of the four OSAH parameters, and they were excluded from the primary analyses. As expected, the significance levels of most of the analyses decreased slightly when the outliers were removed. However, the pattern of results did not differ from those obtained when the outliers were included. Similarly, although the indices of OSAH that were used in the primary analyses were obtained from the entire period of sleep, similar results were obtained when REM and non-REM periods were analyzed separately.

It is unclear why women and men differ in the relationship of depression to the frequency of apneic episodes. Differences between men and women in upper airway anatomy and function, as well as in hormone physiology, could affect the clinical manifestations of OSAHS (22,23). In a recent study comparing a matched sample of 130 women and 130 men with obstructive sleep apnea, Shepertycky and her colleagues observed that women were more likely to be receiving treatment for depression, to report insomnia, and to have hypothyroidism than were men with the same severity of sleep apnea (24). Although the greater prevalence of treated depression in the women in the Shepertycky et al. study may reflect gender differences in depression treatment in the general population,

it is possible that depression and OSAHS may interact differently in men and women. More studies comparing men and women with respect to the etiology and clinical manifestations of OSAHS, as well as of the relationship of OSAH to depression, are needed. In the meantime, because we did not hypothesize these gender differences a priori, they should be interpreted with caution.

One limitation of the study is that it was not possible to recruit an unselected series of patients with CHD. Thus, the participants might not be representative of the population of patients with CHD. Although every effort was made to recruit from a large population of patients with CHD, only 43% of those screened were medically eligible and only 27% of the eligible patients, or 11% of the total sample, were enrolled. Some patients may have wanted to participate in the study primarily because they, or their spouses or roommates, suspected OSAHS, so they took the opportunity to obtain a free polysomnographic evaluation. This could explain why the patients with a just few symptoms of depression, perhaps the "worried well," had less significant OSAH than the patients without depression. During an interview before the sleep study, however, only three patients (two with major and one with minor depression) reported any suspicion that they might have OSAHS. Nevertheless, the possibility of a sampling bias cannot be ruled out.

Another limitation of the study is that patients who were on antidepressants were excluded from participation. This was necessary because nearly all antidepressants affect sleep architecture, especially REM sleep (25,26). Sleep apnea is often more severe during REM sleep, and thus antidepressants may indirectly alter the severity or frequency of apneic episodes. The exclusion of these patients limits the generalizability of the findings. However, most studies of depression in patients with CHD have reported that only a small proportion actually receive treatment for depression (1).

Thermistors were used to detect and measure oral and nasal airflow to help classify episodes of sleep-disordered breathing as either apneas (total cessation of airflow for 10 or more seconds) or hypopneas (partial cessation of airflow for 10 or more seconds). This methodology is widely used (27), but neither thermistors nor other techniques for measuring airflow, including pressure transducers, have perfect sensitivity. As a result, some episodes of sleep-disordered breathing may have been misclassified or missed altogether. However, detection and classification errors should have occurred equally across groups and therefore should not have affected the results. Nevertheless, it must be recognized that apneas and hypopneas may not have been classified correctly in some cases. Therefore, these results should be interpreted with this understanding.

Finally, small differences in sleep apnea between patients with major, minor, or no depression might not be detectable in a study of this size, particularly in covariate-adjusted analyses. Thus, this study should be replicated, and future studies of depression and sleep apnea should use larger samples.

In summary, patients who have OSAHS and MD have longer episodes of obstructive sleep apnea than do patients with md or ND, and male patients with MD tend to have more frequent episodes of obstructive sleep apnea than male patients with md or ND. It is possible that these differences account for at least some of the effects of MD on medical morbidity and mortality that have been observed in patients with CHD, particularly in men. Patients with minor or subsyndromal depression, on the other hand, do not seem to have more severe OSAHS than patients without depression.

The high prevalence of OSAHS in patients with CHD who were not known or suspected to have a sleep disorder, and the risks of medical morbidity and mortality associated with this disorder, underscore the importance of screening for this syndrome. Although it is not feasible to refer all patients with CHD for a polysomnographic study in a sleep laboratory, some form of screening for sleep-disordered breathing is needed. Questions about sleep quality, snoring, and nighttime awakenings should be part of standard care. In addition, routine Holter monitoring, with or without oximetry, can be used to identify nighttime electrocardiography (ECG) patterns associated with sleep-disordered breathing (28). Nighttime ECG monitoring offers a cost-effective way to identify patients with CHD with probable OSAHS. Polysomnographic confirmation of the diagnosis and subsequent treatment could lower the risks associated with this insidious disorder for both depressed and nondepressed patients (29). Furthermore, treatment of OSAHS could also have beneficial effects on depression in some cases (30,31).

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