Published in final edited form as:

J Clin Psychiatry. 2012 January ; 73(1): 31–36. doi:10.4088/JCP.10m06455.

Obstructive Sleep Apnea Hypopnea and Poor Response to Antidepressant Medication in Patients with Coronary Heart Disease

Annelieke M. Roest, MSc¹, Robert M. Carney, PhD², Phyllis K. Stein, PhD², Kenneth E. Freedland, PhD², Hilary Meyer, BA, Brian C. Steinmeyer, MS², Peter de Jonge, PhD^{1,3}, and Eugene H. Rubin, MD, PhD²

¹CoRPS – Center of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, The Netherlands ²Departments of Psychiatry (R.M.C., K.E.F., B.C.S., E.H.R) and Internal Medicine (P.K.S.), Washington University School of Medicine, St. Louis, Missouri, USA

³Department of Psychiatry, University of Groningen, Groningen, The Netherlands

Abstract

Objective—Evidence from several clinical trials in patients with coronary heart disease (CHD) suggests that depression that does not respond to treatment is associated with a particularly high risk of adverse cardiac outcomes. The purpose of this study was to determine whether obstructive sleep apnea/hypopnea (OSAH) is associated with a poor response to antidepressant medication in patients with CHD.

Method—This was an ancillary study of a clinical trial of omega-3 fatty acid augmentation of sertraline for depression in patients with CHD. Cyclical heart rate (HR) patterns associated with OSAH were detected via ambulatory electrocardiography prior to treatment. Symptoms of depression were measured at baseline and follow-up with the Beck Depression Inventory-II (BDI-II) and the Hamilton Rating Scale for Depression (HAM-D-17). The primary endpoint was the BDI-II score at 10 weeks.

Results—Thirty (29%) of the 105 patients were classified as having moderate to severe OSAH, based on HR patterns. Patients with OSAH had significantly higher scores on both the BDI-II ($p=0.01$) and the HAM-D-17 ($p=0.02$) at follow-up as compared to the reference group. Adjustment for the baseline depression score, treatment arm (omega-3 versus placebo), body mass index, and inflammatory markers did not change the results.

Conclusion—OSAH is associated with a relatively poor response to sertraline for depression. Future research should determine the contribution of OSAH to the increased risk of adverse cardiac outcome associated with treatment resistant depression.

Introduction

Depression is associated with morbidity and mortality in patients with coronary heart disease (CHD). (1, 2) Randomized controlled trials focusing on the effects of antidepressant treatment on depression and cardiac outcome have found modest effects on depressive

Corresponding author: Robert M. Carney, PhD Behavioral Medicine Center, Department of Psychiatry, Washington University School of Medicine 4320 Forest Park Ave, Ste 301 St. Louis MO 63108 Carneyr@bmc.wustl.edu.

Potential Conflicts of interest Dr. Carney or a member of his family owns stock in Pfizer, Inc. All other authors report no conflicts of interest.

symptoms but no effect on cardiac outcome.(3, 4) Secondary analyses of these studies have shown that patients who did not respond to the antidepressant treatment were at increased risk of adverse cardiac events.(5, 6) Therefore, depression that does not respond to treatment may be associated with a particularly high risk of mortality or cardiac morbidity in patients with CHD.(7) There are no well established risk factors for nonresponse to antidepressant treatment in CHD patients.(6, 7) Obstructive sleep apnea hypopnea (OSAH) has been linked to treatment-resistant depression in depressed psychiatric patients.(8–10) However, this has not yet been investigated in patients with CHD.

OSAH is a chronic, sleep-related breathing disorder characterized by recurrent, complete (apnea) or partial (hypopnea) blockage of the upper airway. OSAH is a potent trigger of nocturnal myocardial ischemia and dysrhythmias characteristic of cardiac sympathetic predominance, and it is associated with low heart rate variability (HRV). Consequently, OSAH is a significant risk factor for acute myocardial infarction (MI) and sudden cardiac death in patients with CHD.(11–14) OSAH is common in patients with CHD, with an estimated prevalence of 30–50%.(15–17) Despite the high prevalence and associated risk for cardiac events, OSAH is seldom identified or treated in these patients.(18)

OSAH is usually diagnosed by polysomnography at a sleep medicine laboratory. However, Guilleminault et al. (19) observed that OSAH can also be identified from a cyclical heart rate (HR) pattern that begins with a slowing in HR, sometimes leading to bradycardia, shortly after the onset of the apneic episode. HR then shifts abruptly to tachycardia with the resumption of breathing, and concludes with a return to baseline if there is a sufficiently long interval of normal breathing after the apneic episode.(19) Previous studies have reported a correlation of $r=0.96$ between the frequency of apneic events associated with an O_2 desaturation of $\geq 3\%$ during polysomnography, and the frequency of this HR pattern on simultaneous electrocardiography (ECG).(20) The characteristic pattern can be detected in ambulatory ECG data, and has been shown to be a highly sensitive and specific test, with or without oximetry, for moderate to severe OSAH.(20, 21)

The purpose of this study was to test the hypothesis that the presence of OSAH, as identified from the cyclical HR pattern, is associated with a poor response to antidepressant treatment.

Method

Subjects and study design

This question was examined in data collected for a randomized, double blinded, placebo-controlled clinical trial of omega-3 augmentation of sertraline for depression in patients with CHD. The trial found no effects of omega-3 augmentation on depression outcomes.(22) Patients with documented CHD were recruited between May, 2005 and December, 2008 from cardiology practices in St. Louis, MO, and from cardiac diagnostic laboratories affiliated with Washington University School of Medicine. Patients were excluded if they 1) had cognitive impairment, comorbid psychiatric disorders, psychosis, a high risk of suicide, or current substance abuse; 2) had an acute coronary syndrome (ACS) within the previous two months, a left ventricular ejection fraction (LVEF) $<30\%$, advanced malignancy, or were physically unable to participate; 3) were taking an antidepressant, anticonvulsant, lithium, or omega-3 supplements; 4) had a known sensitivity to sertraline or omega-3; or 5) refused to participate or were disqualified by their physician from participating in the study. Those who met the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for a current major depressive episode based on a structured depression interview (23), who scored ≥ 16 on the Beck Depression Inventory (BDI-II) (24), and who met none of the exclusion criteria, were enrolled in the trial. Written informed consent was

obtained from all study participants. The study was approved by the Human Research Protection Office at Washington University.

After a two week run-in phase, patients who continued to meet the depression criteria and who were not excluded for other reasons were fitted with an ambulatory ECG monitor for a 24 hour recording. Following baseline assessments, patients were randomized to receive 50 mg per day of sertraline (Zoloft; Pfizer, Inc.) plus either two capsules per day of omega-3 fatty acid (FA) ethyl esters [930 mg of eicosapentaenoic acid (EPA) and 750 mg of docosahexaenoic acid (DHA); Lovaza, GlaxoSmithKline, Philadelphia, PA] or two corn oil placebo capsules, for 10 weeks. Compliance with both the sertraline and the omega-3 or placebo capsules was checked weekly by pill counts, and by asking the participant to confirm that all pills that had been removed were actually taken as prescribed.

At baseline and 10 weeks, 40 ml of blood was drawn. Red blood cell (RBC) membrane EPA +DHA was measured pre- and post-treatment by capillary gas chromatography and expressed as a percentage of the total RBC FAs (i.e., the omega-3 index).(25) High sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6) were measured by standard techniques. Further details on the design and methods of this study can be found elsewhere. (22)

Ambulatory ECG Recording

The Holter ECG recordings were scanned at the Heart Rate Variability Core Laboratory at Washington University with Cardioscan Holter (Version 52a, DMS Holter, Stateside, NV) or MARS Holter scanning software (Version 7.01, GE Medical Systems, Milwaukee, WI). A continuous stream of instantaneous, accurately annotated (beat-to-beat) interbeat intervals was extracted from the ECG and HR tachograms (plots of instantaneous heart rate vs. time) were produced. Only validated normal-to-normal interbeat intervals were used to produce the tachograms. The cyclical HR pattern criteria required a series of at least 3 abrupt tachycardias, each lasting >10seconds, followed by a return to baseline and occurring >30 and <90seconds apart.(20) This pattern was identified by applying the algorithm developed at the Washington University School of Medicine.(20) In a recent study using this method, the presence of these HR patterns had a sensitivity of 98% and a positive predictive value of >92% for identifying patients with moderate to severe OSAH, defined as 30 episodes of apneas and/or hypopneas per hour of sleep as determined from polysomnography.(26) Patients with at least two consecutive hours of the cyclic variation of HR pattern during sleep were classified as having OSAH. These classifications were confirmed by visual inspection.

Assessment of depressive symptoms

Symptoms of depression were measured at baseline and follow-up with the BDI-II and the Hamilton Rating Scale for Depression (HAM-D-17). The BDI-II is a 21-item depression symptom questionnaire with scores ranging from 0 to 63. The 17-item HAM-D-17 is an interview-based measure of depression symptom severity. Both are widely used for assessing depression outcomes and have established reliability and validity.(27, 28) The primary endpoint was the BDIII score at 10 weeks. The HAM-D score at 10 weeks was used as a secondary outcome.

Statistical analysis

Chi-square tests and analyses of variance (ANOVA) were used to test for differences in demographic, psychiatric, and medical characteristics, and in treatment adherence between patients with vs. without OSAH. Analysis of covariance (ANCOVA) models adjusting for baseline depression scores and treatment assignment (omega-3 augmentation or placebo)

were used to compare patients with vs. without OSAH on week 10 BDI-II and HAM-D scores. The interaction between OSAH and treatment assignment was tested to determine whether the hypothesized effect of OSAH on the response to sertraline depends on the presence or absence of omega-3 augmentation. In additional secondary ANCOVA models, we tested the possible confounding effects of body mass index (BMI), hs-CRP, and IL-6, as obesity and inflammation have been associated with poor treatment response to antidepressant treatment.(29, 30) Cohen's *d* was calculated for the OSAH vs non-OSAH group difference in BDI-II scores at follow-up. To explore whether the difference in depression outcome might be explained by nonspecific symptoms such as fatigue, ANOVA was used to identify differences in individual depressive symptoms at 10 weeks on the BDI-II in patients with vs. without OSAH.

All statistical tests were 2-tailed, with $p < .05$ denoting significance. SAS version 9.1 was used for all statistical analyses.

Results

Of the 122 patients enrolled in the clinical trial, 12 did not undergo 24 hour Holter monitoring because they had a pacemaker and one could not be monitored due to a history of allergic reaction to the ECG lead adhesive. Of those who underwent monitoring, HR could not be measured in 4 patients due to equipment failures. Thus, 105 had usable ECG data at baseline.

Baseline characteristics

As has been found in previous studies (15, 16), the prevalence of OSAH was high in this group of CHD patients. Thirty (29%) of the 105 patients were classified as having OSAH, based on HR patterns during self-reported sleep. Table 1 compares the demographic and medical characteristics of the patients with vs. without OSAH. Patients with OSAH had higher BMIs and higher hs-CRP levels than those without OSAH. There were no differences in the severity or duration of the present depressive episode, history of depression, or history of depression treatment.

Post-treatment (10 week) outcomes

As shown in Table 2, treatment adherence did not differ between patients with and without OSAH. After 10 weeks of treatment, patients with OSAH had a mean score of 19.0 (sd=11.0) on the BDI-II. The mean score of the comparison group was 13.0 (sd=9.2). Patients with OSAH had significantly higher BDI-II ($t_{99} = -2.78$; $p = .01$) and HAM-D ($t_{98} = -2.33$; $p = .02$) scores compared to patients without OSAH. These results remained significant for both the BDI-II ($t_{97} = -2.49$; $p = .01$) and the HAM-D ($t_{95} = -2.03$; $p = .04$) after controlling for the baseline depression score and treatment group (omega-3 or placebo). The interaction between OSAH and treatment group provided no evidence that the association between depression and OSAH differed by group at follow up: BDI-II ($F_{1,96} = 3.30$; $p = 0.07$) and HAM-D ($F_{1,94} = 0.09$; $p = .77$). Further adjustment for BMI, hs-CRP, and IL-6 did not affect the association between OSAH and treatment response to sertraline (Table 2). The standardized effect (Cohen's *d*) of OSAH was 0.62 for the BDI-II follow-up score after controlling for baseline depression, treatment group, BMI and hs-CRP.

Individual depressive symptoms

Compared to patients without OSAH, those with OSAH reported higher item scores on all depressive symptoms measured at follow-up with the BDI-II. The difference was significant for increased appetite ($p = .04$), irritability ($p = .01$), crying ($p = .048$), agitation ($p = .01$), sleep

disturbance ($p=.002$), insomnia ($p=.03$), feelings of past failure ($p=.04$), guilt ($p=.03$), self-dislike ($p=.02$), and worthlessness ($p=.04$).

Discussion

The results of the study show that moderate to severe OSAH, based on HR patterns during sleep, is associated with poor treatment response to sertraline in depressed patients with CHD. After 10 weeks, the mean score on the BDI-II was 6 points higher for patients with OSAH compared to patients without OSAH. This difference could not be attributed to a difference in treatment adherence. The association between OSAH and treatment response to sertraline remained significant after adjustment for baseline depression severity and treatment group. In addition, BMI and inflammatory markers did not account for the relationship between OSAH and treatment response. The patients with OSAH reported significantly higher scores on a variety of depressive symptoms at follow-up, including symptoms not directly related to OSAH, such as self-dislike, feelings of past failure, guilt, and worthlessness. Thus, the difference in depression outcome was not explained solely by symptoms also associated with OSAH, such as sleep problems or fatigue.

This study raises the possibility that resistance to antidepressant medication might be caused in some cases by undiagnosed OSAH. Because OSAH is an independent risk factor for cardiac mortality and morbidity, this could help to explain the adverse cardiovascular outcomes that have been associated in previous studies with treatment-resistant depression. However, OSAH is also a risk factor for depression (31), and OSAH and depression might interact to further increase the risk for cardiac events. There are multiple possible pathways through which depression may lead to adverse outcomes in patients with OSAH. There is evidence that depression is associated with a diminished hypercapnic ventilatory response. (32–34) In patients with OSAH and comorbid depression, this could prolong apneic episodes and produce greater O_2 desaturation, and thereby increase the risk for cardiac events. Consistent with this possibility, we recently found that depression is associated with prolonged episodes of apnea in patients with OSAH.(35) Further research is needed to confirm these findings. Additional physiological mechanisms associated with both OSAH and depression which could lead to more adverse cardiac outcomes include low HRV (36), inflammatory processes, endothelial dysfunction, oxidative stress, platelet aggregation, and metabolic dysfunction.(12, 18, 37, 38)

Although OSAH is a common risk factor for further morbidity and mortality in patients with heart disease, it is seldom diagnosed or treated.(18) A recent review concluded that patients with cardiovascular disease should be routinely screened for OSAH.(18) Although polysomnography is the gold standard for diagnosing OSAH, validated questionnaires and nighttime ECG patterns can be used to screen for the disorder.(12) OSAH can be effectively treated by continuous positive airway pressure (CPAP), which prevents upper airway occlusion during sleep.(39) CPAP has also been shown to lower blood pressure, attenuate signs of early atherosclerosis and, in patients with heart failure, improve cardiac function. (40) Since depression that does not respond to standard antidepressant treatment may be associated with a particularly high risk of adverse medical outcomes in patients with heart disease (7), OSAH is a factor that should be taken into account in future depression treatment trials.

This study has some limitations. First, we assessed the presence of OSAH with ECG recordings, although polysomnography is the gold standard for diagnosing OSAH. However, nighttime ECG patterns can be used to screen for the disorder (12) and previous research has shown that the ECG pattern detected in this study is a reliable and valid method for detecting moderate to severe OSAH.(20) In addition, patients diagnosed with OSAH by the

HR pattern had higher BMIs and higher hs-CRP levels than those without OSAH, both of which are associated with OSAH. Since the cyclical patterns of HR are most prominent in patients with moderate to severe OSAH, it is possible that patients with mild but clinically significant OSAH were not recognized. Moderate to severe OSAH is consistent with an apnea-hypopnea index (AHI); number of apneas and hypopneas per hour of sleep >30, but results from the Sleep Heart Health Study suggest that even an AHI as low as 5 is associated with an increased risk of cardiovascular events.(41)

The study also had a relatively small sample size. However, similar to prior studies of patients with CHD, the prevalence of previously undetected OSAH was high in this group of patients. Furthermore, this study was based on a secondary analysis of a randomized controlled trial to the effect of omega-3 augmentation of sertraline for the treatment of depression in patients with CHD. The participants were treated with a single antidepressant medication at a relatively modest dose. Better outcomes might have been achieved if the participants had been given a higher dose of sertraline or another antidepressant. However, previous studies have found little additional improvement in response rates with higher dosages of sertraline (100–200 mg/d), despite a significant increase in side-effects.(42, 43) Future research should assess the association between OSAH and treatment response to standard antidepressant medications using additional antidepressants and formal definitions of treatment resistance.(44)

In summary, this study showed that OSAH is associated with poor treatment response to sertraline in patients with CHD. This association is not explained by differences in BMI, hs-CRP, or IL-6, or by nonspecific symptoms common to both OSAH and depression. Future research should determine the contribution of OSAH to the increased risks associated with depression and its association with poor response to antidepressant treatment. Additionally, studies are needed to identify better treatments for depression in the presence of OSAH, especially in patients with heart disease.

Acknowledgments

Funding/Support This study was supported in part by Grant No RO1 HL076808 from the National Heart, Lung, and Blood Institute, and from the Lewis and Jean Sachs Charitable Lead Trust.

Dr. de Jonge is supported by a VIDI grant from the Dutch Medical Research Council (Grant no. 016-086-397).

Glaxo-Smith-Kline, Inc supplied Lovaza (omega-3) and placebo capsules, and Pfizer, Inc. supplied Zoloft (sertraline) for this study

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Table 1

Omega-3 Baseline Demographic and Medical Characteristics

Characteristic	Obstructive Sleep Apnea/Hypopnea				P-value
	Present (n=30)		Absent (n=75)		
	n	%	n	%	
Treatment assignment (Omega 3)	17	56.7	37	49.3	.50
Age, mean (sd)	58.7	9.9	58.4	8.8	.89
Female	8	26.7	28	37.3	.30
White	22	73.3	65	86.7	.10
Education > 12 years	20	66.7	48	64.0	.80
BMI, mean (sd)	37.0	9.3	31.6	5.8	<.001
Smoking	9	30.0	15	20.0	.27
Hypertension	24	80.0	57	76.0	.66
Diabetes	13	43.3	26	34.7	.41
History of MI/ACS	17	56.7	44	58.7	.85
History of CABG	14	46.7	22	29.3	.09
History of PTCA	17	56.7	49	65.3	.41
New York Heart Association class					.24
No CHF	51	68.0	17	56.7	
I	7	9.3	3	10.0	
II	15	20.0	6	20.0	
III	1	1.3	3	10.0	
IV	1	1.3	1	3.3	
Total cholesterol (mg/dL), mean, (sd)	173.3	42.8	170.4	42.9	.76
HDL cholesterol (mg/dL), mean (sd)	43.3	16.1	44.6	12.6	.69
Triglycerides, fasting (mg/dL), mean (sd)	205.6	159.7	174.4	104.8	.25
hs-CRP (mg/L), mean (sd)	7.8	7.3	5.0	5.8	.04
IL-6 (pg/ml), mean (sd)	3.9	3.1	3.0	2.4	.12
Medication use					
Aspirin	21	70.0	63	84.0	.11

Characteristic	Obstructive Sleep Apnea/Hypopnea				P-value
	Present (n=30)		Absent (n=75)		
	n	%	n	%	
Calcium channel blockers	12	40.0	22	29.3	.29
Beta blockers	22	73.3	61	81.3	.36
Ace inhibitors	17	56.7	34	45.3	.29
Statins	20	66.7	59	78.6	.20
Depression characteristics					
History of major depression	20	66.7	48	67.6	.93
Duration of current depressive episode (months)	13.7	18.4	13.4	17.1	.93
History of depression treatment	19	63.3	46	61.3	.85
Heart Rate (daytime)					
Very Low Frequency (natural logarithm) mean, (sd)	6.90	.73	6.70	.91	.34
Heart Rate (bpm) mean, (sd)	74.2	10.0	75.1	11.2	.71

OSAH= obstructive sleep apnea hypopnea; BMI= body mass index; MI= myocardial infarction; ACS= acute coronary syndrome; CABG= coronary artery bypass graft; PTCA= percutaneous transluminal coronary angioplasty; CHF= chronic heart failure; HDL= high-density lipoprotein; hs-CRP= high-sensitivity C-reactive protein; IL-6= Interleukin-6.

Table 2

Follow-up patient characteristics

Measure	Obstructive Sleep Apnea/Hypopnea				P-value
	Present (n=30)		Absent ¹ (n=71)		
	mean	sd	mean	sd	
Beck Depression Inventory II					
Baseline score	30.0	9.0	28.2	9.0	.35
Follow-up score	19.0	11.0	13.0	9.2	.01
Adjusted for baseline	18.4	9.1	13.3	9.1	.01
Adjusted for baseline, treatment group	18.3	9.2	13.3	9.1	.01
Adjusted for baseline, treatment group, BMI ²	19.0	9.4	13.2	9.2	.01
Adjusted for baseline, treatment group, BMI, hs-CRP ³	19.5	9.3	13.8	9.1	.01
Adjusted for baseline, treatment group, BMI, IL-6 ⁴	19.3	9.2	13.2	9.0	.01
Hamilton Rating Scale for Depression					
Baseline score	21.2	6.7	20.0	4.8	.30
Follow-up score	11.6	7.4	8.4	5.8	.02
Adjusted for baseline	11.3	5.9	8.6	5.9	.04
Adjusted for baseline, treatment group	11.3	6.0	8.6	6.0	.04
Adjusted for baseline, treatment group, BMI ²	11.7	6.2	8.5	6.1	.03
Adjusted for baseline, treatment group, BMI, hs-CRP ³	12.0	6.2	9.1	6.1	.04
Adjusted for baseline, treatment group, BMI, IL-6 ⁴	11.9	6.2	8.6	6.1	.02
Omega-Index (% EPA + DHA in RBC)					
Baseline score	4.8	1.5	4.6	1.5	.46
Follow-up score	6.5	2.2	5.9	2.1	.26
Cumulative Treatment Adherence (% days pill removed)					
Omega-3/Placebo	96.7	5.4	97.8	2.8	.20
Setraline	98.5	2.6	98.9	2.2	.50

BMI= body mass index; OSAH= obstructive sleep apnea hypopnea; hs-CRP= high-sensitivity C-reactive protein; IL-6= interleukin-6; EPA= eicosapentaenoic acid; DHA= docosahexaenoic acid; RBC= red blood cells.

¹ Four participants without OSAH were lost to follow up

² BMI was missing for 1 participant

³ hs-CRP was missing for 7 participants

⁴ IL-6 was missing for 1 participant